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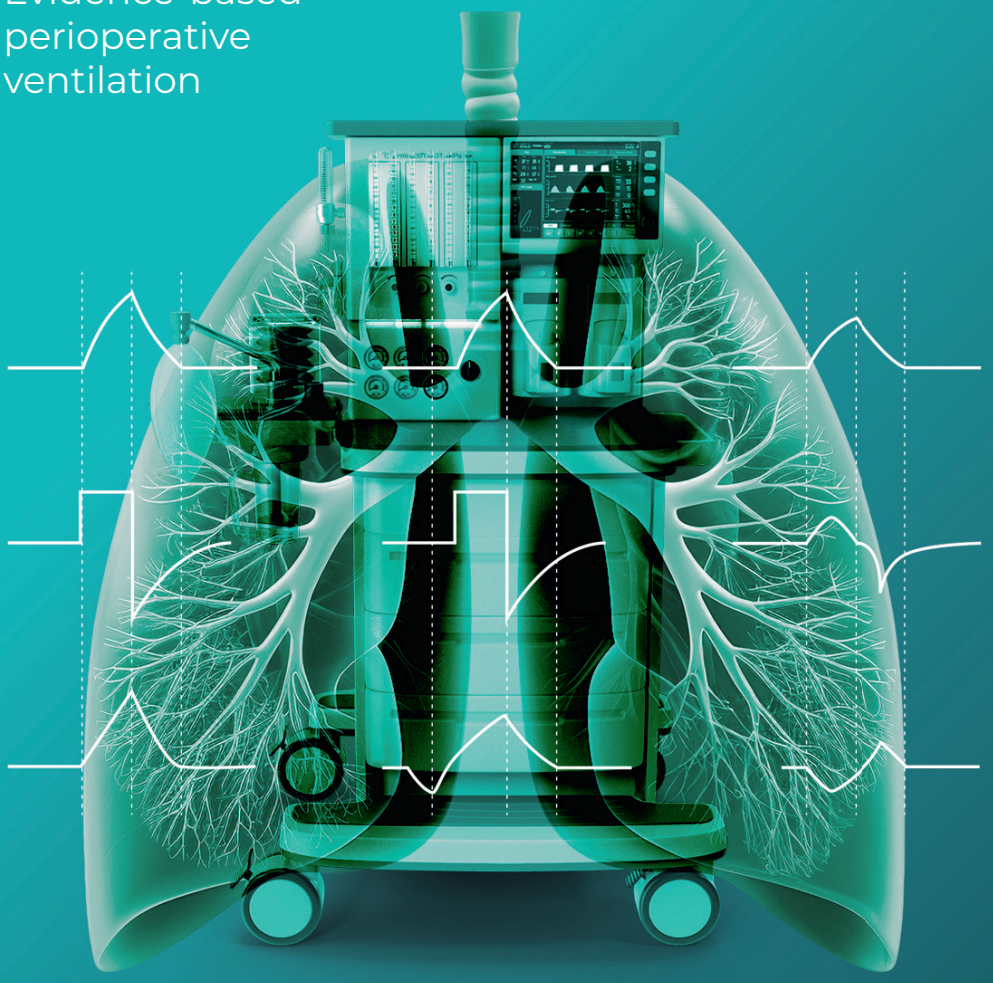
Vol. 76, N. 5 | Sep-Oct 2026 | ISSN 0104-0014

bjan-sba.org

BJAN
Brazilian Journal of Anesthesiology

Brazilian Journal of ANESTHESIOLOGY

Evidence-based perioperative ventilation



Brazilian Journal of Anesthesiology

Vol. 76 N. 5 | September/October 2026

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SBA Sociedade Brasileira de Anestesiologia

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Published by | Publicada por
Elsevier Editora Ltda.
Telefone RJ: +55 21 3970-9300
Telefone SP: +55 11 5105-8555
www.elsevier.com
ISSN: 0104-0014

Brazilian Journal of ANESTHESIOLOGY

Sociedade Brasileira de Anestesiologia

ISSN 0104-0014 • Volume 76 • Number 5 • September—October 2026

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Pillar Zero: a temporal anchor for patient-centered Patient Blood Management (PBM)

Introduction

The three pillars of Patient Blood Management (PBM) – detection and management of anemia, minimization of blood loss, and optimization of physiological tolerance – represent a well-validated, guideline-endorsed framework for reducing perioperative transfusion, complications, and mortality.[1-3] The clinical rationale for each pillar is well established, yet implementation has lagged far behind what the evidence warrants. The reasons are well characterized and include coordination failures, over-reliance on transfusion as residual solution, and cultural inertia.[4] This editorial argues that one specific failure underlies all others: *the absence of a temporal activation point* – a failure that is, at its root, a failure of patient-centered pathway design.

Evidence of a missed opportunity

Two recent Brazilian cohort studies define the scope of this failure. A retrospective study from a quaternary public hospital found that 42.1% of surgical patients were anemic preoperatively – independently associated with 30-day mortality (RR = 1.69, 95% CI 1.44–1.99), transfusion (RR = 4.44, 95% CI 3.90–5.06), and ICU admission (RR = 1.09, 95% CI 1.04–1.16).[5] Over five consecutive years, with no policy changes, the burden remained unchanged; only 10.5% of patients with moderate anemia underwent etiological investigation.[5] A second cohort of 23,579 adults undergoing elective noncardiac surgery documented a severity-dependent mortality gradient: mild anemia doubled in-hospital mortality (adjusted RR = 2.5), moderate anemia increased it more than fourfold (RR = 4.6), and severe anemia carried a nearly 25-fold increase (RR = 24.7, 95% CI 13.3–46.0).[6] The median interval between hemoglobin measurement and surgery was 26.7 days – below the threshold for oral iron but within the window for intravenous iron – yet no intervention was initiated. This window is sufficient for intravenous iron; to preserve the option of oral iron, activation must occur even earlier, at surgical indication.[6] Internationally, the CPOC Anemia Guideline (2025) reports that 67% of anemic surgical patients received no preoperative treatment, including 31% with severe anemia.[7] These figures do not represent a failure of the three pillars; they point to a problem upstream.

The structural problem: provider-centered pathways and the collapsed time window

Perioperative pathways are organized around provider workflow rather than patient needs.[8,9] The Full Blood Count (FBC) is ordered at the preoperative assessment – set for scheduling convenience, typically days before surgery. By the time hemoglobin is communicated, the surgical date is imminent and the clinical decision binary: proceed with an anemic patient, or cancel. Neither option deploys a PBM pillar; both bypass the patient as an agent in their own preparation. This is not a failure of education or protocol adherence. It is a structural failure to anticipate patient needs.

Even when the FBC is ordered in advance, results routinely fall between specialists: the surgeon holds no mandate to act on them, the anaesthetist was not notified, and no named agent owns the finding. The timing failure and the ownership gap are inseparable.[4,8] Oral iron requires a minimum of four weeks to produce a clinically meaningful hemoglobin increment;[7] intravenous iron requires 2–3 weeks.[7,10] The stable anemia prevalence documented over five years in Brazilian surgical populations reflects a system in equilibrium with untreated preoperative anemia – an equilibrium the three pillars alone cannot break because they activate after the therapeutic window, and the patient has already been failed.[5]

The timing failure is compounded by an ownership gap: preoperative anemia is nobody's explicit institutional responsibility. The 2025 ESAIC guidelines on preoperative assessment explicitly recognize this gap: even after a full

https://doi.org/10.1016/j.bjane.2026.844801

preoperative workup, the assessment must be updated within 48 hours of surgery to allow rescheduling when optimization – including correction of preoperative anaemia – remains incomplete.[11] Yet within this framework, if anemia detection occurs only at the preoperative assessment, the remaining time window may be insufficient for oral iron therapy. The deeper obstacle is cultural – the dominant assumption that anemia is the patient's condition, the waiting list an administrative problem, and transfusion the residual solution. Making inaction visible and timestamped is the first step toward contesting them.

Pillar Zero: definition and operational framework

Pillar Zero is defined as the mandatory activation of the PBM workflow at the time surgery is indicated or scheduled, governed by explicit, computationally verifiable patient-level criteria. Two guideline frameworks define its operational basis. The NICE NG45 guideline establishes that FBC is indicated for patients undergoing major surgery (all ASA grades) and for patients undergoing intermediate surgery classified as ASA III or IV.[12] It addresses both structural failures simultaneously: the activation event ties the FBC to a specific, documentable moment week to months before surgery, and explicit ownership is assigned to the surgical team at that same consultation, so that the result does not fall between specialists. Pillar Zero does not directly challenge the cultural beliefs described above, but by making inaction visible and timestamped, it creates the conditions under which they can be contested. The CPOC Anemia Guideline (2025) states that 'PBM should start at the time surgery is booked.[7] Pillar Zero converts this principle into an institutional rule with a defined patient population and a defined activation event (Table 1). When criteria are met, three actions are triggered simultaneously: the FBC is requested at surgical indication – not at the preoperative assessment; if anemia is identified, structured etiological workup is initiated in parallel with surgical planning; and a documented PBM plan is generated covering the full perioperative period.

The PBM plan initiated at surgical indication is subsequently reviewed and ratified by an expert anesthetist at the early preoperative assessment – the second governance node of the pathway – who integrates findings into the comprehensive anesthetic risk assessment and coordinates specialist referrals as needed.

No new test is required. The FBC is already indicated by NICE NG45 for this population; the change is only when it is ordered, and by whom. The marginal cost of this displacement is zero. The gain is the 4–12 week window between surgical indication and surgical date, currently available in most elective settings and systematically wasted.

The Brazilian context: an unused optimization window and the patient within it

In the Brazilian public health system (SUS), the surgical waiting list – generally viewed as a bottleneck – functions as an optimization window that goes unused.[5,6] The 26.7-day median hemoglobin-to-surgery interval confirms that a therapeutic window already exists – sufficient for intravenous iron, and extendable to oral iron when activation occurs at surgical indication rather than at the preoperative assessment; what is missing is not time, but the activation signal. Early risk stratification, described by Grocott as "patient staging" in parallel to pathology staging, creates conditions for shared decision-making, prehabilitation, and comorbidity management that the traditional pathway forecloses.[9]

In the Immich et al. cohort, moderate-to-high functional capacity was the only modifiable variable independently associated with reduced risk of prolonged hospitalization (RR = 0.6),[6] positioning prehabilitation as a core PBM component equally dependent on early temporal activation.

Screening must adopt a sex-unified hemoglobin threshold of 13 $g.dL^{-1}$ for all adult patients, consistent with the International Consensus Statement[13] and the 2024 WHO PBM guidance.[14] Women constituted 82.4% of the mild anemia group in the Immich et al. cohort[6] – a proportion systematically under detected under sex-differentiated cutoffs. Adopting the unified threshold is a matter of equitable care, one of the IOM's six foundational quality aims.[8]

The Western Australia statewide PBM program reduced hospital mortality by 28%, transfusion rates by 41%, and generated cost savings of US$ 78–97 million over six years.[15] In the SUS, Pillar Zero must be incorporated as an institutional performance indicator – a contractual or accreditation metric – rather than a clinical recommendation. Recommendations are filed; indicators are measured, reported, and acted upon.

Conceptual contribution to the PBM model

The three established pillars are domains of intervention. Pillar Zero is distinct in kind: it is the enabling condition for the other three and the point at which the patient enters the pathway as an active participant rather than a passive recipient. Without it, each pillar remains individually valid, but the three together cannot deliver what they promise, because their shared precondition – time, and patient engagement within that time – is not built into the model itself. Table 2 contrasts the structural consequences of operating with and without Pillar Zero. Pillar

Table 1 Pillar Zero activation criteria and downstream actions (derived from NICE NG45).[12]

Activation criterion	ASA grade	Action triggered
Major or complex surgery	Any (I–IV)	FBC at surgical indication + PBM pathway open; ownership assigned to surgical team
Intermediate surgery	ASA III or IV only	FBC at surgical indication + PBM pathway open; ownership assigned to surgical team
Minor surgery OR intermediate with ASA I–II	Any	Pillar Zero not activated; standard pathway

ASA, American Society of Anesthesiologists physical status; FBC, Full Blood Count; PBM, Patient Blood Management.

Table 2 Structural comparison of PBM workflow with and without Pillar Zero, with ESAIC 2025 alignment.[11]

PBM element	Without Pillar Zero	With Pillar Zero	ESAIC 2025 alignment ref.[11]
FBC timing	Preoperative assessment (days before surgery)	Surgical indication (weeks to months before surgery)	R1.4 (CPS): early assessment for high-risk patients to allow optimization
Anemia detected	Too late for oral iron; IV iron often infeasible	Within therapeutic window: oral iron (≥ 4 wk) or IV iron (≥ 2 wk)	R1.3 (CPS): assessment updated within 48h if optimization (e.g., anemia) required
Sex threshold applied	Sex-differentiated cutoffs; women systematically underdetected	Unified Hb < 13 $g.dL^{-1}$ for all adult patients	–
Patient role	Passive recipient: pathway decided by providers	Active participant in shared decision-making and prehabilitation	R1.2 (1B): telemedicine and standardized questionnaires to improve patient accessibility and satisfaction
Functional assessment	Not assessed in PBM window	Validated functional capacity assessed (DASI or equivalent); prehabilitation initiated if indicated	R3.3 (1A): subjective METs discouraged as standalone measure; DASI recommended
Clinical governance	No named specialist owns the finding	Surgical team activates; anesthetist reviews and ratifies at early preoperative assessment	R2.2 (CPS): expert anesthetist coordinates preoperative evaluation and MDT
Decision available	Proceed with anemia OR cancel surgery	Treat anemia before surgery; proceed optimized	R1.1 (1C): early outpatient assessment reduces day-of-surgery cancellations
Audit metric	Was anemia treated?	Was PBM activated in time – and with the patient – to treat anemia?	–

DASI, Duke Activity Status Index; FBC, Full Blood Count; IV, Intravenous; MDT, Multidisciplinary Team; PBM, Patient Blood Management; CPS, Clinical Practice Statement; Hb: hemoglobin; METs: Metabolic Equivalents.

Zero is necessary but not sufficient; cultural inertia and fragmented institutional responsibility will continue to attenuate downstream implementation.[4]

A program that audits pillar adherence without auditing activation timing will consistently find protocols followed but outcomes unchanged, because the measurement frame excludes the causal variable. The ICCAMS recommendations[13] and the Frankfurt Consensus[1] both recognize early detection as foundational to effective PBM. Pillar Zero formalizes this into an explicit, auditable system requirement: not just 'was anemia treated?' but 'was PBM activated in time – and with the patient – for treatment to be effective?'

Implementation and digital integration

Pillar Zero's operational rule – surgical complexity plus ASA classification triggering early FBC – is fully computable. Both variables are already documented at surgical indication, requiring no additional clinical judgment. This makes Pillar Zero uniquely suitable for digital perioperative screening workflows and AI-assisted preoperative assessment tools, where patient-facing interfaces can simultaneously activate hemoglobin screening, functional capacity assessment, and patient education at the moment of surgical indication – consistent with current guideline support for telemedicine and standardized questionnaires as components of preoperative anesthesia care.[11]

In a digital model, when criteria are met the system automatically triggers a physician alert and a draft FBC request; the order is only placed upon explicit physician confirmation, consistent with Brazilian SaMD regulation and the principle that laboratory ordering remains a medical act; upon confirmation, the structured PBM pathway opens with sex-unified thresholds as standard. The activation event must be designed as irreversible within the workflow: non-activation requires explicit documentation, making inaction as visible and accountable as action.

Conclusion

Patient Blood Management will remain under implemented as long as its temporal precondition goes unnamed, and as long as perioperative pathways are designed around provider convenience rather than patient needs. The evidence is unambiguous: preoperative anemia is prevalent, consequential, and treatable, including in the low-complexity elective procedures that constitute the bulk of any surgical system. The gap between knowledge and action persists because the current model does not specify when action must begin, nor that the patient has a legitimate interest in that decision. Adopting Pillar Zero requires no additional resources, tests,

or protocols: only a change in timing and orientation. We call for Pillar Zero to be formally incorporated into the Brazilian PBM framework and implemented in digital perioperative tools as a mandatory activation rule, with sex-unified thresholds, validated functional capacity assessment, and patient engagement as standard components. Patient blood management must begin at the moment surgery is considered, not in the final days before it is performed.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Use of AI-assisted technology in writing

AI-assisted tools (Claude, Anthropic) were used to support manuscript drafting and language editing. All scientific content, clinical reasoning, and conclusions were generated and verified by the authors, who assume full responsibility for the integrity of the work.

Ethics statement

This editorial does not involve human subjects, animal experiments, or patient data. Institutional ethical approval is not required.

Authors' contributions (ICMJE)

Flávio Takaoka: Conceptualization; Original draft preparation; Scientific validation; Clinical reasoning; Critical revision for intellectual content, and final approval.

Maria José Carvalho Carmona: Critical revision for important intellectual content; Editorial review, and final approval.

Renato Carneiro de Freitas Chaves: Critical revision for important intellectual content; Co-authorship contributions, and final approval.

Paulo Roberto Silva Garcez dos Santos: Critical revision for important intellectual content; Co-authorship contributions, and final approval.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 4 June 2026; Accepted 2 July 2026
Available online 22 July 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

The paradox of mechanical ventilation: life-saving, injurious, and pro-inflammatory — lung protection during general anesthesia with neuromuscular blockade

In this issue of the journal, the Brazilian Society of Anesthesiology releases Consensus Recommendations on Perioperative Mechanical Ventilation Strategies.[1] This Editorial analyzes and summarizes the different steps that led to these recommendations since the 1950s, with a specific attention to tidal volume (TV) and recruitment maneuvers.

From the early 1950s to the 1980s: the use of mechanical ventilation and the rationale for delivering tidal volumes ≥ 10 mL.kg^{-1}

In the mid-20th century, two major medical innovations revolutionized surgery and medicine: general anesthesia and mechanical ventilation. Both are tightly linked: the administration of anesthetic agents for inducing sleep, opioids for controlling pain and muscle relaxants for ensuring a quiet operating theater implies mechanical ventilation for supporting gas exchange. A critical step was the 1952 poliomyelitis epidemic in Copenhagen: the life of thousands of patients dying from muscle paralysis-induced respiratory failure was saved by inserting a tube in the trachea and squeezing intermittently an air oxygen mixture into the lungs.[2] Two-hundred and fifty medical students and 260 nurses were hired for ensuring 24-hour manually gas insufflation until recovery from respiratory muscles paralysis. Mortality rate decreased from 87 to 25%. Critical Care Medicine was born.[3] For the next 20 years, artificial respirators providing mechanical ventilation (MV) were manufactured, offering the possibility of individualizing ventilator settings: tidal volume (TV), respiratory rate, inspiratory time, positive end-expiratory pressure (PEEP), and sighs (recruitment maneuvers). The early introduction of large screens displaying flow and pressure waveforms and the possible monitoring of physiologic respiratory parameters allowed to personalize MV.[4]

With the widespread development of intraoperative MV in the 1960s, anesthesiologists noticed that anesthetized patients became hypoxemic soon after anesthetic induction. In a physiologic study performed in 22 patients undergoing upper abdominal surgery and mechanically ventilated with physiologic TV, Bendixen and co-workers demonstrated that radiologic atelectasis occurred in dependent lung regions, causing a right-to-left shunt and a 22% average drop in PaO_2 despite the use of 100% oxygen.[5] Lung collapse and hypoxemia were reversed by three consecutive vital capacity inflations.[6] In series of patients anesthetized for various types of surgery, mechanical ventilation using TV ≥ 10 mL.kg^{-1} of ideal body weight also reversed arterial hypoxemia.[7-9] These studies established the rationale for using TV of 10-12 mL.kg^{-1} with periodic sighs in Anesthesiology and Critical Care for the next 40 years. Between 1970 and 2010, generations of residents in Anesthesiology and Critical Care were trained to deliver extra-physiologic TV, to control $PaCO_2$ by setting respiratory frequency between 10 and 15 bpm, and target FiO_2 to get an oxygen saturation ranging between 95 and 100%.

The period 1980-2000: mechanical ventilation in patients with acute respiratory distress syndrome and the rationale for delivering tidal volumes ≤ 6 mL.kg^{-1}

The first warning about the dangers of delivering TV ≥ 10 mL.kg^{-1} came to the forefront in the mid-1980s. A high-permeability type pulmonary edema was produced in normal rats after a 20-minute period of MV delivering a TV of 45 mL.kg^{-1} at a peak inspiratory pressure of 45 cmH_2O.[10] Alveolar flooding by an albumin-rich edema resulted from a disruption of the alveolar-capillary barrier, the cause of which was excessive TV (volutrauma) rather than excessive airway

https://doi.org/10.1016/j.bjane.2026.844822

pressure (barotrauma).[11] At first glance, these experimental conditions seemed extravagant, without human equivalent and considered lacking clinical relevance. However, the understanding that these experiments were relevant to critically ill patients with severe Acute Respiratory Distress Syndrome (ARDS) was rapidly acknowledged.

The ARDS lung is characterized by a massive loss of lung aeration resulting from alveolar flooding by protein-rich edema, infiltration of alveolar space by inflammatory cells, diffuse lung inflammation and bronchiolar collapse/obstruction. Of note, computed tomography images showed that the aeration loss was often heterogeneously distributed (Fig. 1): in a high proportion of ARDS patients lying in the supine position, dependent lung regions (lower lobes) were non aerated whereas nondependent regions (upper and middle lobes) remained partially or fully aerated, defining the focal ARDS morphology.[12] In other ARDS patients the aeration loss was more homogeneously distributed, involving dependent and non dependent regions, defining the diffuse ARDS morphology.[12,13] In very severe forms of ARDS, the aerated lung volume was found to be reduced to less than 25%, and "functional lung" dimensions become close to the size of a "baby lung".[12,14] It was then understood that TV of 10-12 mL.kg^{-1} administered to such ARDS lungs were equivalent to TV of 40-50 mL.kg^{-1} delivered to healthy lungs, exposing the "functional" ARDS lung to volutrauma. In 2000, the negative impact of large TV on ARDS outcome was demonstrated by the ARDS network randomized controlled trial,[15] where

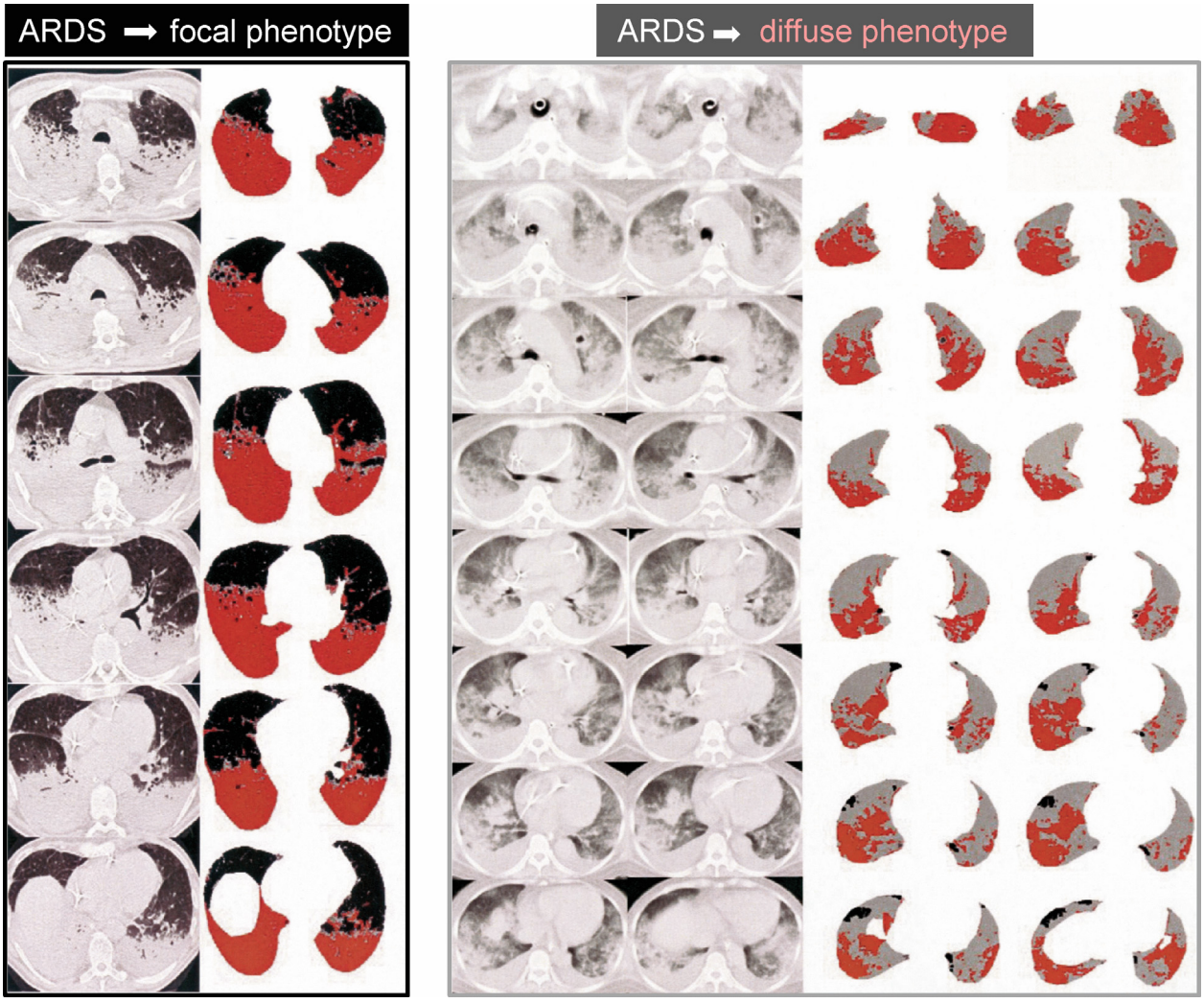

Figure 1 Acute Respiratory Distress Syndrome (ARDS) phenotypes based on the distribution of aeration loss (lung morphology). (A) Focal ARDS phenotype. Computed tomographic (CT) scan was performed in a 61 yr-old patient with ARDS caused by aspiration pneumonia in the postoperative period of a hip replacement. The color-coded CT sections show the distribution of normal aeration in black [CT attenuations ranging between -900 and -500 Hounsfield units (HU)], partial loss of aeration in gray (CT attenuations ranging between -500 and -100 HU) and total loss of aeration in red (CT attenuations ranging between -100 and +100 HU). Dependent parts of upper, middle and lower lobes are non aerated whereas nondependent parts show normal aeration. The proportion of poorly aerated lung is small. (B) Diffuse ARDS phenotype. CT scan was obtained in a 50 yr-old patient with ARDS caused by *Pneumocystis carinii*. Poorly and non aerated lung regions are predominant and homogeneously distributed. The proportion of normally aerated lung is small and essentially present in nondependent parts of the right middle lobe. Reproduced from reference[13] with permission of the publisher.

traditional ventilation delivering a TV of 12 mL.kg^{-1} was compared to a low-TV ventilation delivering a TV of 6 mL.kg^{-1}. The trial was stopped after the enrollment of 861 patients because mortality was 20% lower in the group treated with low TV (31% vs. 40%, p = 0.007). From the 2000s, TV $\leq$ 6 mL.kg^{-1} of ideal body weight became the reference for the ventilation of ARDS patients. However, a TV of 6 mL.kg^{-1} does not always protect against ventilator-induced lung injury.[16] There is a basic reason for that: scaling the TV to the healthy lung size does not fit the conditions of the ARDS lung, whose aerated part — the "functional" lung — is much smaller than the total lung volume. The ARDS lung is stiff because small and the reduction of respiratory compliance (Crs) is correlated to the volume of the functional lung.[17] Therefore, it appears logical to scale the TV to the respiratory compliance rather than to the lung size. The ratio TV/Crs defines the driving pressure (mmHg), which is equal to plateau pressure minus PEEP in mechanically ventilated patients fully assisted by the ventilator.[18] In the mid-2000s, it was demonstrated that a driving pressure > 10 cmH$_2$O is highly predictive of excess mortality in ARDS patients.[18,19] The safe TV, expressed in mL.kg^{-1}, is the TV which provides the lowest driving pressure (10-15 cmH$_2$O) and enough CO_2 elimination to achieve a ph $\geq$ 7.15.

It also became evident that in patients with focal ARDS, PEEP- and recruitment maneuver-induced recruitment was inextricably linked to overdistention (Fig. 2).[20-22] These data seriously questionned the safety and the validity of the "open lung" concept.[23] As shown by the ART randomized controlled trial, an "open lung strategy",[24] including a mean

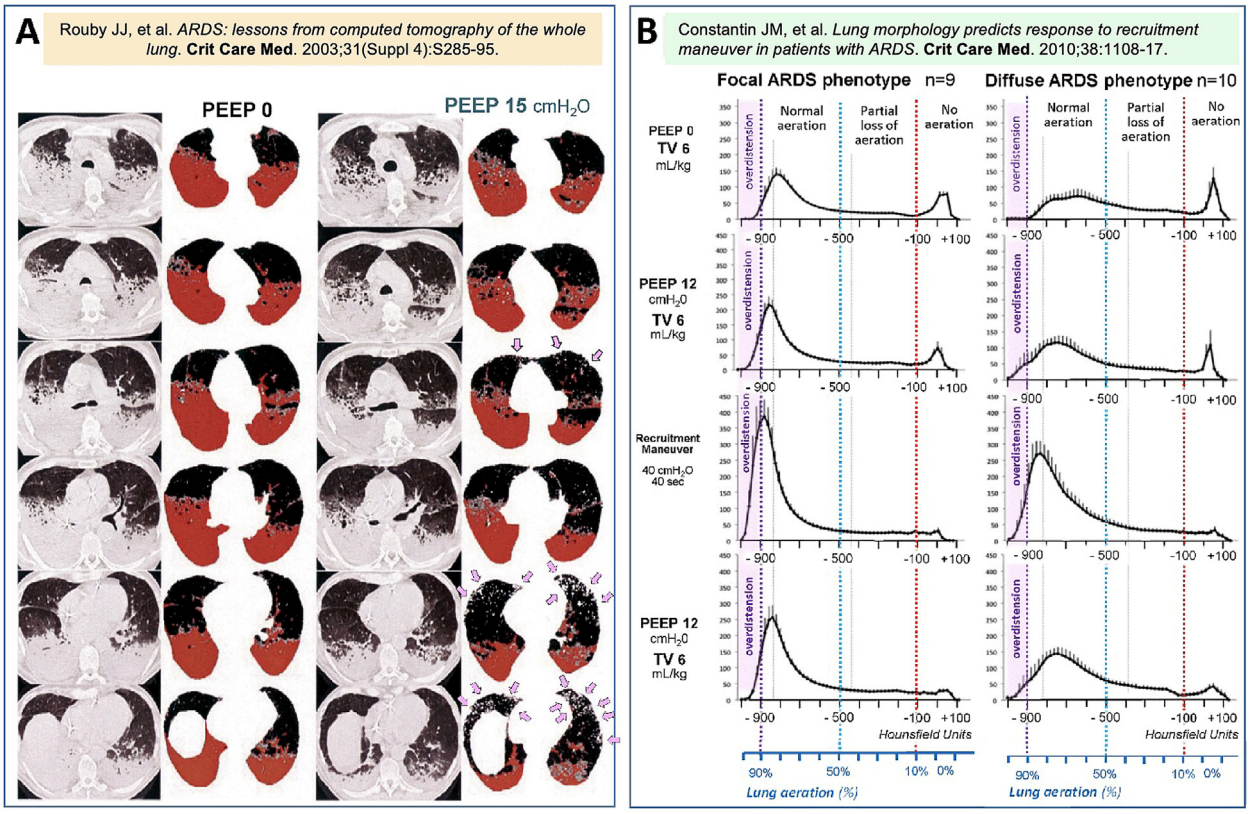

Figure 2 Positive end-expiratory pressure (PEEP) greater than 10 cmH$_2$O and high-pressure recruitment maneuvers recruit some parts of the lung and overdistend simultaneously some other parts. (A) Effect of high PEEP in focal ARDS phenotype. Computed tomographic (CT) scan obtained in a 61 yr-old patient with ARDS caused by aspiration pneumonia in the postoperative period of a hip replacement. CT sections were obtained at end expiration without PEEP and after PEEP 15 cmH$_2$O. The color-coded CT sections show the distribution of overdistension in white [CT attenuations lower than -900 Hounsfield units (HU)], normal aeration in black (CT attenuations ranging between -900 and -500 HU), partial loss of aeration in gray (CT attenuations ranging between -500 and -100 HU) and total loss of aeration in red (CT attenuations ranging between -100 and +100 HU). At PEEP 15, overdistended lung areas are visible in nondependent parts of upper and middle lobes (purple arrows) and recruitment is visible in dependent parts of lower lobes (red color replaced by gray or black color). Reproduced from reference[13] with permission of the publisher. (B) Effect of high PEEP and high-pressure recruitment maneuver in focal (n = 9) and diffuse (n = 10) ARDS phenotypes. Volumic distribution of CT attenuations (Y-axis) is expressed in Hounsfield Units (X-axis). The Hounsfield scale is based on the gas/tissue ratio and reflect the aeration expressed in % (blue X-axis at the bottom of the figure). All patients are receiving a TV of 6 mL.kg^{-1}. Four conditions are studied: PEEP 0, PEEP 12 cmH$_2$O, high-pressure recruitment maneuver (40 cmH$_2$O for 40 sec), and again PEEP 12 cmH$_2$O. In all patients, high PEEP and recruitment maneuver recruited non aerated lung regions and overdistended previously aerated lung regions. PEEP-induced overdistension was 327 $\pm$ 143 mL in focal ARDS and remained very low in diffuse ARDS, 49 $\pm$ 68 mL. Reproduced from reference[22] with permission of the publisher.

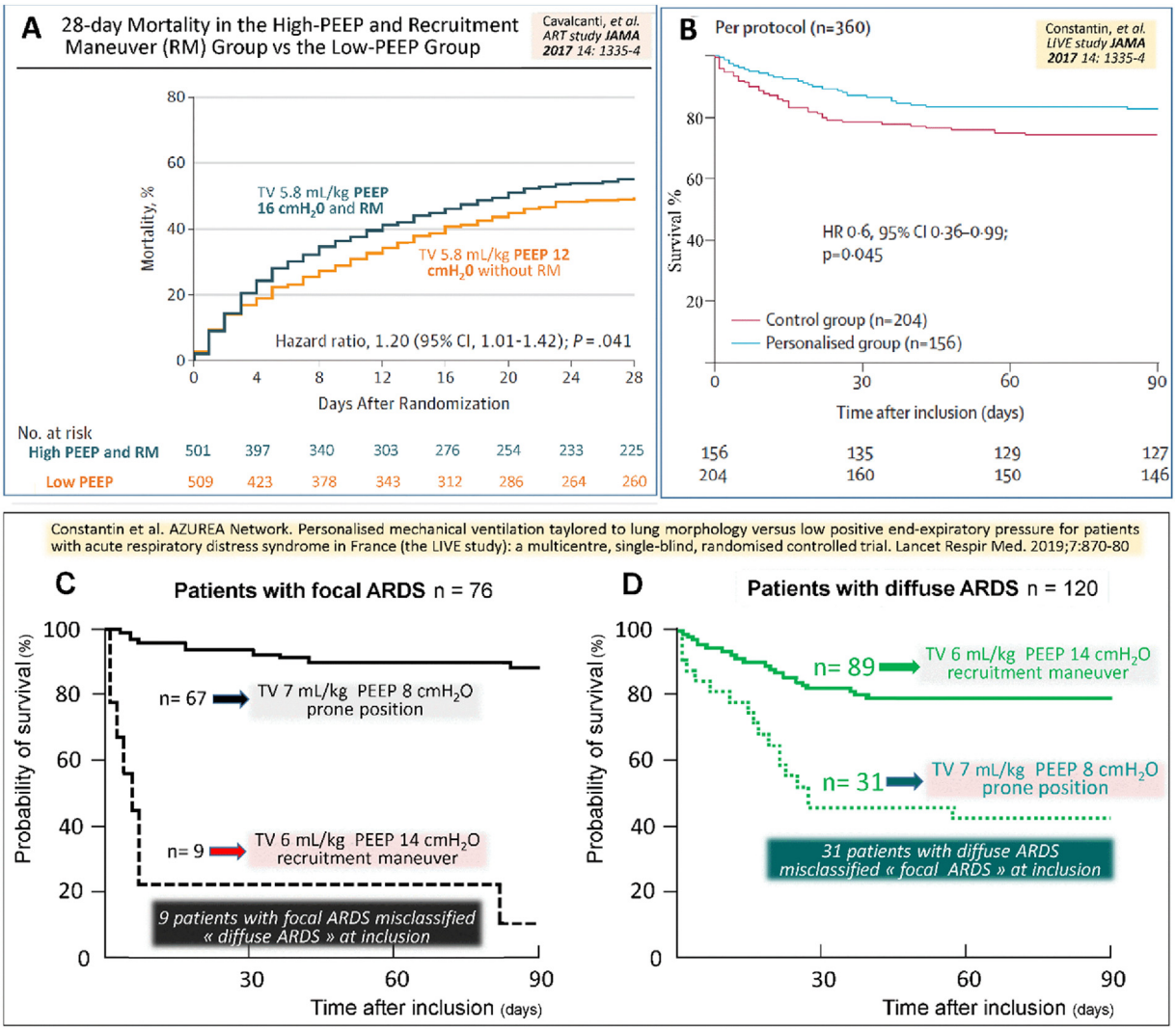

Figure 3 Effects of high positive end-expiratory pressure (PEEP) and high-pressure recruitment maneuver on ARDS patients' outcome. (A) In the ART multicenter randomized controlled trial, 1010 patients were randomized to high PEEP (16 cmH_2O) with high-pressure recruitment maneuvers vs moderate PEEP (12 cmH_2O) without recruitment maneuver. All patients received TV of 5.8 mL.kg^{-1}. Compared with the moderate PEEP strategy, the high-PEEP strategy increased 28-day mortality, decreased the number of ventilator-free days, increased the risk of pneumothorax requiring drainage and the risk of barotrauma. There were no significant differences in the length of ICU stay, length of hospital stay, ICU mortality, and in-hospital mortality. Reproduced from reference[24] with permission of the publisher. (B) Effect of personalized ventilatory support according to ARDS phenotype. At inclusion in the LIVE multicenter randomized controlled trial, ARDS morphology was classified into focal or diffuse (nonfocal) phenotype. 156 patients were correctly classified (76 focal and 120 diffuse) and 40 were misclassified (9 focal patients were classified as diffuse ARDS and 31 diffuse patients were classified as focal ARDS). In the personalised group, patients with focal ARDS were treated with low PEEP, no recruitment maneuver, and prone position and patients with diffuse ARDS were treated with high PEEP and high-pressure recruitment maneuvers. In the per protocol analysis (156 patients correctly classified), 28-day and 3-month survival was higher when the respiratory support was tailored to lung morphology. Reproduced from reference[26] with permission of the publisher. (C) Among the 76 patients with focal ARDS, 9 were misclassified as diffuse and were treated with high PEEP and high-pressure recruitment maneuvers. Survival at day 28 was reduced to 20%. (D) Among the 120 patients with diffuse ARDS, 31 were misclassified as focal and were treated with low PEEP, no recruitment maneuver, and prone position. Survival at day 28 was reduced to 40%. Reproduced from reference[26] with permission of the publisher.

PEEP of 17 ± 4 cmH_2O (titrated according to the best Crs[25]) and intermittent recruitment maneuvers, increased mortality when applied indiscriminately to patients fulfilling ARDS criteria.[24] The LIVE randomized controlled trial then demonstrated that a ventilator strategy misaligned with lung morphology substantially increases mortality (Fig. 3): patients with focal ARDS treated by an open lung strategy (PEEP 14 ± 3 cmH_2O, titrated to reach a P_{plat} of 30 cmH_2O) had a mortality of 80% versus 20% when treated by a moderate PEEP (5-10 cmH_2O) combined with prone positioning.[26]

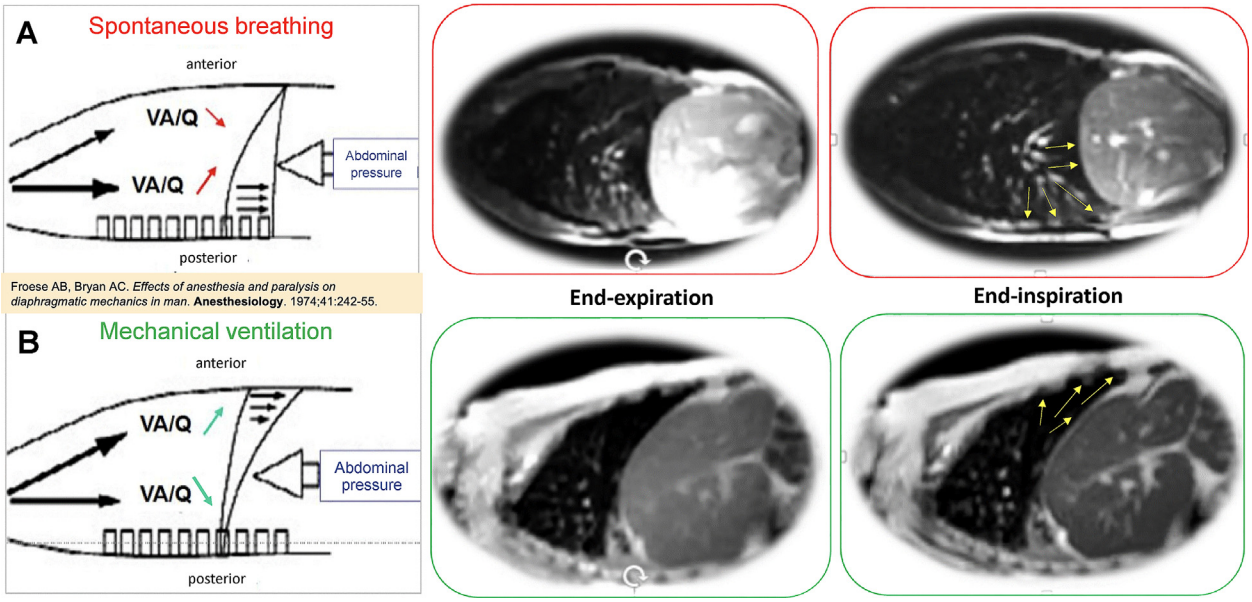

Figure 4 Effects of general anesthesia, muscle relaxation and mechanical ventilation on lung volume and diaphragm activity. (A) In spontaneous breathing, the increase in lung volume during inspiration results from the contraction of inspiratory muscles. The contraction of intercostal muscles increases the antero-posterior dimension of the thorax whereas the contraction of the diaphragm increases its cephalo-caudal dimension. The diaphragm contraction predominates in postero-basal regions and counteracts the abdominal pressure and the cardiac weight (yellow arrows). Ventilation perfusion ratio (VA/Q) increases markedly in dependent and paravertebral lung regions. (B) General anesthesia and muscle relaxation eliminate respiratory muscles activity. During mechanical ventilation, the TV enters the respiratory system as a result of the driving pressure. It is directed towards anterior and nondependent regions, the more compliant parts of the lung (yellow arrows). During inspiration, posterior parts of the diaphragm do not move anymore caudally, the abdominal pressure and the cardiac weight are not counteracted and compression atelectasis occurs, decreasing VA/Q to 0 in dependent lung regions (atelectasis). Lung images are obtained from dynamic magnetic resonance imaging.

The period 2000-2026: mechanical ventilation in patients with healthy lungs and the rationale for delivering tidal volumes ≤ 8 mL.kg^{-1} during general anesthesia

The understanding of benefits and harms of MV in critically ill patients incited anesthesiologists, who play a major role in critical care medicine, to reconsider their practice. MV in anesthetized patients without lung injury and MV in ARDS patients have similarities and differences. Both are associated with loss of lung aeration, but the degree of aeration loss differs markedly between the two.

Massive in ARDS, aeration loss in patients undergoing general anesthesia is more limited, reaching 5% of the lung volume in general surgery,[27] and 25% in cardiac surgery with cardiopulmonary bypass.[28] Atelectasis of dependent regions of lower lobes appears immediately following anesthetic induction,[27] and is caused by the passive mobilization of the relaxed diaphragm by the gas flow coming from the ventilator (Fig. 4).[29] The compression of lower lobes by the heart[30,31] and the abdominal content contributes to lung collapse. Because aeration loss during general anesthesia was found limited, delivering TV 10-12 mL.kg^{-1} was not considered to expose the lungs to volutrauma like observed in ARDS. However, from the mid-2000s onwards, intraoperative TV were progressively reduced to reach 8 mL.kg^{-1} in 2013.[32]

The rationale for delivering low TV during anesthesia came from studies performed in ventilated critically ill patients without ARDS. A meta-analysis of 2822 ventilated critically ill patients enrolled in 20 studies, 15 of which were randomized controlled trials, provided evidence that delivering 5-8 mL.kg^{-1} TV prevented the onset of ARDS, atelectasis, and pulmonary infection, reduced the length of intensive care unit stay and decreased mortality by 36%.[33] In other words, low TV ventilation in the critically ill free of lung injury prevented respiratory complications and reduced mortality. By analogy with mechanical ventilation in ARDS patients,[34] two mechanisms were implicated to explain how high TV could predispose to respiratory complications in critically ill patients with healthy lungs: 1) the "lung biotrauma", defined by the release of pro-inflammatory cytokines by alveolar macrophages, pulmonary epithelial and endothelial cells submitted to positive pressure MV-induced mechanical stretch; 2) the "two hit hypothesis": MV administered to patients without acute lung injury, generates a pulmonary inflammation, akin to priming, that is limited, contained and restrained; infectious challenge or any other inflammatory agression act as secondary hits, that generate an inflammatory response which escapes regulatory mechanisms and may lead to respiratory complications and death.[34]

Biotrauma was initially identified in an isolated rat model.[35] MV-induced "lung biotrauma" was evidenced first in

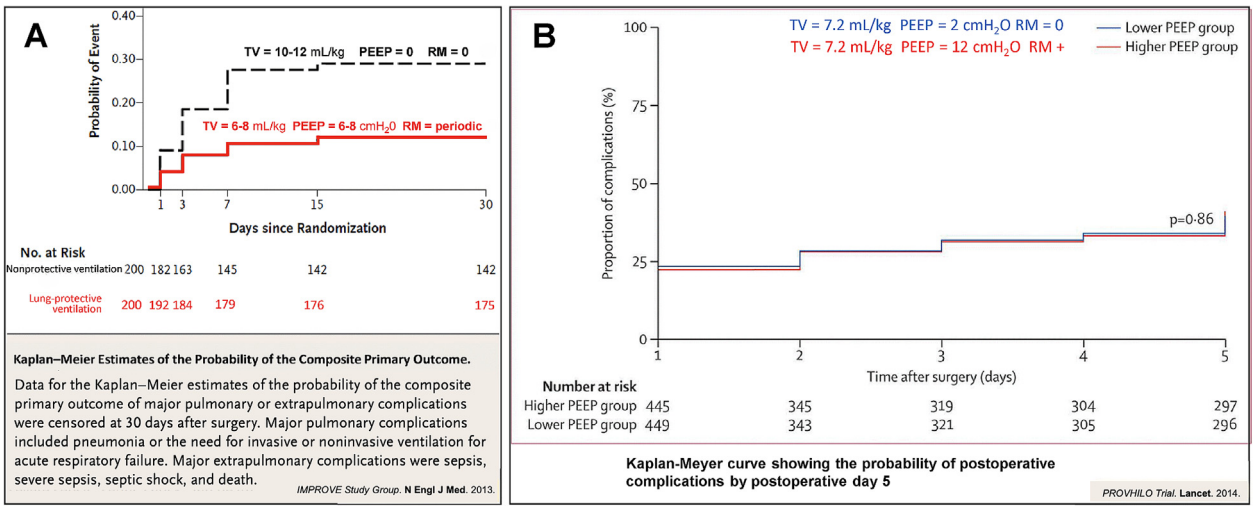

Figure 5 Respective effects on postoperative pulmonary complications of tidal volume (TV) and positive end-expiratory pressure (PEEP) in patients undergoing major abdominal surgery. (A) The IMPROVE multicenter randomized controlled trial randomly assigned 400 adult patients at intermediate to high risk of pulmonary complications after major abdominal surgery to either nonprotective mechanical ventilation (high tidal volume, no PEEP) or a strategy of lung-protective ventilation (low tidal volume, moderate PEEP, high-pressure recruitment maneuvers). Lung-protective ventilation reduced the risk of pulmonary and extrapulmonary complication and reduced the length of hospital stay. Reproduced from reference[40] with permission of the publisher. (B) The PROVHILO multicenter randomized controlled trial randomly assigned 688 adult patients at intermediate to high risk of pulmonary complications after major abdominal surgery to either low PEEP (tidal volume of 7.2 mL.kg^{-1}, PEEP < 2 cmH_2O, no recruitment maneuver) or high PEEP (tidal volume of 7.2 mL.kg^{-1}, PEEP of 12 cmH_2O, recruitment maneuvers). The incidence of postoperative pulmonary complication was not affected by the PEEP level. Reproduced from reference[41] with permission of the publisher.

ARDS patients,[36] then in critically ill patients without lung injury,[37] and last but not least in patients with healthy lungs undergoing major thoracic or cardiac surgery.[38,39] In the randomized controlled trials performed in ventilated critically ill patients with[36] and without ARDS,[37] pro-inflammatory cytokins (TNF-α, IL-6, IL-8, and IL-1β), were found initially elevated in the bronchoalveolar lavage fluid in all patients. They remained stable after a period of MV delivering low TV (5 and 8 mL.kg^{-1}) and markedly increased when 10-12 mL.kg^{-1} TV were used. In the 2 randomized controlled trials performed in anesthetized patients undergoing thoracic or cardiac surgery, pro-inflammatory cytokins [TNF-α, IL-6, IL-8, and soluble intercellular adhesion molecule (sICAM-1)], were found initially low in the bronchoalveolar lavage fluid. TNF-α, IL-8, and sICAM-1 increased after one-lung ventilation, but bronchoalveolar concentrations were lower in patients receiving a TV of 5 mL.kg^{-1} vs 10 mL.kg^{-1}.[38,39] In patients undergoing cardiac surgery, IL-6 and IL-8 were found initially low in the bronchoalveolar lavage fluid. They increased markedly after cardiopulmonary bypass and continued to increase when MV was resumed. After 6h of MV, they were lower in patients receiving TV of 8 mL.kg^{-1} than in patients receiving TV of 10-12 mL.kg^{-1}.[39] These data illustrate the "two hit hypothesis". The lung inflammation resulting from high TV (first hit), cumulates with inflammation resulting from one-lung ventilation or cardiopulmonary bypass (second hit), which facilitates the onset of respiratory complications.

In 2013 in the IMPROVE multicenter, double-blind, randomized controlled trial, 400 patients at risk of pulmonary complications after major abdominal surgery were randomly assigned to receive either non-protective mechanical ventilation (TV of 10-12 mL.kg^{-1}, no PEEP and no recruitment maneuver) or lung-protective ventilation (TV of 6-8 mL.kg^{-1}, PEEP of 6-8 cmH_2O, periodic high-pressure recruitment maneuvers).[40] The primary outcome was a composite of major pulmonary and extrapulmonary complications occurring within the first 7 days after surgery. As shown in Figure 5, the lung-protective ventilation reduced the incidence of pulmonary and extrapulmonary complications from 27.5% to 10.5% and the hospital stay by two and half days.

A subsequent RCT, where TV of 8 mL.kg^{-1} was delivered in all patients, showed no benefit to use high PEEP (12 cmH_2O) associated to high-pressure recruitment maneuvers versus low PEEP (< 2 cmH_2O) without recruitment maneuver.[41] A recent RCT showed that selecting the highest PEEP according to the lowest driving pressure did not change the incidence of pulmonary and extrapulmonary complications.[42] In both studies, intraoperative hypotension requiring the use of vasopressors was a common complication. From the mid-2010s, TV $\leq$ 8 mL.kg^{-1} of ideal body weight associated with moderate PEEP and periodic sigh rather than high-pressure recruitment maneuvers, became the reference for the intraoperative ventilation of patients undergoing major surgery.

The Consensus Recommendations on Perioperative Mechanical Ventilation Strategies, developed under the coordination of the Brazilian Society of Anesthesiology, have taken into consideration the evidence accumulated for more than 70 years.[1] One of the most important recommendations is to reduce intraoperative TV to 6-8 mL.kg^{-1} predicted body weight and avoid systematic high PEEP and high-pressure recruitment maneuvers. Specificities concerning each type of surgery are detailed. Recognizing that inappropriate mechanical ventilation can contribute to postoperative

pulmonary complications and affect outcomes of major surgery represents an important step toward improving the quality of anesthesiology care.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Available online 3 September 2026

Brazilian Journal of Anesthesiology 2026;76(5): 844814

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SPECIAL ARTICLE

Consensus recommendations on perioperative mechanical ventilation strategies: an evidence-based guideline by the Brazilian Society of Anesthesiology

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https://doi.org/10.1016/j.bjane.2026.844814

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Received 7 October 2025; accepted 9 June 2026
Available online 18 August 2026

KEYWORDS
Anesthesia;
GRADE;
Mechanical ventilation;
Perioperative care;
Protective ventilation;
Pulmonary complications

Abstract
Background: Postoperative Pulmonary Complications (PPCs) are a leading cause of morbidity, mortality, and prolonged hospitalization in surgical patients. Intraoperative mechanical ventilation plays a critical role in mitigating these risks, yet clinical practices remain heterogeneous and often not guided by evidence-based standards.
Objective: To develop evidence-based recommendations on perioperative mechanical ventilation strategies for surgical patients, aiming to optimize respiratory care, reduce PPCs, and standardize practice in Brazil.
Methods: This guideline was developed under the coordination of the Brazilian Society of Anesthesiology (SBA) by a panel of anesthesiologists and intensivists from multiple institutions. Seventeen clinical questions were structured in the PICO format (Population, Intervention, Comparison, Outcome). Systematic literature searches were conducted in PubMed, Embase, Cochrane Library, and Scopus up to July 2025. The strength of recommendations and certainty of evidence were assessed using the GRADE methodology. A modified Delphi process was applied to obtain agreement among collaborators, and consensus was discussed only when the predefined threshold of at least 80% agreement was not achieved. All recommendations were standardized in a uniform format.
Results: Seventeen thematic chapters were developed, covering topics from respiratory physiology and the definition of PPCs to advanced intraoperative monitoring, special populations (obese, pediatric, thoracic and cardiac surgery), and patients with or without acute lung injury. Key recommendations include the routine use of lung-protective strategies low tidal volumes of 6—8 mL.kg^{-1} PBW in patients without ARDS and 4—8 mL.kg^{-1} PBW in patients with ARDS, Positive End-Expiratory Pressure [PEEP] titrated to physiology, driving pressure $\Delta P \leq 15$ cm H_2O, and Plateau Pressure [Pplat] ≤ 30 cm H_2O), individualized approaches in high-risk patients, avoidance of unnecessary high fraction of inspired oxygen (FiO_2), and selective use of recruitment maneuvers. Standardized definitions of PPCs and structured monitoring were emphasized as essential to improving patient outcomes.
Conclusion: These consensus-based recommendations provide clinicians with a practical, evidence-informed framework for perioperative mechanical ventilation. Adoption of protective

strategies and standardized definitions is expected to improve respiratory outcomes and reduce variability in perioperative care.

Introduction

Perioperative mechanical ventilation is a cornerstone of anesthetic and surgical management, directly influencing pulmonary outcomes and overall postoperative recovery.[1] Postoperative Pulmonary Complications (PPCs) remain among the most frequent adverse events following surgery, and are strongly associated with increased morbidity, mortality, longer hospital stays, and higher healthcare costs.[2] Their incidence can be mitigated through the adoption of protective ventilation strategies supported by evidence-based perioperative practices.[3]

Respiratory physiology applied to perioperative mechanical ventilation

General anesthesia, neuromuscular blockade, mechanical ventilation, and surgical positioning induce profound changes in respiratory physiology.[4,5] These include reductions in Functional Residual Capacity (FRC), airway closure in dependent lung regions, alveolar collapse (atelectasis), and reduced compliance of the respiratory system.[6]

The FRC, the volume of gas remaining in the lungs after passive expiration, typically decreases about approximately 0.4–0.5 L during general anesthesia.[7] This reduction approximates lung volume to closing capacity, predisposing small airways to collapse, particularly in dependent regions. The combination of controlled ventilation, neuromuscular blockade, and abdominal forces contributes to diaphragmatic dysfunction and cephalad displacement of the diaphragm.[8] This mechanical shift further compresses dependent lung zones, exacerbating atelectasis and reducing FRC.[2] As a result, ventilation becomes heterogeneous, with impaired compliance and increased elastance of the respiratory system. These changes lead to ventilation-perfusion mismatch, increased intrapulmonary shunt, and impaired oxygenation.[9]

Perioperative clinical implications

When FRC decreases toward closing capacity, the likelihood of airway closure increases.[6] At the same time, elevated elastance and reduced compliance heighten susceptibility to Ventilator-Induced Lung Injury (VILI)[10] (Fig. 1). General anesthesia further aggravates these effects by attenuating hypoxic pulmonary vasoconstriction and altering respiratory drive, thereby compromising gas exchange.[11] A thorough understanding of these physiological mechanisms provides the basis for tailoring ventilatory strategies to individual patients and surgical contexts. By maintaining end-expiratory lung volume above closing capacity, reducing ventilation heterogeneity, and minimizing potentially injurious mechanical forces, clinicians can optimize respiratory care. This physiology-guided approach has been associated with a lower incidence of PPCs, shorter hospital stays, and reduced perioperative mortality.[1]

Although protective mechanical ventilation is well established in intensive care, particularly for patients with Acute Respiratory Distress Syndrome (ARDS),[12] its systematic translation into intraoperative practice has been inconsistent. Unique aspects of the perioperative setting including surgical positioning, neuromuscular blockade, pneumoperitoneum during laparoscopy, and patient-specific conditions such as obesity or pre-existing lung disease require tailored ventilatory strategies.

In response to this need, the Brazilian Society of Anesthesiology (SBA) convened a panel of experts in anesthesiology and intensive care to develop a comprehensive, evidence-based guideline. The goal of this document is to provide clinicians with safe, protective, and individualized ventilation strategies for surgical patients, based on the best available scientific evidence and adapted to real-world perioperative practice.

This guideline is structured around 17 clinical questions developed in the PICO format (Population, Intervention, Comparison, Outcome). Recommendations are explicitly graded according to the GRADE system (Grading Recommendations, Assessment, Development and Evaluation). Each chapter provides a rationale supported by the literature and a summary table to guide clinical application. This guideline does not establish a minimum standard of practice or replace clinical judgment. It should be used as a tool to support decision-making and not as a rigid protocol.

Methods

This guideline was developed under the coordination of the Brazilian Society of Anesthesiology (SBA), following a structured and transparent process based on the principles recommended by the GRADE Working Group and international standards for the development of clinical practice guidelines.[13-16] The project involved anesthesiologists, intensivists, experts in perioperative medicine, and methodologists from different institutions across Brazil.

Panel composition and scope

This guideline is intended to assist clinicians involved in the perioperative management of surgical patients requiring mechanical ventilation, including anesthesiologists, intensivists, and perioperative care teams. It covers intraoperative and immediate postoperative periods and includes general and specific recommendations for high-risk populations (e.g., obese, pediatric, thoracic or cardiac surgery patients). The working group was organized into thematic

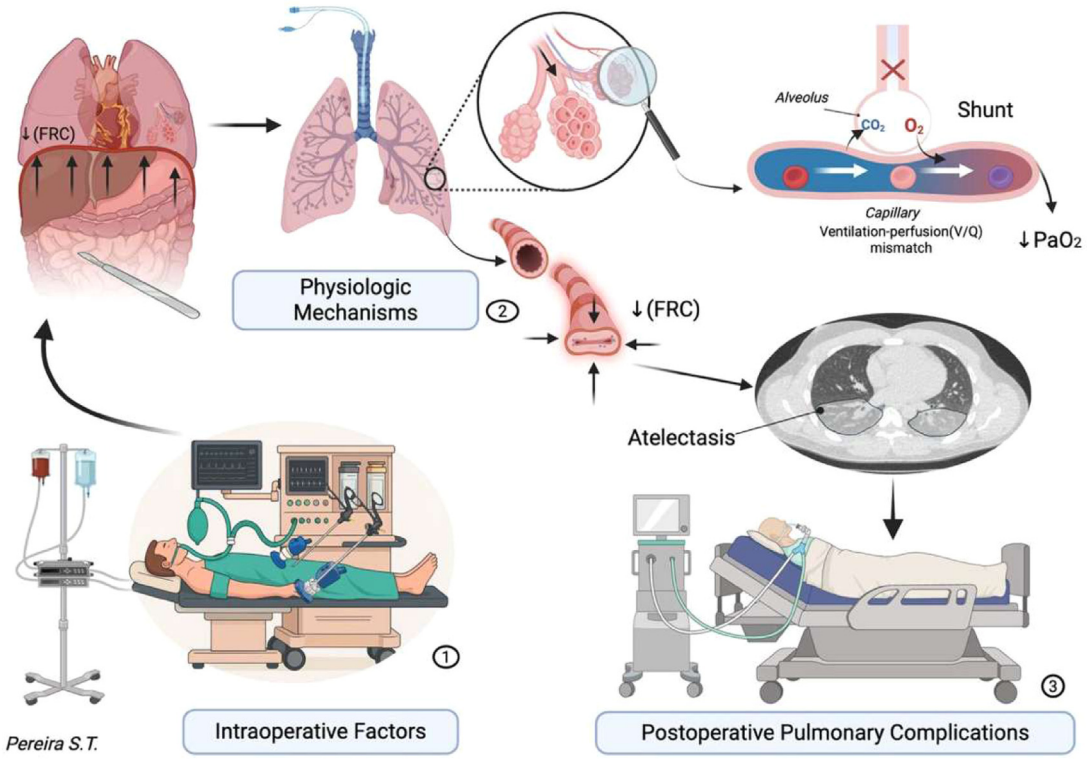

Figure 1 Schematic representation of respiratory physiology in the perioperative context. The central component depicts an anesthetized patient under mechanical ventilation during a surgical procedure, serving as the foundation for understanding subsequent physiological changes. Surrounding elements illustrate how general anesthesia, neuromuscular blockade, patient-related predisposing factors (such as obesity and aging), and surgical trauma contribute to diaphragmatic dysfunction, reduction in Functional Residual Capacity (FRC), alveolar collapse, and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. These changes are accompanied by impaired lung mechanics, including decreased static compliance. The graphic structure highlights the interplay between physiological mechanisms, anesthetic interventions, and postoperative risk, reinforcing the importance of preserving respiratory physiology as a cornerstone of lung-protective ventilation. Created in BioRender by Talison Silas Pereira (Pereira S.T.).

subgroups, each assigned to specific perioperative topics related to mechanical ventilation. Each subgroup consisted of two members with recognized expertise in the assigned topic. All members were selected based on their clinical, academic, or research experience in perioperative care.

Development process

Seventeen structured clinical questions were formulated using the PICO format (Population, Intervention, Comparison, Outcome), addressing key challenges in perioperative ventilatory care. Each question guided the systematic search, analysis, and synthesis of available evidence, as well as the development of the corresponding recommendations.

Literature review and data sources

A comprehensive literature search was conducted using MEDLINE (via PubMed), Embase, the Cochrane Library, and Scopus. Searches focused on identifying randomized controlled trials, meta-analyses, observational studies, and high-quality reviews relevant to each PICO question. Manual reference tracking was also performed. Search strategies and date ranges were tailored for each topic, covering studies from database inception up to July 2025.

Detailed search strategies, inclusion and exclusion criteria, study selection processes, and risk of bias assessment methods are provided in the Supplementary Material.

Assessment of evidence and GRADE classification

The quality of evidence and strength of recommendations were assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The GRADE methodology considers the quality of evidence (high, moderate, low, or very low) and balances the benefits and harms of interventions. Each recommendation was explicitly labeled with its strength (strong or weak/conditional) and the corresponding level of evidence. Interpretation of conditional recommendations: in this guideline, weak/conditional recommendations with low or very low certainty of evidence should be interpreted as potentially useful strategies in selected patients or specific contexts, particularly in centers with expertise and available resources.[16,17] The panel considered these interventions relevant to maintain as conditional options despite the limitations of the evidence. Detailed voting results and agreement rates for all recommendations are presented in Supplementary Table S1.

It should also be emphasized that, according to the GRADE framework, the strength of a recommendation does not always reflect the quality of evidence. In some circumstances, a strong recommendation may be warranted even with low or very low certainty (e.g., when the intervention has clear benefit, minimal risk, low cost, or lack of safe alternatives). Conversely, weak recommendations may arise despite moderate or high-quality evidence when uncertainties persist regarding risks, variability in patient values, or feasibility of implementation.

Risk of bias was assessed according to study design using established tools, and these assessments informed the certainty of evidence within the GRADE framework, as detailed in the Supplementary Material.

Development of recommendations and consensus process

Each subgroup drafted initial recommendations based on the available evidence. These were refined through iterative rounds of review within the panel. Agreement was assessed using a modified Delphi process.[18] When the predefined threshold of at least 80% agreement was not achieved, recommendations were discussed until consensus was reached. The final recommendations and supporting rationale were standardized and approved for inclusion in the guideline.

Review and editorial standardization

A central editorial committee oversaw the final review, formatting, and standardization of the document. All chapters were structured uniformly, including background, clinical question (PICO), methodology, explicit recommendations with GRADE classification, rationale grounded in the literature, and a Summary Table.

Conflict of interest and funding

All contributors disclosed potential conflicts of interest, which were managed in accordance with SBA policy. No commercial entities were involved at any stage of the guideline development or had any influence over its content.

Results — Recommendations overview

Definition of postoperative pulmonary complications in surgical patients

Postoperative Pulmonary Complications (PPCs) are major contributors to morbidity, mortality, prolonged hospitalization, and increased costs after surgery.[2] A key limitation in care and research is the heterogeneity of definitions. Standardized criteria, applied within a prespecified time window, are essential for reproducible identification, inter-study comparability, and guiding preventive strategies. In this guideline, PPCs are assessed during the index admission or up to Day 7; major events (pneumonia, ARDS, unplanned reintubation, death) are also captured through Day 30. PPCs should be defined using standardized clinical, radiological, and laboratory criteria, aligned with EPCO (European Perioperative Clinical Outcome)[19] and StEP (Standardised Endpoints in Perioperative Medicine).[20,21] Pneumonia should follow CDC/NHSN definitions,[22] and ARDS should be defined by the Berlin definition, acknowledging the New Global Definition, which extends Berlin (e.g., High-Flow Nasal Cannula and SpO_2/FiO_2) and may be applied when arterial blood gases are unavailable.[23]

PICO clinical question

In adult surgical patients (P), does using standardized definitions for postoperative pulmonary complications (I), compared with heterogeneous or non-standardized criteria (C), improve reproducibility and prognostic validity, enhance inter-study comparability, and facilitate implementation of preventive strategies (O)?

Evidence-based recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
PPCs should be defined using standardized clinical, radiological, and laboratory criteria.	Strong	High.[19,24]
Definitions should rely on objective parameters to allow reproducibility and comparability across studies.	Strong	Moderate.[25,26]
A core set of complications, such as respiratory failure, pleural effusion, pneumothorax, atelectasis, bronchospasm, aspiration pneumonitis, pneumonia, and ARDS should be routinely assessed.	Strong	High.[27,28]
Using harmonized definitions improves benchmarking, outcome tracking, and implementation of protective strategies.	Strong	Moderate.[2,29]

PPCs, Postoperative Pulmonary Complications; ARDS, Acute Respiratory Distress Syndrome; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

This core set should be applied consistently in clinical practice and research, while allowing for updates as new diagnostic tools become available.

Rationale and literature-based discussion

PPCs are prevalent and clinically relevant across surgical populations. Studies report an incidence of 2%—10% in general surgical patients and up to 40% in high-risk groups.[2] Despite their significance, the absence of standardized definitions across studies impairs comparison and meta-analysis of results.

Summary Table 1 Operational definitions of common postoperative pulmonary complications.

Complication	Operational definition	Key clinical note
Respiratory failure.[1,9,19,27,32]	Any one of: $PaO_2/FiO_2 < 300$; $SpO_2 \leq 90\%$ on room air with need for supplemental O_2; unplanned NIV/HFNC or invasive ventilation; unplanned reintubation for a respiratory cause; hypercapnic failure with pH < 7.30 attributable to ventilatory pump failure.	Core outcome; associated with longer length of stay, ICU admission, and higher mortality.
Pleural effusion.[19,27,32-34]	Lung ultrasound showing a mobile anechoic collection or Chest X-Ray (CXR) with meniscus/costophrenic blunting in a compatible context.	Common after thoracic/cardiac surgery; may worsen hypoxemia and delay recovery.
Pneumothorax.[1,3,9,19,27,32-34].	CXR with a visceral pleural line and absent distal lung markings, or lung ultrasound with absent lung sliding and barcode/stratosphere sign on M-mode (lung point – when present – is highly specific).	Prompt recognition prevents deterioration; may follow positive-pressure barotrauma or central line insertion.
Atelectasis.[8,9,19,27,32-34]	Opacity with volume loss (fissure/mediastinal shift or hemidiaphragm elevation), segmental or lobar.	Most frequent PPC; anesthesia-induced collapse; contributes to hypoxemia.
Bronchospasm.[8,9,19,27,32-34]	New expiratory wheeze requiring bronchodilator therapy with clinical/ventilatory improvement.	Frequent in asthma/COPD; may complicate extubation.
Aspiration pneumonitis.[1,9,19,27,32,33]	Acute lung injury after witnessed/suspected gastric aspiration with a new infiltrate within 2—24 hours and hypoxemia.	Preventable with airway protection; can progress to ARDS.
Pneumonia.[3,9,10,19,32-34]	Preferred: CDC/NHSN surveillance criteria (NV-HAP/VAP).[22] Alternative (where surveillance is not feasible): CXR new/progressive infiltrate plus ≥ 2 of fever, leukocytosis/leukopenia, purulent secretions, or worsening oxygenation. Specify which criterion was used.	Increases morbidity and mortality; enables benchmarking when CDC/NHSN is used.
Acute respiratory distress syndrome (ARDS).[23]	**Global Definition of ARDS (2023):** bilateral opacities on CXR/CT or lung ultrasound by a trained professional; onset ≤ 1 week after a known risk; not explained by cardiogenic edema/overload. **Hypoxemia – non-intubated:** HFNC ≥ 30 $L.min^{-1}$ or CPAP/NIV with PEEP ≥ 5 cm H_2O, and $S/F \leq 315$ measured with $SpO_2 \leq 97\%$. **Severity**: mild, $200 < P/F \leq 300$ or $235 < S/F \leq 315$; moderate, $100 < P/F \leq 200$ or $148 < S/F \leq 235$; severe, $P/F \leq 100$ or $S/F \leq 148$.	Severe but less common; requires ICU-level management.

PaO_2, Arterial Oxygen tension; FiO_2, Fraction of inspired oxygen; SpO_2, Peripheral Oxygen saturation; O_2, Oxygen; NIV, Non-Invasive Ventilation; HFNC, High-Flow Nasal Cannula; ICU, Intensive Care Unit; CXR, Chest X-Ray; CT, Computed Tomography; COPD, Chronic Obstructive Pulmonary Disease; CDC, Centers for Disease Control and Prevention; NHSN, National Healthcare Safety Network; NV-HAP, Non-Ventilator Hospital-Acquired Pneumonia; VAP, Ventilator-Associated Pneumonia; ARDS, Acute Respiratory Distress Syndrome; CPAP, Continuous Positive Airway Pressure; PEEP, Positive End-Expiratory Pressure; S/F, SpO_2/FiO_2 ratio; P/F, PaO_2/FiO_2 ratio.

Several prospective studies and clinical guidelines have proposed diagnostic frameworks incorporating objective criteria such as PaO_2/FiO_2 ratios, SpO_2 thresholds, radiographic findings, and treatment requirements (e.g., oxygen therapy, bronchodilators, or antibiotics).[12,19-21] The use of unified criteria has enabled robust comparisons in large multicenter studies and trials, LAS VEGAS[30] and iPROVE.[31]

Conditions such as pneumonia, atelectasis, and aspiration pneumonitis require specific diagnostic markers due to their pathophysiological and therapeutic implications. A structured diagnostic approach supports clinical decisions, guides ventilatory strategies, and enables integration into quality metrics in perioperative care. Although CDC National Healthcare Safety Network (NHSN) surveillance criteria are recommended for the definition of postoperative pneumonia, their application in the immediate postoperative period requires caution. Early radiographic abnormalities are common after surgery and often reflect atelectasis, residual anesthetic effects, or inflammatory changes rather than true infection. Therefore, in surgical patients, CDC/NHSN-based pneumonia definitions should be interpreted in conjunction with clinical evolution, systemic signs of infection, and microbiological data when available, to avoid misclassification of early postoperative pulmonary changes such as pneumonia (Summary Table 1)

Postoperative pulmonary complications: risk factors and preventive strategies

Postoperative Pulmonary Complications (PPCs) are a significant cause of increased morbidity, mortality, and healthcare costs in surgical patients.[29] Early identification of risk factors, especially modifiable ones, is essential to guide

preventive strategies and improve perioperative respiratory care, ultimately reducing the incidence of PPCs across surgical settings.

PICO clinical question

In adult surgical patients (P), does identifying and addressing perioperative risk factors (I), compared to not managing such risk factors (C), reduce the incidence of postoperative pulmonary complications (O)?

COPD optimization with bronchodilators, correction of anemia, and nutritional support are associated with improved outcomes. Smoking cessation has consistently been linked to a reduction in PPCs, with greater benefit observed when cessation occurs at least four weeks before surgery.

Non-pharmacologic strategies, including incentive spirometry, chest physiotherapy, and early mobilization, are recommended in high-risk populations, although evidence is heterogeneous. Surgical approaches also play a major role; laparoscopic and minimally invasive techniques are associated with lower PPC incidence compared with open procedures.

Finally, multimodal bundles that integrate risk stratification, optimization, and intra- and postoperative strategies have shown the greatest impact in reducing PPCs, underscoring the need for integrated perioperative care.

Evidence-based recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Preoperative risk stratification using validated tools (e.g., ARISCAT score) is recommended to identify patients at high risk for PPCs.	Strong	High.[30,35]
Optimization of comorbidities (e.g., COPD, heart failure, malnutrition, anemia) should be undertaken before surgery whenever possible.	Strong	Moderate.[36,37]
Smoking cessation should be recommended at least 4 weeks before surgery, ideally 4–8 weeks, to reduce the risk of PPCs.	Strong	Moderate.[38,39]
Supervised respiratory physiotherapy and early mobilization, including prehabilitation for thoracic/cardiac surgery and structured postoperative therapy in high-risk patients, may be considered.	Weak	Moderate.[40,41]
Minimally invasive approaches (e.g., laparoscopy) are associated with reduced PPCs when feasible; however, surgical positioning and pneumoperitoneum-related effects should be considered in high-risk patients.	Strong	Moderate.[42,43]
Bundle-based preventive strategies (multimodal perioperative protocols) are encouraged to maximize impact on reducing PPCs.	Strong	Moderate.[28,44]

Rationale and literature-based discussion

Identification and mitigation of risk factors are crucial in reducing PPCs. Several patient-related factors, such as advanced age, obesity, pre-existing lung disease, smoking, and poor functional status are strongly associated with increased risk. Surgical factors including prolonged operative time, upper abdominal or thoracic incisions, and emergency procedures further increase susceptibility.[32]

Summary Table Risk Factors and Prevention of PPCs.

Domain	Key Strategies	Clinical Considerations
Risk Stratification	Use ARISCAT or other validated tools	Identify patients requiring tailored perioperative strategies
Comorbidities	Optimize COPD, CHF, malnutrition, anemia	Improve perioperative resilience and recovery
Smoking	Cessation $\geq$ 4–8 weeks before surgery	Reduce PPC risk; counseling should be offered
Non-pharmacologic interventions	Supervised respiratory physiotherapy and early mobilization; include prehabilitation when feasible	Beneficial in high-risk patients; evidence is heterogeneous
Surgical approach	Favor minimally invasive surgery when feasible	Associated with lower incidence of PPCs
Bundles	Apply multimodal protocols	Greater effectiveness than isolated interventions

ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart Failure; PPCs, Postoperative Pulmonary Complications.

The ARISCAT score[35] has been widely validated as a practical tool for predicting PPCs, incorporating variables such as age, preoperative SpO_2, type of surgery, and duration. Although not perfect, its use provides a structured framework for preoperative risk stratification.

Modes and modalities of invasive mechanical ventilation during the intraoperative period

The choice of ventilation mode can influence intraoperative gas exchange, pulmonary mechanics, hemodynamics, and

the risk of postoperative pulmonary complications.[42] Understanding the application and physiological implications of different ventilation modes in the operating room is key to implementing lung-protective ventilation strategies tailored to surgical patients.

PICO clinical question

In adult surgical patients under general anesthesia (P), do different ventilatory modes (I), compared to other available modes (C), reduce intraoperative complications and improve gas exchange or respiratory mechanics (O)?

reduced pulmonary compliance (e.g., obesity, laparoscopic procedures).

PCV with Volume Guarantee (PCV-VG) combines the benefits of both VCV and PCV, ensuring target tidal volumes while adapting pressure delivery. This mode is increasingly used in intraoperative settings with variable compliance.

Despite theoretical benefits, there is no strong evidence that one ventilation mode is superior to another in reducing postoperative pulmonary complications if protective settings are properly applied.

Evidence-based recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Volume-Controlled Ventilation (VCV) and Pressure-Controlled Ventilation (PCV) provide comparable outcomes when protective settings are applied.	Strong	Moderate.[45-47]
Dual-control modes (e.g., PCV-VG) may be considered to optimize tidal volume delivery in patients with variable compliance, particularly in obesity and laparoscopy.	Weak	Low.[48,49]
Use pressure-controlled ventilation when peak airway pressures are a concern, recognizing that this strategy may limit peak pressure but at the expense of tidal volume delivery.	Weak	Low.[45,50]
Avoid high-frequency oscillatory ventilation or unconventional modes intraoperatively outside research settings.	Strong	Moderate.[51,52]
In patients with compromised respiratory mechanics, individualized mode selection is encouraged.	Strong	Low.[53,54]

VCV, Volume-Controlled Ventilation; PCV, Pressure-Controlled Ventilation; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

The two most used ventilation modes during surgery are Volume-Controlled Ventilation (VCV) and Pressure-Controlled Ventilation (PCV). Both allow for the application of protective strategies with low tidal volumes, moderate PEEP, and monitoring of driving pressure.

Basic monitoring of intraoperative mechanical ventilation

Intraoperative monitoring of mechanical ventilation is a fundamental aspect of implementing protective ventilation strategies and minimizing PPCs. Basic respiratory mechanics monitoring

Summary Table Ventilation modes and intraoperative considerations.

Mode	Characteristics	Considerations
Volume-Controlled (VCV)	Constant flow, fixed tidal volume	Reliable delivery of volume; may increase peak pressure in low compliance lungs
Pressure-Controlled (PCV)	Decelerating flow, pressure-targeted	Reduces peak pressure; tidal volume varies with compliance/resistance
PCV-VG (dual control)	Pressure-targeted, volume guaranteed	Combines benefits of VCV and PCV; useful in obesity/laparoscopy
Advanced/Unconventional	Includes HFOV, PAV, NAVA	Limited role intraoperatively; not routinely recommended

VCV, Volume-Controlled Ventilation; PCV, Pressure-Controlled Ventilation; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; HFOV, High-Frequency Oscillatory Ventilation; PAV, Proportional Assist Ventilation; NAVA, Neurally Adjusted Ventilatory Assist.

Studies comparing VCV and PCV show similar clinical outcomes when protective parameters are maintained. However, PCV may reduce peak inspiratory pressures due to its decelerating flow, which is beneficial in patients with

techniques such as pressure and flow curves, loops, and specific pressure measurements (plateau, peak, driving, and transpulmonary pressure) provide critical real-time feedback to individualize mechanical ventilation and reduce VILI.

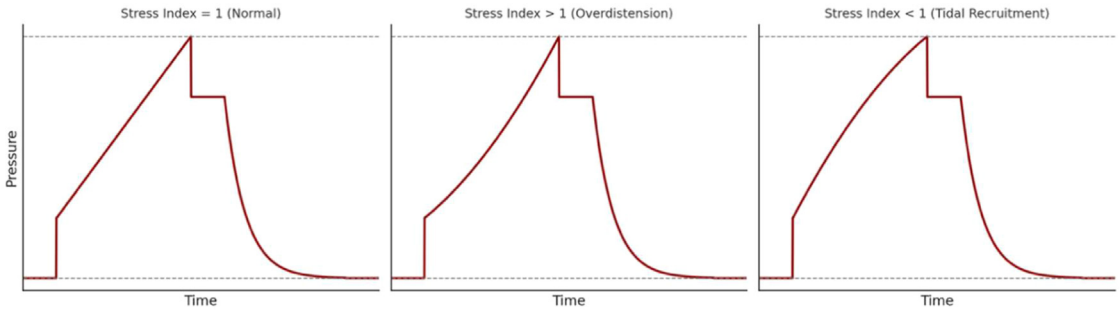

Figure 2 Pressure-time curve during volume-controlled mechanical ventilation.

PICO clinical question

In adult surgical patients under general anesthesia (P), does intraoperative monitoring of basic ventilatory parameters such as pressure-time and flow-time curves and loops (I), compared to no structured monitoring (C), reduce postoperative pulmonary complications (O)?

Recommendations and Quality of Evidence (GRADE).

Recommendation	GRADE Recommendation	Evidence Quality
Suggest monitoring the pressure-time curve to detect overdistension or alveolar recruitment using the stress index (SI ≈ 1).	Weak	Low.[55,56]
Recommend using the flow-time curve to detect auto-PEEP, especially in high respiratory rate situations.	Strong	Very Low.[57,58]
Pressure-volume and flow-volume loops may aid in assessing compliance and resistance.	Weak	Very Low.[59,60]
Recommend monitoring plateau pressure and maintaining it below 25–30 cm H_2O.	Strong	Very Low.[61,62]
Suggest interpreting plateau pressure with caution in cases of altered chest wall mechanics.	Weak	Very Low.[63]
Transpulmonary pressure monitoring (via esophageal balloon) may be useful in individualizing PEEP in complex cases, provided expertise and equipment are available.	Weak	Very Low.[63]
Recommend monitoring driving pressure (ΔP) aiming for values ≤ 15 cm H_2O.	Strong	Moderate.[64-66]
Mechanical power monitoring may help adjust ventilatory parameters to reduce PPCs.	Weak	Low.[67,68]

SI, Stress Index; auto-PEEP, Intrinsic Positive End-Expiratory Pressure; PEEP, Positive End-Expiratory Pressure; ΔP, Driving Pressure; PPCs, Postoperative Pulmonary Complications; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

Pressure-time curve. The pressure-time curve helps evaluate dynamic compliance and alveolar behavior during the inspiratory phase. A linear slope (SI = 1) indicates stable compliance, while SI > 1 suggests overdistension and SI < 1 indicates recruitment. Adjusting tidal volume or PEEP based on the stress index may reduce VILI (Fig. 2).

Flow-time curve. Failure of expiratory flow to return to zero before the next breath suggests the presence of auto-PEEP, often caused by insufficient exhalation time or high respiratory rate. Auto-PEEP increases the risk of dynamic hyperinflation and hemodynamic instability.

Pressure-volume and flow-volume loops. Pressure-volume loops provide a visual understanding of compliance changes and inflection points for alveolar opening and overdistension. Flow-volume loops help detect airway obstruction or leaks, especially in the presence of bronchospasm, secretion accumulation, or ventilator circuit issues.

Peak pressure. Although nonspecific, an increase in peak pressure may reflect increased airway resistance. It should be interpreted alongside plateau pressure to distinguish elastic versus resistive contributions.

Plateau pressure. Obtained via an inspiratory pause, plateau pressure reflects alveolar pressure and should be kept ≤ 30 cm H_2O to minimize overdistension. Its interpretation must consider conditions like obesity or pneumoperitoneum that increase pleural pressures.

Transpulmonary pressure (P_L). Estimated using esophageal pressure, it reflects the distending force on the lung. While promising for tailoring PEEP, its role remains limited in routine intraoperative care due to technical complexity and lack of strong evidence in non-injured lungs.

Driving Pressure (ΔP). Defined as plateau pressure minus PEEP or as VT/compliance, it is a key predictor of PPCs. Lower ΔP is associated with improved outcomes, making it a valuable target in intraoperative ventilatory strategy.

Mechanical power. Mechanical Power (MP): quantifies the energy delivered to the lungs per minute, integrating Vt, RR, PEEP, and ΔP. Higher MP is associated with increased VILI/PPC risk; however, clinical uptake is limited not only by complexity but primarily by the absence of RCTs and validated targets to guide adjustments.

Summary Table Monitoring parameters and clinical use.

Parameter	Clinical Application	Suggested Target
Pressure-Time Curve	Identifies overdistension or recruitment (via Stress Index)	SI $\approx$ 1
Flow-Time Curve	Detects auto-PEEP and dynamic hyperinflation	Flow returns to zero before next breath
Pressure-Volume Loop	Assesses compliance and alveolar opening/overdistension	Visual inspection
Flow-Volume Loop	Identifies airway obstruction or leakage	Visual inspection
Peak Pressure	Indicates resistance (e.g., tube kinking, bronchospasm)	$<$ 35–40 cm H_2O
Plateau Pressure	Reflects alveolar pressure, risk of overdistension	$\leq$ 25–30 cm H_2O
Transpulmonary Pressure	Guides individualized PEEP (if available)	Based on esophageal pressure (Pes)
Driving Pressure (ΔP)	Strong predictor of PPCs, correlates with lung stress	$\leq$ 15 cm H_2O
Mechanical Power	Represents total ventilator-induced lung energy	Keep as low as possible, no universal threshold. Use trends to trigger reassessment of Vt (PBW), RR, PEEP, and flow/Ti.

SI, Stress Index; auto-PEEP, Intrinsic Positive End-Expiratory Pressure; PEEP, Positive End-Expiratory Pressure; Pes, Esophageal Pressure; ΔP, Driving Pressure; PPCs, Postoperative Pulmonary Complications; Vt, Tidal Volume; PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material (Supplementary Appendix S1); RR, Respiratory Rate; Ti, Inspiratory Time.

Advanced monitoring of intraoperative mechanical ventilation

Technological advances in perioperative care have expanded the tools available for individualized monitoring of mechanical ventilation. Novel imaging and electrical techniques, such as Lung Ultrasound (LUS) and Electrical Impedance Tomography (EIT) allow real-time evaluation of alveolar recruitment, ventilation distribution, and the impact of ventilatory settings. These tools aim to enhance ventilatory support, optimize gas exchange, and minimize PPCs, particularly in high-risk populations undergoing laparoscopic or thoracic procedures.[69,70]

PICO clinical question

In adult surgical patients under general anesthesia and mechanical ventilation (P), do advanced monitoring modalities such as lung ultrasound or electrical impedance tomography (I), compared to standard monitoring (C), improve ventilatory accuracy and reduce postoperative pulmonary complications (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use of lung ultrasound (LUS) to guide alveolar recruitment is suggested in laparoscopic or thoracoscopic surgery.	Strong	Moderate.[70-72]
EIT may be used intraoperatively to titrate PEEP and improve oxygenation and compliance, where available.	Weak	Moderate.[69,73,73]

LUS, Lung Ultrasound; EIT, Electrical Impedance Tomography; PEEP, Positive End-Expiratory Pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

Lung ultrasound (LUS). Atelectasis is common during general anesthesia, especially in patients undergoing laparoscopic or Trendelenburg procedures. Several RCTs demonstrate that LUS-guided recruitment improves lung aeration, reduces driving pressure, and decreases PPCs when compared to conventional maneuvers:

- Lung ultrasound-guided recruitment consistently improved oxygenation, aeration, and reduced atelectasis compared with standard strategies across randomized trials in laparoscopic and thoracoscopic surgery.[70-72]

Electrical Impedance Tomography (EIT). EIT is a non-invasive, bedside, radiation-free imaging modality that monitors ventilation in real time. Its intraoperative use allows for individualized PEEP titration:

- Meta-analyses consistently demonstrated that EIT-guided PEEP optimization improves oxygenation, enhances compliance, and reduces driving pressure in surgical patients.[74,69,73]

These modalities provide dynamic functional insights and can be integrated into intraoperative decision-making to optimize mechanical ventilation in real time.

Summary Table Applications and benefits of advanced monitoring techniques.

Modality	Indication	Main Benefits
Lung Ultrasound (LUS)	Laparoscopic/Thoracoscopic surgeries	Improves aeration, reduces driving pressure, and PPCs reduction reported in selected subgroups only.
Electrical Impedance Tomography (EIT)	General surgeries requiring PEEP titration	Enhances oxygenation, improves compliance, lowers ΔP

LUS, Lung Ultrasound; EIT, Electrical Impedance Tomography; PEEP, Positive End-Expiratory Pressure; ΔP, Driving Pressure; PPCs, Postoperative Pulmonary Complications.

Noninvasive mechanical ventilation and high-flow nasal cannula in the perioperative period

Non-invasive respiratory support has become an important adjunct in perioperative care, particularly in patients at risk of hypoxemia or postoperative pulmonary complications.[75] Non-Invasive Ventilation (NIV) improves gas exchange and reduces respiratory effort through positive airway pressure, while High-Flow Nasal Cannula (HFNC) delivers heated, humidified oxygen at high flows, providing low levels of positive pressure and enhanced comfort. Evidence shows that both modalities can be beneficial as preoxygenation strategies in high-risk patients, as selective intraoperative tools, and especially in the postoperative period, where NIV reduces reintubation and pneumonia and HFNC improves oxygenation and tolerance.[76]

PICO clinical question

In adult surgical patients (P), does the use of Non-Invasive Ventilation (NIV) or high-flow nasal cannula (HFNC) in the perioperative period (I), compared with conventional oxygen therapy (C), reduce hypoxemia, reintubation, and postoperative pulmonary complications (O)?

Rationale and literature-based discussion

Evidence synthesized up to 2025 confirms the important role of NIV and HFNC in perioperative care.[75] Preoperatively, both modalities can improve preoxygenation and extend safe apnea time, particularly in obese or hypoxemic patients, with HFNC often better tolerated. Intraoperatively, their role is limited to specific scenarios under sedation or regional anesthesia where intubation is undesirable. Postoperatively, NIV has the strongest evidence, significantly reducing reintubation, pneumonia, and ICU stay in acute hypoxemic respiratory failure, while HFNC improves oxygenation and comfort in high-risk patients, although with less consistent outcome data. Routine prophylactic use in unselected patients is not recommended, and both modalities should never delay timely intubation. Preoxygenation with NIV or HFNC enhances oxygen reserve and prolongs safe apnea time during induction, especially in obese patients, those with reduced FRC, or severe hypoxemia.[81]

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
NIV is recommended for the treatment of acute postoperative hypoxemic respiratory failure in cooperative, hemodynamically stable patients.	Strong	High.[77,78]
HFNC is recommended as an alternative to conventional oxygen therapy after extubation in high-risk surgical patients to improve oxygenation and comfort.	Strong	Moderate.[79,80]
NIV or HFNC may be considered for preoxygenation before intubation in obese or hypoxemic patients to prolong safe apnea time and reduce desaturation.	Weak	Moderate.[76,81]
NIV is not recommended in patients with contraindications such as airway obstruction, hemodynamic instability, impaired consciousness, or copious secretions.	Strong	Moderate.[82,83]
Routine prophylactic use of NIV in unselected postoperative patients is not recommended, especially after abdominal or thoracic surgery.	Strong	High.[84,85]
HFNC may be considered in patients intolerant to NIV interfaces or when NIV is contraindicated.	Weak	Moderate.[86,87]

NIV, Non-Invasive Ventilation; HFNC, High-Flow Nasal Cannula; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Summary Table Perioperative use of NIV and HFNC.

Perioperative Phase	Evidence-Based Application	Clinical Considerations
Preoperative	Effective for preoxygenation in obese/hypoxemic patients; prolongs safe apnea.	HFNC may be better tolerated; not required for all patients.
Intraoperative	Option in selected non-intubated patients under regional anesthesia or sedation.	Limited evidence requires close monitoring.
Postoperative	NIV reduces reintubation and pneumonia in acute hypoxemia; HFNC effective after extubation in high-risk patients.	Avoid routine prophylaxis; do not delay intubation in case of failure.

NIV, Non-Invasive Ventilation; HFNC, High-Flow Nasal Cannula.

Intraoperative mechanical ventilation in patients with or without acute lung injury

Intraoperative mechanical ventilation has evolved from a secondary anesthetic concern to a cornerstone of perioperative care. While previously based on high tidal volumes and minimal PEEP, it is now well established that non-protective ventilation strategies, even during short-term surgery can cause VILI and increase the risk of PPCs.[88,89] Both patients with healthy lungs and those with Acute Lung Injury (ALI) benefit from ventilation strategies tailored to minimize pulmonary stress and improve clinical outcomes.[90]

PICO clinical question

In adult surgical patients with or without acute lung injury (P), do lung-protective ventilatory strategies (I), compared to conventional ventilation (C), reduce the risk of postoperative pulmonary complications and ventilator-induced lung injury (O)?

Rationale and literature-based discussion

Protective ventilation strategies minimize alveolar overdistension and atelectasis. In patients with healthy lungs, high tidal volumes increase transpulmonary pressures and can precipitate VILI. Trials such as PROVHILO and iPROVE[88,96] have shown that low tidal volumes (6—8 mL.kg^{-1} PBW) reduce PPCs and improve recovery.

For patients with acute lung injury, intraoperative ventilatory care should mimic ARDS management in the ICU, focusing on low plateau pressures ($\leq$ 30 cm H_2O) and driving pressure reduction, with data from Amato et al.[97] highlighting the strong predictive value of driving pressure for mortality.

PEEP remains essential to counteract intraoperative atelectasis, especially in at-risk populations such as the obese and those undergoing laparoscopy. While PEEP $<$ 5 cm H_2O is inadequate, individualized titration based on compliance or driving pressure may enhance safety and efficacy. Esophageal pressure monitoring and EIT are useful tools where available.

Respiratory rate should be titrated to avoid hypercapnia and maintain $PaCO_2$ between 38—43 mmHg.[55,94] In all cases, early extubation when feasible, and avoiding hyperoxia, are important for enhancing outcomes.[55,96] PEEP: Use individualized PEEP titrated to oxygenation and respiratory mechanics (ΔP/compliance); avoid routine ZEEP in higher-risk contexts (e.g., obesity, pneumoperitoneum/Trendelenburg).

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use tidal volumes of 6—8 mL.kg-1 PBW in surgical patients without ARDS	Strong	High.[88,91]
Avoid tidal volumes > 10 gt; 10 mL.kg^{-1} PBW.	Strong	High.[88,92]
Maintain plateau pressure $\leq$ 30 lt; 30 cm H_2O.	Strong	High.[88,90]
Target driving pressure $\leq$ 15 lt; 15 cm H_2O, ideally $\leq$ 12 cm H_2O.	Strong	Moderate.[91,93]
Use individualized PEEP titrated to oxygenation and respiratory mechanics (ΔP/compliance); avoid routine ZEEP* in higher-risk contexts (e.g., obesity, pneumoperitoneum/Trendelenburg).	Strong	Moderate.[90,94]
Favor early extubation in stable patients.	Strong	High.[55,93]
Consider individualized PEEP guided by physiological signals (e.g., esophageal pressure or EIT) in higher-risk settings (obesity, pneumoperitoneum/Trendelenburg) to optimize oxygenation and mechanics; evidence for reducing PPCs remains.	Weak	Moderate.[90,95]

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; PEEP, Positive End-Expiratory Pressure; ΔP, Driving Pressure; ZEEP, Zero End-Expiratory Pressure; EIT, Electrical Impedance Tomography; PPCs, Postoperative Pulmonary Complications; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Summary Table Recommended intraoperative ventilation strategies.

Parameter	Recommended Strategy	Clinical Considerations
Tidal Volume	6–8 mL.kg^{-1} PBW; avoid tidal volumes > 10 mL.kg^{-1} PBW	Low tidal volumes reduce the risk of VILI and PPCs. Use 6–8 mL·kg^{-1} PBW in patients without ARDS. In patients with ARDS, use 4–8 mL·kg^{-1} PBW, adjusted to maintain lung protective pressure targets.
Plateau Pressure (Pplat)	Maintain ≤ 30 cm H_2O	Prevents alveolar overdistension; critical in patients with ALI/ARDS.
Driving Pressure (ΔP)	Keep ≤ 15 cm H_2O	Strong predictor of mortality; minimizing ΔP is more protective than VT alone.
PEEP	≥ 5 cmH_2O in all patients; individualized in ALI/obese	Counters atelectasis; titration based on compliance or ΔP is preferable.
Respiratory Rate	Adjust to maintain $PaCO_2$ 38–43 mmHg	Prevents hypercapnia and ensures adequate minute ventilation.
FiO_2	Use lowest FiO_2 to keep SpO_2 92%–97%	Avoids both hypoxemia and oxygen toxicity.
Extubation	Favor early extubation in stable patients	Reduces PPCs and facilitates recovery.
Advanced Monitoring	Consider esophageal-pressure monitoring or EIT in obesity / ALI/ Pneumoperitoneum / Trendelenburg to individualize PEEP; use in trained teams.	Useful for individualized PEEP and improved safety.

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; VILI, Ventilator-Induced Lung Injury; PPCs, Postoperative Pulmonary

Intraoperative pulmonary recruitment maneuvers

Intraoperative pulmonary Recruitment Maneuvers (RMs) are designed to reverse anesthesia-induced atelectasis and optimize gas exchange during mechanical ventilation.[89,90] Despite their potential benefits, such as improved oxygenation and lung compliance, these techniques may carry risks, particularly hemodynamic compromise. Therefore, RMs should be applied selectively and based on individualized patient assessments and physiologic responses.

PICO clinical question

In adult surgical patients under general anesthesia (P), do intraoperative recruitment maneuvers (I), compared to no recruitment maneuvers (C), improve oxygenation, lung compliance, and reduce postoperative pulmonary complications (O)?

Rationale and literature summary

Intraoperative atelectasis is common during general anesthesia as functional residual capacity decreases, the diaphragm shifts cephalad, and dependent airways close. Recruitment Maneuvers (RMs) are intended to reverse atelectasis and improve gas exchange. Stepwise, physiology-guided approaches (e.g., graded PEEP increases followed by titration) are generally better tolerated hemodynamically than sustained inflations. A Bayesian individual-patient-data meta-analysis[98] pooling PROVHILO,[101] iPROVE,[100] and PROBESE[102] suggests a moderate reduction in PPCs when higher-PEEP strategies combined with RMs are embedded within lung-protective ventilation, with a clearer signal in laparoscopic surgery. By contrast, the parent trials (PROVHILO[101]; PROBESE[102]) reported more intraoperative hypotension and no consistent improvement in hard outcomes in unselected populations. Consistent with additional recent syntheses,[99] we

Evidence-Based Recommendations (GRADE).

Recommendation	GRADE Recommendation	Evidence Quality
Use recruitment maneuvers in combination with low tidal volume ventilation and individualized PEEP in high-risk patients	Weak	Moderate.[88,94]
Apply recruitment maneuvers in cases of intraoperative hypoxemia or suspected reversible atelectasis	Weak	Moderate.[98,99]
Avoid routine high-pressure RMs (≥ 40 cm H_2O for 30s) in all patients, especially without hemodynamic monitoring	Strong	Moderate.[55,100]

RM, Recruitment Maneuver; PEEP, Positive End-Expiratory Pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

recommend that RMs be applied selectively, triggered by intraoperative hypoxemia or suspected reversible atelectasis and integrated with low tidal volumes and individualized PEEP, with appropriate hemodynamic monitoring.

Summary Table Intraoperative recruitment maneuvers.

Technique	Mechanism / Application	Benefits	Risks / Limitations
Stepwise PEEP Recruitment	Incremental PEEP increase followed by titration	Better compliance, oxygenation	Requires hemodynamic monitoring
Sustained Inflation	Continuous pressure (30 −40 cm H_2O for 30−40s)	Atelectasis reversal	Hypotension, not well tolerated in all patients
Cyclic / Periodic RM	Applied every 30−60 min or after disconnections	Maintains aeration during long procedures	Limited data on long-term outcomes
RM + Decremental PEEP Titration	RM followed by PEEP titration to optimize oxygenation/compliance	May individualize PEEP	Requires specialized monitoring and experience

RM, Recruitment Maneuver; PEEP, Positive End-Expiratory Pressure.

Hypoxemia and hyperoxia in surgical patients

Hypoxemia is a frequent postoperative complication and has been associated with increased morbidity and mortality.[103] Conversely, excessive oxygen administration, especially in the absence of hypoxemia, may contribute to oxidative stress, atelectasis, and worsened clinical outcomes.[104] Current evidence suggests that avoiding both extremes, hypoxemia and hyperoxia, is essential to optimizing patient safety. A balanced and individualized approach to oxygen therapy in surgical patients is strongly recommended.

To facilitate bedside decision making, a concise stepwise algorithm for the practical management of perioperative hypoxemia is provided in the Supplementary Material (Supplementary Appendix S2).

Clinical question (PICO)

In adult surgical patients (P), does targeting intraoperative and postoperative peripheral oxygen saturation (SpO_2) between 92%−97% (I), compared to values below 92% or above 97% (C), reduce postoperative pulmonary complications and oxygen-related adverse outcomes (O)?

hemodynamic alterations. A structured and systematic approach is therefore essential to rapidly identify reversible causes and guide timely corrective interventions. For the purpose of this guideline, perioperative hypoxemia is operationally defined as a peripheral oxygen saturation (SpO_2) below 90%, a threshold consistently associated with adverse clinical outcomes in observational and interventional studies.

Postoperative hypoxemia ($SpO_2 < 90\%$) is commonly observed in patients recovering from general anesthesia and is strongly associated with adverse outcomes, including increased mortality at 30 days and 1-year. Large cohort studies have reported that even transient episodes of severe desaturation are linked to ischemic events and increased healthcare utilization.[110]

On the other hand, liberal oxygen strategies using high inspired oxygen fractions ($FiO_2 \geq 0.8$) or targeting $SpO_2 \geq 98\%$ may increase the risk of oxygen toxicity, absorption atelectasis, and pulmonary inflammation. Trials such as the Oxygen-ICU and HYPERS2S demonstrated worse clinical outcomes in patients exposed to hyperoxia.[104,111] Conservative oxygen strategies, as explored in the ICU-ROX and HOT-ICU studies,[112,113] showed non-inferior results with potential reductions in oxygen-related adverse events.

The collective findings support a U-shaped curve relating SpO_2 and patient outcomes, indicating that both hypoxemia and hyperoxia can be detrimental. Aiming for an SpO_2 range of 92%−97% offers a practical and safe target, optimizing oxygen delivery while avoiding unnecessary harm. Unless otherwise specified, this SpO_2 range (92%−97%) should be considered the default oxygenation target for most adult surgical patients throughout the intraoperative and early postoperative periods.

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Maintain SpO_2 between 92% and 97% during the perioperative period.	Weak	Moderate.[105,106]
Avoid liberal oxygen therapy ($SpO_2 \geq 98\%$) in the absence of hypoxemia.	Weak	Moderate.[107,108]
Avoid targeting $SpO_2 < 90\%$ intra- and postoperatively due to the increased risk of mortality.	Strong	Moderate.[104,109]

SpO_2, Peripheral Oxygen saturation; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

Perioperative hypoxemia is often multifactorial and may result from atelectasis, ventilation perfusion mismatch, residual anesthetic effects, patient positioning, pneumoperitoneum, or

Exceptions may include patients with chronic hypercapnic respiratory failure, severe pulmonary hypertension, cyanotic congenital heart disease, or other conditions in which individualized oxygenation targets are clinically justified.

necessary, and respiratory physiotherapy according to institutional protocols may contribute to secretion clearance, patient comfort, preservation of lung function, and optimization of perioperative respiratory support.

Summary Table Oxygen saturation targets and clinical implications in surgical patients.

SpO_2 Range	Clinical Implications	Notes
92%—97%	Optimal range balancing oxygen delivery and avoidance of oxidative stress	Recommended target for most intra- and postoperative scenarios
> 97%	Risk of atelectasis, oxidative injury, and potential increase in mortality	Should be avoided unless clinically indicated
< 90%	Associated with increased mortality, ischemia, and adverse neurological outcomes	Requires prompt intervention to restore adequate oxygenation
Overall	Gas exchange must be interpreted globally	Oxygenation targets should be considered together with $PaCO_2$ and arterial pH, ensuring physiological tolerance

SpO_2, Peripheral Oxygen saturation.

Oxygen therapy in surgical patients should be titrated based on real time monitoring, individual comorbidities, and surgical risk, avoiding the routine use of high FiO_2 in patients with normal oxygenation. In parallel, ventilatory adjustments should aim to maintain arterial carbon dioxide tension ($PaCO_2$) and arterial pH within physiologically acceptable ranges. In most patients, this corresponds to $PaCO_2$ values close to normal and an arterial pH $\geq$ 7.25. Mild to moderate hypercapnia may be tolerated as part of a lung protective strategy when it represents a physiological consequence of limiting tidal volume and airway pressures to reduce lung stress, rather than inadequate ventilation, provided that arterial pH remains acceptable and that no contraindications are present, such as severe pulmonary hypertension, intracranial hypertension, or significant right ventricular dysfunction. Ventilatory settings should therefore be individualized, balancing lung protection with adequate carbon dioxide clearance and overall physiological tolerance. In addition to ventilator adjustments, supportive respiratory care measures should be maintained throughout the perioperative period. Adequate analgesia, airway humidification when indicated, endotracheal suctioning when clinically

Cardiopulmonary interactions during intraoperative mechanical ventilation

Mechanical ventilation alters the natural cardiopulmonary physiology by applying positive airway pressure, which changes intrathoracic pressure and pulmonary volume dynamics.[94] These effects influence venous return, cardiac preload and afterload, particularly affecting the right ventricle, and vary according to lung compliance and ventilatory settings.[55] Understanding these interactions is crucial for optimizing hemodynamic stability and guiding protective ventilation strategies during surgery.

PICO clinical question

In adult surgical patients under general anesthesia and mechanical ventilation (P), how do different ventilatory modes and parameters (I), compared to conventional ventilatory strategies (C), affect cardiopulmonary interactions and hemodynamic function (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Pressure-Controlled Ventilation (PCV) and Volume-Controlled Ventilation (VCV) have similar hemodynamic effects when airway pressures are matched.	Strong	Moderate.[114,115]
Consider PC-IRV instead of VCV to improve oxygenation and reduce peak inspiratory pressure in selected patients, acknowledging potential reduction in cardiac output.	Weak	Low.[116,117]
Consider PC-IRV over PCV in ARDS patients to enhance oxygenation and CO_2 clearance, acknowledging the potential for reduced cardiac output.	Weak	Low.[118]

PCV, Pressure-Controlled Ventilation; VCV, Volume-Controlled Ventilation; PC-IRV, Pressure-Controlled Inverse Ratio Ventilation; ARDS, Acute Respiratory Distress Syndrome; CO_2, Carbon Dioxide; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

During positive pressure ventilation, increased Intrathoracic Pressure (ITP) reduces the gradient for venous return by increasing right atrial pressure, which may reduce cardiac output.[115] Right ventricular preload is influenced by ITP and lung volume, while right ventricular afterload is primarily determined by Pulmonary Vascular Resistance (PVR), which follows a U-shaped relationship with lung volumes being elevated both in atelectasis and overdistension.

Thus, the choice of ventilatory mode must balance the respiratory benefits with potential cardiovascular effects, especially in patients with compromised hemodynamics or preexisting heart disease.

PICO clinical question

In adult surgical patients with obstructive lung disease undergoing general anesthesia and mechanical ventilation (P), how do individualized ventilatory strategies (I), compared to standard ventilation protocols (C), affect the incidence of intraoperative and postoperative respiratory complications (O)?

Summary Table Hemodynamic considerations for ventilatory modes.

Mode / Strategy	Hemodynamic Considerations	Clinical Notes
PCV vs. VCV	Equivalent cardiac output if airway pressures and tidal volumes are matched	PCV may limit peak pressures; choose based on lung mechanics and surgical needs
PC-IRV vs. VCV	May reduce cardiac output due to high mean airway pressure and decreased venous return	Potential benefit in gas exchange; use cautiously in unstable patients
PC-IRV in ARDS	Improves oxygenation and CO_2 clearance; ↓ CO may occur without RV failure	Monitor perfusion and volume status; use individualized targets

PCV, Pressure-Controlled Ventilation; VCV, Volume-Controlled Ventilation; PC-IRV, Pressure-Controlled Inverse Ratio Ventilation; ARDS, Acute Respiratory Distress Syndrome; CO_2, Carbon dioxide; CO, Cardiac Output; RV, Right Ventricle.

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use low tidal volumes (6—8 mL.kg^{-1} PBW) and prolonged expiratory times to minimize dynamic hyperinflation.	Strong	Moderate.[120,121]
Maintain low respiratory rates (e.g., 8—10 breaths/min) to increase expiratory time and reduce air trapping.	Conditional	Low.[122]
Monitor for auto-PEEP and consider external PEEP ≤ 80% of measured auto-PEEP only when patient triggering is impaired.	Conditional	Low.[123-125]
Avoid high PEEP and recruitment maneuvers unless clear evidence of atelectasis-induced hypoxemia.	Strong	Low.[102]
Use Pressure-Controlled Ventilation (PCV) or Volume-Controlled Ventilation (VCV) with decelerating flow pattern for optimal control of peak pressure.	Conditional	Low.[126,127]
Adjust Inspiratory-to-Expiratory (I:E) ratio (e.g., 1:3 to 1:4) and increasing inspiratory flow to minimize air trapping.	Strong	Moderate.[122,125]
Evaluate plateau pressure and driving pressure to detect early signs of dynamic hyperinflation.	Conditional	Low.[97,128]

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; auto-PEEP, Intrinsic Positive End-Expiratory Pressure; PEEP, Positive End-Expiratory Pressure; PCV, Pressure-Controlled Ventilation; VCV, Volume-Controlled Ventilation; I:E, Inspiratory-to-Expiratory ratio; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Mechanical ventilation in the intraoperative period for patients with obstructive lung disease

Patients with obstructive lung diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD) present unique intraoperative challenges due to increased airway resistance, air trapping, dynamic hyperinflation, and risk of barotrauma.[119] Anesthesiologists must adapt ventilation strategies to avoid complications related to positive pressure ventilation, especially when surgical factors (e.g., pneumoperitoneum, Trendelenburg position) further compromise respiratory mechanics.

Rationale and literature-based discussion

Obstructive lung diseases are characterized by increased airway resistance and expiratory flow limitation, often leading to air trapping and dynamic hyperinflation.[119] During general anesthesia and mechanical ventilation, these pathophysiological alterations can result in increased intrathoracic pressure, auto-PEEP, impaired venous return, and hemodynamic instability.

Summary Table Clinical considerations for ventilation in obstructive disease.

Strategy	Clinical Consideration
Low tidal volume (6–8 mL.kg^{-1} PBW)	Reduces barotrauma and minimizes hyperinflation
Reduced RR (e.g., 8–10 bpm)	Allows for adequate expiration and prevents air trapping
Adjusted I:E ratio (e.g., 1:3–1:4)	Enhances alveolar emptying in expiratory-limited lungs
Monitor plateau and driving pressure	Identifies risk of hyperinflation and optimizes protective ventilation
Use external PEEP only if auto-PEEP detected	Apply ≤ 80% of auto-PEEP and avoid unnecessary overdistension
Avoid routine recruitment maneuvers	May cause overdistension and hemodynamic instability in obstructive physiology

Mechanical ventilation in obese surgical patients

Obesity is an increasingly prevalent condition and presents significant challenges for perioperative management, especially regarding mechanical ventilation.[30] Obese patients exhibit altered respiratory mechanics due to increased intra-abdominal pressure, reduced chest wall compliance, decreased Functional Residual Capacity (FRC), and a tendency for atelectasis formation. These changes increase the risk of intraoperative hypoxemia and Postoperative Pulmonary Complications (PPCs).[102] Therefore, individualized ventilatory strategies are required to optimize gas exchange, ensure lung protection, and improve outcomes.

PICO clinical question

In obese adult surgical patients under general anesthesia (P), do individualized protective ventilatory strategies (I), compared to conventional ventilation (C), improve intraoperative gas exchange and reduce postoperative pulmonary complications (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use tidal volumes between 6–8 mL.kg^{-1} of Predicted Body Weight (PBW), based on the ARDSNet formula, regardless of actual body weight.	Strong	High.[54,102]
Consider Recruitment Maneuvers (RM) in cases of persistent SpO_2 < 94%.	Weak	Low.[129,130]
Consider performing RM during PEEP titration to identify the PEEP associated with better compliance or lower driving pressure.	Conditional	Low.[129,130]
Prefer ventilator-guided RM over manual "bag-squeeze" techniques.	Strong	Moderate.[102,131]
Use a reduced FiO_2 (e.g., 0.4–0.6) during RM to minimize reabsorption atelectasis and oxidative stress.	Strong	Moderate.[132,133]
In morbidly obese patients, plateau pressures up to 40 cm H_2O may be required during RM, provided that close monitoring is maintained.	Conditional	Moderate.[34,129,130]
Prefer Pressure-Controlled Ventilation with Volume Guarantee (PCV-VG) when available, especially in laparoscopic procedures.	Conditional	Moderate.[48,49]
Consider conventional pressure-controlled ventilation when PCV-VG is unavailable, acknowledging potential tidal volume variability.	Weak	Low.[48]
Volume-controlled ventilation is also acceptable when PCV-VG is unavailable and fixed tidal volume delivery is a priority.	Weak	Low[49]
Maintain peak airway pressure (Ppeak) ≤ 35 lt; 35 cm H_2O when possible.	Strong	High.[134]
Maintain plateau pressure (Pplat) ≤ 30 cm H_2O when possible.	Strong	High.[61,135]
In specialized centers, consider using estimated transpulmonary pressure (via esophageal balloon) to guide fine-tuning of ventilation in superobese patients (BMI > 50 kg.m^{-2}).	Conditional	Low.[95,136]
Aim to reduce driving pressure (ΔP) and maintain values ≤ 15 lt; 15 cm H_2O.	Strong	Low.[64,97,128]
Maintain PEEP ≥ 5 cm H_2O or individualized titration to optimize PaO_2/FiO_2 ratio intraoperatively.	Strong	Moderate.[137,138]
Consider titrating PEEP to ≥ 10 cm H_2O to optimize PaO_2/FiO_2 ratio and compliance.	Strong	Low.[137,138]
Avoid low PEEP levels (< 5 lt; 5 cm H_2O) in obese patients; individualized PEEP is safe when paired with adequate hemodynamic monitoring.	Strong	High.[102]

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; ARDSNet, Acute Respiratory Distress Syndrome Network; RM, Recruitment Maneuver; PEEP Positive End-Expiratory Pressure; FiO_2, Fraction of inspired oxygen; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; Ppeak, Peak inspiratory pressure; Pplat, Plateau Pressure; BMI, Body Mass Index; ΔP, Driving Pressure; PaO_2/FiO_2, Ratio of arterial oxygen tension to fraction of inspired oxygen; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

Obesity alters respiratory mechanics by increasing pleural pressures, reducing lung volumes, and promoting airway closure. These changes reduce FRC below closing capacity and increase the risk of atelectasis, especially in the dependent lung regions.[138] During anesthesia and mechanical ventilation, these effects are exacerbated, demanding protective ventilatory strategies.[137]

The use of tidal volumes based on Predicted Body Weight (PBW) prevents volutrauma. Even in obese patients, using actual body weight can result in excessive volumes and lung stress.[138]

frequently involve steeper and more sustained Trendelenburg positioning, longer operative times, and limited physical access to the patient after docking. These factors can accentuate reductions in respiratory system compliance, increase airway pressures, and make frequent circuit adjustments or recruitment maneuvers less practical once docking is complete.[139] In this setting, protective ventilation based on predicted body weight remains the default strategy, but it becomes particularly important to anticipate physiologic deterioration, to monitor respiratory mechanics trends closely, and to prioritize ventilatory adjustments that can be implemented safely without repeated disconnections,

Summary Table Protective strategies for mechanical ventilation in obese surgical patients.

Strategy	Recommended Target	Clinical Considerations
Tidal Volume	6–8 mL.kg^{-1} of predicted body weight (PBW)	Prevents volutrauma; actual body weight leads to excessive VT and lung stress.
Peak Inspiratory Pressure (Ppeak)	< 35 lt; 35 cm H_2O	Higher values may reflect increased resistance; requires monitoring of delivered VT.
Plateau Pressure (Pplat)	≤ 30 cm H_2O	Limits alveolar overdistension, especially important in reduced compliance.
Driving Pressure (ΔP)	≤ 15 cm H_2O	Marker of lung stress; reduction correlates with improved outcomes.
PEEP	≥ 5 cm H_2O or individualized	Counteracts atelectasis; titration based on compliance/ΔP improves oxygenation.
Recruitment Maneuvers (RM)	Apply in hypoxemia or during PEEP titration	Ventilator-guided maneuvers preferred safety and consistency.
FiO_2 during RM	0.4–0.6	Reduces risk of absorption of atelectasis and oxygen toxicity.
Ventilatory Mode	Prefer PCV-VG; PCV or VCV acceptable	PCV-VG ensures target VT with lower peak pressures; alternatives require close monitoring.
Transpulmonary Pressure Monitoring	Consider in superobese (BMI > 50 gt; 50 kg.m^{-2})	Esophageal balloon helps individualize PEEP and limit overdistension.
Extubation	Early when feasible	Prevents prolonged exposure to high pressures; ensure adequate reversal of NMB and respiratory drive.

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; VT, Tidal Volume; Ppeak, Peak inspiratory pressure; Pplat, Plateau Pressure; ΔP, Driving Pressure; PEEP, Positive End-Expiratory Pressure; RM, Recruitment Maneuver; FiO_2, Fraction of inspired oxygen; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; PCV, Pressure-Controlled Ventilation; VCV, Volume-Controlled Ventilation; BMI, Body Mass Index; NMB, Neuromuscular Blockade.

Mechanical ventilation during laparoscopic surgery

Laparoscopic surgery significantly alters respiratory mechanics through pneumoperitoneum and surgical positioning (e.g., Trendelenburg), leading to cephalad diaphragm displacement, decreased pulmonary compliance, ventilation-perfusion mismatch, and atelectasis.[139] These changes increase the risk of PPCs, underscoring the need for lung-protective and individualized ventilation strategies.

Robot-assisted laparoscopic surgery

Robot-assisted laparoscopic procedures deserve specific consideration within the laparoscopic context, because they

such as careful titration of PEEP, reassessment of driving pressure, and attention to hemodynamic tolerance during any recruitment strategy.[140] This pragmatic framing aligns the general principles of laparoscopy with the operational constraints and physiologic burden commonly seen during robotic surgery in steep Trendelenburg.

PICO clinical question

In adult surgical patients undergoing laparoscopic procedures (P), do tailored ventilatory adjustments (I), compared to conventional strategies (C), improve oxygenation and reduce postoperative pulmonary complications (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use protective ventilation (6–8 mL.kg^{-1} predicted body weight + PEEP ≈5 cm H_2O) as the standard intraoperative strategy.	Strong	High.[141,142]
Avoid conventional ventilation (8–10 mL.kg^{-1}, no PEEP) due to increased complications and poorer oxygenation.	Strong	High.[141,143]
Consider using PCV-VG over VCV to reduce airway pressures and improve compliance.	Weak	Low.[144,145]
Consider using PCV instead of VCV for improved inflammatory response and compliance in select patients.	Weak	Low.[143,146]
Prefer individualized PEEP titration (guided by ΔP, compliance, or EIT) rather than fixed PEEP (e.g., 5 cm H_2O or ZEEP).	Strong	High.[147,148]
Consider alveolar Recruitment Maneuvers (RMs) to restore compliance and reduce atelectasis, especially after pneumoperitoneum deflation.	Weak	Moderate.[149,150]

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; PEEP, Positive End-Expiratory Pressure; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; VCV, Volume-Controlled Ventilation; PCV, Pressure-Controlled Ventilation; ΔP, Driving Pressure; EIT, Electrical Impedance Tomography; ZEEP, Zero End-Expiratory Pressure; RM, Recruitment Maneuver; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

Laparoscopic surgery induces physiological alterations that reduce functional residual capacity, displace the diaphragm upward, and promote lung collapse, especially in dependent regions. Protective ventilation strategies have been associated with decreased incidence of atelectasis, hypoxemia, and VILI.[142] Conventional ventilation increases pulmonary stress and systemic inflammation, even in patients with healthy lungs, and should be avoided.[137]

Summary Table Ventilatory strategies in laparoscopic surgery.

Strategy	Impact / Recommendation
Protective ventilation (6–8 mL.kg^{-1} + PEEP)	Reduces PPCs and improves oxygenation
Avoid conventional ventilation (no PEEP)	Increases risk of VILI and complications
PCV-VG over VCV	Reduces peak pressures and improves ΔP
PCV over VCV	May reduce airway pressures
Individualized PEEP	Improves compliance and intraoperative oxygenation
Recruitment maneuvers (after desufflation)	Restore compliance and reduce atelectasis

PEEP, Positive End-Expiratory Pressure; PPCs, Postoperative Pulmonary Complications; VILI, Ventilator-Induced Lung Injury; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; VCV, Volume-Controlled Ventilation; PCV, Pressure-Controlled Ventilation; ΔP, Driving Pressure.

Recommendation in the area of clinical uncertainty

Pressure-Controlled Ventilation (PCV) compared with Volume-Controlled Ventilation (VCV) did not reach the predefined threshold of expert consensus in the Delphi process. While PCV may confer physiological advantages, such as reduced peak inspiratory pressures in patients with impaired pulmonary compliance, the current body of evidence is insufficient and inconsistent with respect to meaningful clinical outcomes. This intervention should therefore be regarded as falling within an area of clinical uncertainty, highlighting the need for further high-quality randomized controlled trials before routine adoption into perioperative practice can be recommended.

Mechanical ventilation in critically Ill neurosurgical patients

Mechanical ventilation in critically ill neurosurgical patients presents unique challenges. It requires balancing optimal gas exchange and protective ventilation while avoiding secondary neurological insults. Elevated Intracranial Pressure (ICP), impaired autoregulation, and altered cerebrovascular reactivity must all be considered when defining ventilation strategies during the perioperative period (Fig. 3).[151]

PICO clinical question

In adult neurosurgical patients under general anesthesia (P), do protective ventilatory strategies (I), compared to conventional strategies (C), optimize gas exchange while maintaining intracranial and cerebral hemodynamic stability (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Protective ventilation (VT 6—8 mL.kg^{-1} PBW + PEEP ≈5 cm H_2O) should be the standard approach in neurosurgical patients.	Strong	High.[151,152]
Avoid high tidal volumes (> 10 gt; 10 mL.kg^{-1} PBW) and ZEEP ventilation.	Strong	High.[152,153]
Avoid permissive hypercapnia ($PaCO_2$ > 45 mmHg) in patients with elevated ICP or impaired autoregulation.	Strong	Moderate.[154,155]
Maintain normocapnia ($PaCO_2$ 35—40 mmHg), especially in patients with elevated ICP.	Strong	Moderate.[154,155]
In patients with invasive neuromonitoring (ICP, $PbtO_2$), consider individualized CO_2 targets guided by cerebral parameters.	Conditional	Low.[156,155]

VT, Tidal Volume; PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; PEEP, Positive End-Expiratory Pressure; ZEEP, Zero End-Expiratory Pressure; $PaCO_2$, Arterial Carbon dioxide tension; ICP, Intracranial Pressure; $PbtO_2$, Brain tissue oxygen tension; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

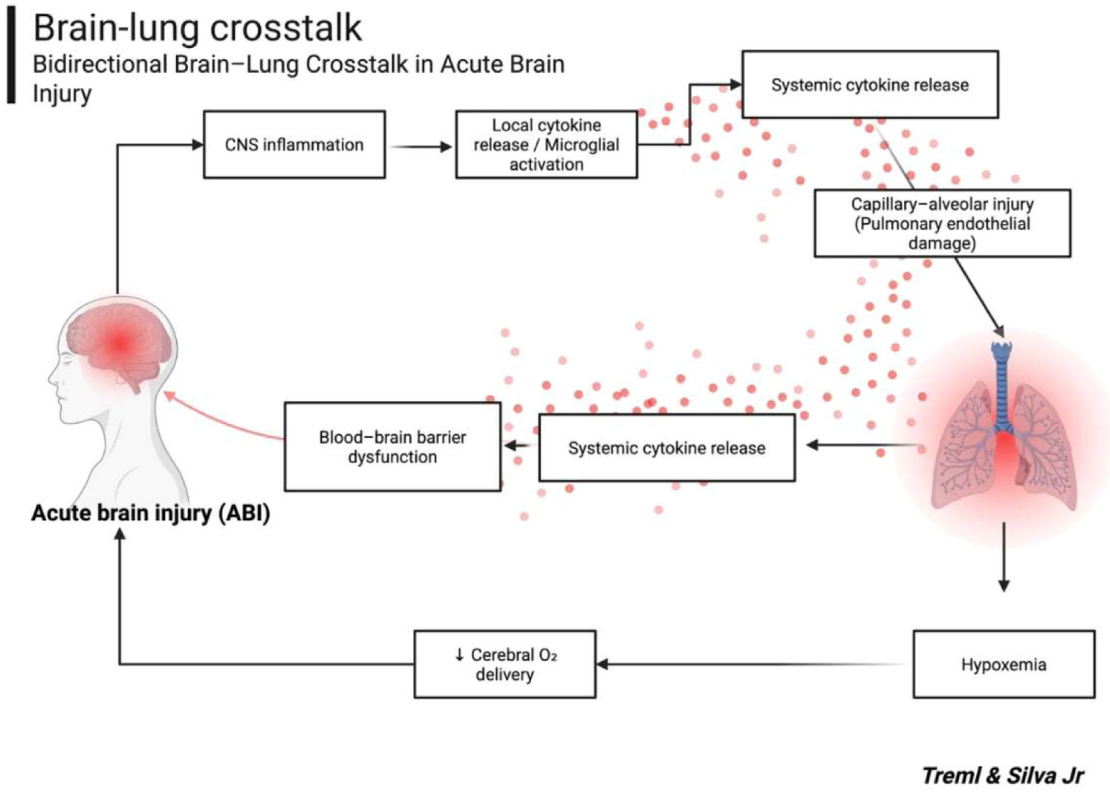

Figure 3 Brain-lung crosstalk. ABI, Acute Brain Injury; O_2, Oxygen; CNS, Central Nervous System.

Rationale and literature-based discussion

Ventilatory management in acute brain injury requires balancing cerebral perfusion and Intracranial Pressure (ICP), both of which are highly sensitive to arterial CO_2. While hypercapnia increases cerebral blood flow and ICP, hypocapnia can reduce ICP but risks cerebral hypoperfusion, especially in patients with impaired autoregulation. For this reason, maintaining normocapnia ($PaCO_2$ 35—40 mmHg) is generally recommended,[155] and routine hypocapnia should be avoided due to its association with increased mortality.[154] Protective ventilation with moderate tidal volumes (6—8 mL.kg^{-1} PBW) and low PEEP (~5 cm H_2O) is generally safe and minimizes lung injury without worsening ICP, as long as perfusion is preserved.[156] However, the PROLABI trial showed increased mortality in patients without ARDS using this strategy, suggesting it should not be applied universally.[153]

Avoiding high tidal volumes and ZEEP is critical, as both are linked to pulmonary complications and systemic inflammation, which may worsen neurological outcomes.[152]

When neuromonitoring is available, CO_2 targets and ventilator settings should be individualized. Although hypercapnia may be tolerated in ARDS, it is contraindicated in brain injury due to the risk of exacerbating ICP and cerebral edema.[155]

Summary Table Key ventilation strategies in surgical patients with acute brain injury.

Clinical Strategy	Practical Considerations and Physiological Impact
Protective ventilation (VT 6—8 mL.kg^{-1} PBW + PEEP ≈5)	Minimizes VILI and atelectasis; well tolerated in most patients; monitor closely in absence of ARDS
Avoid high VT (10 mL.kg^{-1}) and ZEEP	Associated with increased risk of atelectasis, pneumonia, inflammation, and neuroinjury biomarkers.
Moderate PEEP ≥ 5 cm H_2O	Supports alveolar recruitment; safe for cerebral hemodynamics in stable patients.
Maintain normocapnia ($PaCO_2$ 35—40 mmHg)	Optimizes balance between cerebral perfusion and ICP; preferred in most scenarios.
Avoid permissive hypercapnia	May worsen ICP and cerebral edema; not recommended unless under advanced neuromonitoring.
Individualized CO_2 targets	Adjust $PaCO_2$ based on ICP, $PbtO_2$, or jugular venous saturation when monitoring is available.

VT, Tidal Volume; PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; PEEP, Positive End-Expiratory Pressure; VILI, Ventilator-Induced Lung Injury; ICP, Intracranial Pressure; $PaCO_2$, Arterial Carbon Dioxide Tension; $PbtO_2$, Brain tissue oxygen tension.

Mechanical ventilation in thoracic surgery

Thoracic surgery poses unique challenges for intraoperative ventilation. One-Lung Ventilation (OLV), often required for exposure, alters mechanics, reduces functional residual capacity, and increases the risk of hypoxemia and VILI. Protective strategies are therefore essential to ensure gas exchange and reduce complications.[157]

Given the high incidence of hypoxemia during one-lung ventilation, a structured stepwise approach is essential to guide timely corrective interventions. A practical one-page algorithm for the management of hypoxemia during OLV is provided in the Supplementary Material (Supplementary Appendix S3).

PICO clinical question

In adult patients undergoing thoracic surgery requiring one-lung ventilation (P), do protective ventilatory strategies (I), compared to conventional ventilation (C), improve oxygenation and reduce postoperative pulmonary complications (O)?

Rationale and literature-based discussion

Thoracic surgery with OLV imposes unique challenges, including increased risk of hypoxemia, volutrauma, and atelectrauma due to asymmetric ventilation. Protective ventilation strategies are critical to mitigate these risks.[162]

During OLV, hypoxemia is predominantly driven by shunt and ventilation—perfusion mismatch and may be exacerbated by tube malposition, inadequate PEEP in the dependent lung, or excessive collapse of the non-dependent lung. A systematic evaluation of these factors is therefore required before escalation of rescue therapies.

RCTs and meta-analyses confirm that low tidal volumes (4—6 mL.kg^{-1} PBW) reduce barotrauma and Postoperative Pulmonary Complications (PPCs) during OLV.[157] Recruitment maneuvers during OLV should not be applied routinely and are best reserved as rescue interventions for severe or refractory hypoxemia, with careful attention to hemodynamic tolerance and surgical conditions.

In cases of refractory hypoxemia during one-lung ventilation, additional rescue strategies may be considered after optimization of ventilatory settings and oxygenation

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use low tidal volumes (4—6 mL.kg^{-1} PBW) during OLV to reduce lung stress and prevent VILI.	Strong	High.[158,159]
Apply moderate PEEP (5—10 cm H_2O) to the dependent lung to prevent atelectasis during OLV.	Strong	Moderate.[160,161]
Avoid routine use of ZEEP during OLV due to increased risk of alveolar collapse.	Strong	Moderate.[162,163]
Prefer Pressure-Controlled Ventilation (PCV) or volume-guaranteed pressure modes to limit peak pressure.	Conditional	Moderate.[47,164]
Maintain plateau pressure ≤ 30 lt; 30 cm H_2O and driving pressure ideally ≤ 12 lt; 12 cm H_2O, maximum 15 cm H_2O.	Strong	Moderate.[165,166]
Consider individualized PEEP titration based on driving pressure or compliance.	Conditional	Low.[167]
Avoid unnecessary hyperoxia; target SpO_2 92%—96% during OLV.	Strong	Moderate.[168,169]
Recruitment maneuvers may be considered as rescue therapy for severe hypoxemia.	Weak	Low.[163,170]

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; OLV, One-Lung Ventilation; VILI, Ventilator-Induced Lung Injury; PEEP, Positive End-Expiratory Pressure; ZEEP, Zero End-Expiratory Pressure; PCV, Pressure-Controlled Ventilation; FiO_2, Fraction of inspired oxygen; SpO_2, Peripheral Oxygen saturation; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

measures. These include selective pulmonary vasodilators, jet ventilation to the non-dependent lung, and optimization of anesthetic depth to preserve hypoxic pulmonary vasoconstriction when clinically appropriate. Although evidence supporting these interventions remains limited, they may be useful in selected patients and should be individualized according to surgical, physiological, and hemodynamic conditions. A practical stepwise approach to the management of hypoxemia during one-lung ventilation is provided in Supplementary Appendix S3.

Rationale and literature-based discussion

Cardiopulmonary Bypass (CPB) leads to transient but significant loss of pulmonary aeration due to factors like lung deflation during extracorporeal circulation and systemic inflammation. Studies show that this promotes atelectasis formation, gas exchange impairment, and subsequent development of PPCs such as hypoxemia, pneumonia, or acute lung injury.[176]

During cardiopulmonary bypass, lung ventilation is often reduced or temporarily interrupted, which may further exacerbate atelectasis and pulmonary inflammation. When technically feasible, the application of low-level continuous positive airway pressure or very low tidal volume ventilation during CPB has been proposed to mitigate lung collapse, although available evidence remains heterogeneous and does not support a uniform approach. Therefore, ventilatory management during CPB should be individualized according to surgical conditions and institutional practice, with emphasis on prompt re-establishment of lung-protective ventilation strategies immediately after separation from bypass.

Recruitment Maneuvers (RMs) following CPB have been shown to reopen collapsed alveolar units and restore functional residual capacity. When followed by PEEP titration based on best compliance or driving pressure, the likelihood of alveolar stability increases, and oxygenation is maintained.[172]

Summary Table Protective ventilation strategies for thoracic surgery.

Strategy	Clinical Application and Considerations
Low tidal volume (4–6 mL.kg^{-1} PBW)	Reduces alveolar overdistension and risk of VILI during OLV
Moderate PEEP (5–10 cm H_2O)	Improves oxygenation and lung compliance in the dependent lung
Plateau pressure $\leq$ 30 cm H_2O	Avoids excessive alveolar stretch and barotrauma
Driving Pressure $\leq$ 15 lt; 15 cm H_2O (ideally $\leq$ 12 lt; 12 cm H_2O)	Strong predictor of outcomes.
Pressure-controlled or PCV-VG modes	May reduce peak inspiratory pressure and improve distribution of ventilation
Avoid hyperoxia	Target SpO_2 between 92%–96% to prevent oxidative injury
Individualized PEEP titration	Optimize compliance and driving pressure in selected patients
Recruitment Rescue in severe hypoxemia	Use cautiously, not routine.

PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; VILI, Ventilator-Induced Lung Injury; OLV, One-Lung Ventilation; PEEP, Positive End-Expiratory Pressure; PCV, Pressure-Controlled Ventilation; PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; SpO_2, Peripheral Oxygen saturation.

Ventilatory strategies during cardiac surgery

Cardiac surgery with Cardiopulmonary Bypass (CPB) induces significant pulmonary dysfunction due to factors like lung deflation, ischemia-reperfusion, hypothermia, and systemic inflammation, leading to atelectasis, impaired gas exchange, and increased risk of PPCs.[171]

PICO clinical question

In adult patients undergoing cardiac surgery with cardiopulmonary bypass (P), do lung-protective ventilation strategies, including recruitment maneuvers and individualized PEEP (I), compared to conventional ventilation (C), improve gas exchange and reduce postoperative pulmonary complications (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Perform alveolar recruitment maneuvers at the end of CPB to re-expand collapsed lung regions.	Strong	Moderate.[172–174]
Use individualized PEEP titration (e.g., based on compliance or driving pressure) after RM to maintain alveolar patency.	Conditional	Moderate.[173,174]
Avoid high fixed PEEP levels without prior RM due to potential overdistension and hemodynamic compromise.	Strong	Moderate.[171,172]
Use protective ventilation (6–8 mL.kg^{-1} PBW, Pplat $\leq$ 30 cm H_2O) throughout surgery, including before and after CPB.	Strong	Low.[10,175]

CPB, Cardiopulmonary Bypass; PEEP, Positive End-Expiratory Pressure; RM, Recruitment Maneuver; PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; Pplat, Plateau Pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Summary Table Protective strategies in cardiac surgery.

Strategy	Clinical Application and Considerations
Alveolar recruitment maneuvers post-CPB	Re-expand atelectatic lung regions and restore aeration
Individualized PEEP titration	Maintains alveolar patency and optimizes compliance or driving pressure
Avoid high fixed PEEP without RM	Prevents overdistension and hemodynamic instability
Protective ventilation (6—8 mL.kg^{-1} PBW)	Minimizes VILI and supports lung-protective intraoperative care

CPB, Cardiopulmonary Bypass; PEEP, Positive End-Expiratory Pressure; RM, Recruitment Maneuver; PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; VILI, Ventilator-Induced Lung Injury.

Pediatric intraoperative mechanical ventilation: modalities and settings

Perioperative mechanical ventilation in pediatric patients can negatively impact pulmonary function even in the absence of pre-existing lung disease.[177] Specific ventilatory strategies can minimize complications such as atelectasis, hypoxemia, and VILI, promoting better perioperative outcomes.[178] Evidence in pediatric perioperative ventilation remains limited, with most recommendations extrapolated from adult studies or based on small pediatric trials.[179] Therefore, these recommendations should be interpreted with caution and adapted to individual patient characteristics.

PICO clinical question

In pediatric surgical patients under general anesthesia (P), do protective ventilatory strategies (I), compared to conventional ventilation (C), improve intraoperative oxygenation and reduce postoperative pulmonary complications (O)?

Evidence-Based Recommendations.

Recommendation	GRADE Recommendation	Evidence Quality
Use Pressure-Controlled Ventilation with Volume Guarantee (PCV-VG) in healthy pediatric patients.	Weak	Moderate.[180]
Consider Pressure Support Ventilation (PSV) with PEEP to maintain spontaneous breathing.	Conditional	Moderate.[181,182]
Avoid spontaneous ventilation without ventilatory support.	Strong	Moderate.[182]
Use tidal volumes of 5—8 mL.kg^{-1} of ideal body weight.	Strong	High.[177,179]
Avoid tidal volumes > 10 gt; 10 mL.kg^{-1}.	Strong	High.[177,179]
Plateau pressure $\leq$ 28 cm H_2O in healthy lungs or $\leq$ 32 cm H_2O in obstructive disease.	Conditional	Moderate.[183,184]
Maintain driving pressure $\leq$ 15 lt; 15 cm H_2O.	Conditional	Moderate.[183]
Use PEEP between 5—8 cm H_2O to prevent alveolar collapse.	Conditional	Low.[178]
Perform intermittent alveolar recruitment maneuvers, particularly after induction or disconnection.	Strong	High.[185,186]
Combine recruitment maneuvers with PEEP.	Conditional	High.[185,186]
Use bedside lung ultrasound to guide recruitment strategies and detect atelectasis.	Conditional	Moderate.[187]
Avoid routine use of FiO_2 = 1.0 due to risk of absorption atelectasis and heterogeneous ventilation.	Strong	High.[188,189]
Prefer FiO_2 < 0.8 throughout the perioperative period, titrated according to need.	Conditional	Moderate.[188]
Consider use of PEEP or CPAP during induction and emergence to reduce atelectasis.	Conditional	Low.[189]

PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; PSV, Pressure Support Ventilation; PEEP, Positive End-Expiratory Pressure; PBW, Predicted Body Weight. For practical bedside application, the predicted body weight calculation formula and a simplified height-based reference table are provided in the Supplementary Material; ΔP, Driving pressure; RM, Recruitment Maneuver; FiO_2, Fraction of inspired oxygen; CPAP, Continuous Positive Airway Pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

Rationale and literature-based discussion

Pediatric patients are more vulnerable to ventilator-induced lung injury because of their small airway diameter, high chest wall compliance, and immature alveoli[177], and thus strategies that minimize airway pressures are preferred. PCV-VG achieves the target tidal volume with lower airway pressures. PCV may reduce barotrauma risk,

while VCV remains safe with modern ventilators despite variations in respiratory compliance.[180] Moreover, supporting spontaneous breathing with PSV and PEEP reduces atelectasis and facilitates recovery compared to unsupported ventilation.[181,182] Likewise, using tidal volumes of 5–8 mL.kg^{-1} reduces inflammation, whereas higher volumes increase complications, and limiting plateau and driving pressures further prevents lung injury.[179,183] In addition, PEEP stabilizes alveoli and prevents collapse, while recruitment maneuvers and bedside lung ultrasound help reopen and detect atelectasis.[178] Finally, high oxygen fractions (= 1.0) promote absorption atelectasis and heterogeneity, whereas keeping FiO_2 below 0.8 and using CPAP or PEEP during induction and emergence improves homogeneity and reduces collapse.[189]

- Individualization of PEEP and FiO_2 is essential to optimize gas exchange while minimizing harm.[34,74,98]
- Driving pressure and plateau pressure are valuable bedside markers of lung protection and should be monitored routinely.[64,65,128]
- Recruitment maneuvers should not be used indiscriminately but remain an important rescue intervention in selected patients.[34,129,131]
- Standardized definitions of PPCs are crucial for clinical care, research, and benchmarking.[19-21]

Implementation and quality indicators

The clinical impact of perioperative mechanical ventilation strategies depends not only on the strength of evidence, but also on their consistent implementation and monitoring in routine practice. Translating these recommendations into institutional protocols, checklists, and education programs may facilitate adherence and reduce unwarranted variability in perioperative care.

The use of simple and measurable quality indicators may support implementation and audit processes. Examples include the proportion of patients ventilated with tidal volumes based on predicted body weight, documentation of intraoperative oxygenation targets, avoidance of unnecessary hyperoxia, and the systematic identification of postoperative pulmonary complications using standardized definitions. Monitoring these indicators over time allows benchmarking, identification of gaps in care, and continuous quality improvement.

Importantly, implementation strategies should be adapted to local resources, case mix, and organizational structures, ensuring feasibility while preserving the core principles of lung protection and patient safety outlined in this consensus.

Summary Table Pediatric protective ventilation strategies.

Strategy	Application in Pediatric Intraoperative Ventilation
PCV-VG or PCV modes	Reduced barotrauma risk and better volume control
PSV + PEEP	Maintains spontaneous ventilation with reduced atelectasis risk
Avoid unsupported spontaneous breathing	Risk of hypoventilation and alveolar collapse
Tidal volume 5–8 mL.kg^{-1}	Optimal lung protection
Plateau pressure $\leq$ 28–32 cm H_2O	Minimizes barotrauma
Driving pressure $\leq$ 15 lt; 15 cm H_2O	Limits lung stress
PEEP 5–8 cm H_2O	Prevents atelectasis
Recruitment maneuvers	Re-expand collapsed alveoli post-induction or disconnection
Bedside lung ultrasound	Atelectasis detection and recruitment guidance
$FiO_2 < 0.8$	Reduces oxidative injury and ventilation heterogeneity
PEEP/CPAP during induction/emergence	Prevents collapse and improves recovery

PCV-VG, Pressure-Controlled Ventilation with Volume Guarantee; PCV, Pressure-Controlled Ventilation; PSV, Pressure Support Ventilation; PEEP, Positive End-Expiratory Pressure; ΔP, Driving Pressure; FiO_2, Fraction of inspired oxygen; CPAP, Continuous Positive Airway Pressure.

Discussion

This consensus guideline represents the most comprehensive effort to date in Brazil to standardize perioperative mechanical ventilation practices based on current evidence. While protective strategies are well established in critical care, their translation into the intraoperative setting has historically been inconsistent. Our recommendations reinforce the concept that even short-term exposure to injurious ventilatory patterns, such as high tidal volumes, low or absent PEEP, excessive FiO_2, or unchecked driving pressures may result in atelectasis, impaired oxygenation, ventilator-induced lung injury, and ultimately, PPCs.

A central strength of this work is its structured methodology: 17 clinical questions formulated using the PICO framework, systematic literature searches, evidence grading with the GRADE system, and consensus-building through panel discussions. This process ensured transparency, reproducibility, and alignment with international standards. Furthermore, the inclusion of specific surgical populations (obese, pediatric, thoracic and cardiac surgery, and patients with or without acute lung injury) increases the applicability of these recommendations to diverse perioperative contexts.

Several key principles emerged consistently across chapters:

- Protective ventilation strategies should be applied to all surgical patients, not only to those at high risk or with preexisting lung disease.[31,138,177]

Strengths and limitations

Despite these strengths, limitations should be acknowledged. The available evidence in some areas, particularly advanced monitoring, pediatric patients, and neurosurgical or cardiac surgery contexts remains limited or heterogeneous. As such, some recommendations are conditional and

based on moderate or low certainty of evidence. Furthermore, the guideline reflects consensus among Brazilian experts and may require contextual adaptation in other health systems with different resources and perioperative practices. Ongoing research and periodic updates will be necessary to maintain relevance as new evidence emerges.

Conclusion

This guideline provides an evidence-based, consensus-driven framework for perioperative mechanical ventilation in adult surgical patients. By addressing 17 structured clinical questions across diverse perioperative scenarios, it emphasizes the consistent application of protective ventilation strategies, the standardization of definitions, and the individualization of ventilatory settings to patient physiology and surgical context.

Adoption of these recommendations by anesthesiologists and perioperative teams is expected to reduce postoperative pulmonary complications, improve patient outcomes, and harmonize clinical practice across institutions in Brazil. These guidelines are also a foundation for future research and continuous improvement in perioperative respiratory care. These recommendations should be periodically reviewed and updated, ideally every five years or sooner if disruptive new evidence emerges to ensure ongoing alignment with best practices in perioperative respiratory care.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI disclosure statement

The authors used ChatGPT (OpenAI) exclusively for language editing and text refinement. All scientific content, evidence appraisal, recommendations, interpretations, and conclusions were developed, reviewed, and approved by the authors, who take full responsibility for the manuscript.

Funding

This work was supported by the Brazilian Society of Anesthesiology (SBA).

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This consensus was developed under the auspices of the Brazilian Society of Anesthesiology (SBA), with the contribution of the Perioperative Mechanical Ventilation Guideline Panel.

The authors thank Martins Fideles dos Santos Neto (Faculdade de Ciências da Saúde de Barretos Dr. Paulo Prata, Barretos, Brazil; ORCID: 0000-0003-2996-2222) for his methodological guidance and valuable contributions to the development of this guideline.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844814.

Associate Editor

Eric Benedet Lineburger

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Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

School-based cardiopulmonary resuscitation training for high school students in Brazil: a pre-post educational intervention with 3-month follow-up

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Received 8 September 2025; accepted 17 June 2026
Available online 1 July 2026

KEYWORDS
Basic life support;
Cardiopulmonary resuscitation;
Health education;
Heart arrest;
Schools;
Students

Abstract

Background: Cardiac Arrest (CA) is considered a medical emergency and survival after CA is approximately 10%. Recognizing and providing effective intervention can have a significant impact on a patient's outcome.

Objective: To evaluate baseline knowledge of Cardiopulmonary Resuscitation (CPR) and the impact of a CPR training intervention to high school students in Aracaju, Sergipe.

Methods: This study was a pre—post educational intervention with 3-month follow-up involving 5 institutions that were chosen randomly from March to October 2023. The intervention was delivered in Portuguese, in four stages, aligned with the Kids Save Lives initiative: a pre-test was applied in 410 students before starting the course with questions regarding CPR and students' expectations; a theoretical-practical course was taught; after the course, students answered a post-test, an evaluation and satisfaction questionnaire. Finally, three months later, 343 students answered the post-test.

Results: The primary outcome was mean total score on a validated 14-item BLS knowledge test. We observed an increase in scores after training from 5.8 (2.2) pre-test to 10.9 (2.0) three months after. Scores decreased significantly from the immediate post-test to the 3-month follow-up, with a mean difference of 0.9 points (95% CI 0.61 to 1.13; Cohen's d = 0.354), but remained substantially higher than baseline. Self-perceived ability to perform CPR increased from 10.9% before training to 91% immediately after the course.

Conclusion: Teaching CPR in educational institutions can improve CPR knowledge retention at 3 months following the intervention, supporting the feasibility of integrating

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https://doi.org/10.1016/j.bjane.2026.844787

similar programs in Brazilian schools and alignment with the trend of Brazilian education policies.

Institutional Research Board approval: CAAE number: 57353622.0.0000.5546.

Introduction

The American Heart Association (AHA) defines Cardiac Arrest (CA) as the sudden complete loss of cardiac function in an individual, regardless of whether they have a history of heart disease, and symptoms being present or not beforehand.[1] The overall survival rate in out-of-hospital CA cases is currently around 10%, and this rate is directly related to the circumstances in which the event occurs, such as whether it happens at home, whether it is witnessed, and whether emergency services are accessible nearby, among other factors.[1–3] Prompt recognition and the provision of swift and effective initial intervention can have a significant impact on the patient's clinical outcome.[4] This involves following the ongoing guidelines provided by AHA, an organization that, among its various initiatives, promotes the dissemination of Basic Life Support (BLS) practices to the general public.

In 2015, the World Health Organization (WHO) endorsed the Kids Save Lives (KSL) project, which was launched in 2012 in Italy and Germany. The objective of this project is to introduce the teaching of CPR in schools in order to spread knowledge and improve social indicators related to out-of-hospital CA deaths.[5–8] In Brazil, the initiative began to be implemented by USP (Universidade de São Paulo) and spread to other states. However, there is still no record of its application in Sergipe.

The primary objective was to evaluate the effect of a structured CPR training intervention in Portuguese on high school students' knowledge using a 14-item test, measured before, immediately after, and at 3 months post-training. This initiative was conducted within the public-school network of Aracaju and aligned with the national Kids Save Lives Brazil ("KSLB") efforts (https://sites.usp.br/kidssavelivesbrasil/).[9–11]

Methods

This is an exploratory, descriptive, and longitudinal study with a quantitative approach based on data obtained through questionnaires. The study involved 343 students from five randomly selected public and private educational institutions, conducted from March to October 2023. The training consisted of theoretical and practical courses with an average duration of three hours, focusing on the topic of BLS. The theoretical portion was delivered through a lecture, followed by a practical session using manikins to demonstrate the BLS procedures.

The methodology of this study, as well as its ethical aspects, was evaluated by the Research Ethics Committee of the University Hospital of the Federal University of Sergipe, which issued an approval opinion under CAAE number 57353622.0.0000.5546. Written informed consent was obtained from all participants and/or their guardians as per local requirements, in Portuguese.

The study included high school students of any gender from public and private schools. The exclusion criteria were incomplete questionnaire responses and failure to complete the training course.

The study was divided into four stages: the first consisted of a pre-test (objective theoretical questions) and an expectations questionnaire before the course, that was applied to 410 students; the second was the theoretical-practical course; in the third, immediately after the course, students completed a post-test identical to the pre-test and a satisfaction/evaluation questionnaire; and finally, in the fourth stage, a follow-up post-test was administered three months after the course, to 343 students.

The data collection instrument used to assess technical knowledge in BLS (pre-test, immediate post-test, and delayed post-test) comprised 14 questions, each worth one point, totaling a maximum score of 14. Questions 1 to 3 addressed initial CPR measures; questions 4 and 5 addressed CA recognition; questions 6 to 9 focused on seeking help; and questions 10 to 14 covered CPR techniques. The full list of the items used to assess understanding is provided in Supplementary Data. Content validation was conducted by a panel of CPR experts, and the questions were based on international guidelines and KSL initiatives.

The expectation and satisfaction/evaluation questionnaires included variables using the Likert scale format, with some questions expressed numerically and others categorized as: strongly agree, agree, neutral, disagree, and strongly disagree.

The sample size was estimated using a two-sided $\alpha = 0.05$, power = 0.80, and assumed a medium effect size (Cohen's $d = 0.50$). Sample size was adjusted for clustering using a design effect calculated with an Intraclass Correlation Coefficient (ICC) of 0.05 and an average cluster size of 80 students. An additional 30% inflation was applied to account for anticipated loss to follow-up. The final required sample size was 223 students. However, although an a priori sample size calculation was estimated, the final sample should be interpreted as a convenience sample based on feasibility and the availability of participating schools.

Categorical variables were analyzed by determining the absolute and relative frequencies of the responses, while numerical variables were characterized using means and standard deviations. The variation in scores between the pre- and post-tests was analyzed using repeated measures analysis of variance (ANOVA), considering the influence of the educational institutions. The effect of time on mean scores between the pre-test, immediate post-test, and delayed post-test (three months later) was evaluated using repeated measures ANOVA. To control for the effects of the different schools (since the educational activities occurred on different days and locations), the model was adjusted accordingly considering school as a random effect to

Table 1 Description of the individuals included.

Variable	n = 343[a]
Gender	
Female	181 (52.8%)
Male	160 (46.6%)
Not informed	2 (0.6%)
Educational Institution	
A	49 (14.3%)
B	41 (12%)
C	70 (20.4%)
D	121 (35.3%)
E	62 (18%)
School Year	
First Year	30 (8.7%)
Second Year	119 (34.7%)
Third Year	194 (56.6%)
Age (years)[b]	17 (16-18)

[a] n (%).
[b] Median (IQR).

account for the clustering of students within educational. A significance level of 5% was adopted to determine the statistical importance of the results. Statistical analysis was performed using R software, version 4.2.3.

Results

The study included 343 high school students from five schools in a Brazilian municipality, comprising four private institutions and one public institution. The description of the participants is presented in Table 1. Initially, 410 students were enrolled in the study, 410 completed the pre-test, 410 the immediate post-test, and 343 the 3-month follow-up. The main reasons for this reduction in sample size were participant absence during data collection and difficulties in establishing contact or securing follow-up for some individuals. All statistical analyses were therefore performed using only the final group of students who completed the entire study (n = 343).

Most participants were female (52.8%), with 46.6% being male students, and only 0.6% chose not to disclose their gender. Additionally, 56.6% of the participants were enrolled in the third year of high school. It is important to note that this study did not differentiate between private and public institutions.

In Figure 1, shown below, data relate to the participants' expectations regarding the CPR course, in the BLS training.

The enthusiastic participation of 78% of those involved in the CPR course is a notable highlight, contrasting with the small percentage of 3.8% who appeared less motivated. Additionally, 7.3% remained neutral regarding their motivation. Regarding current knowledge, 39.4% felt prepared, 37% expressed uncertainty, and 25% chose not to state an opinion. When it came to practical skills, 10.9% felt confident, while 60% revealed lack of confidence, and 20% were undecided.

The will to learn was evident, with 95% eager to expand their knowledge during the course. This outlook was shared by the vast majority (88%) who hoped to master resuscitation techniques, and by 87% who were confident in their ability to assimilate the proposed content. The simulation with manikins was considered essential by 89% of the participants.

The quality of the resources and activities offered in the course was also a point of confidence, with an impressive 82% of participants believing it would be sufficient for their learning. Furthermore, the majority (94%) expected to rely on the indispensable support of the tutors for good performance, and 95% were confident that the instructors would be accessible to clarify any doubts that might arise.

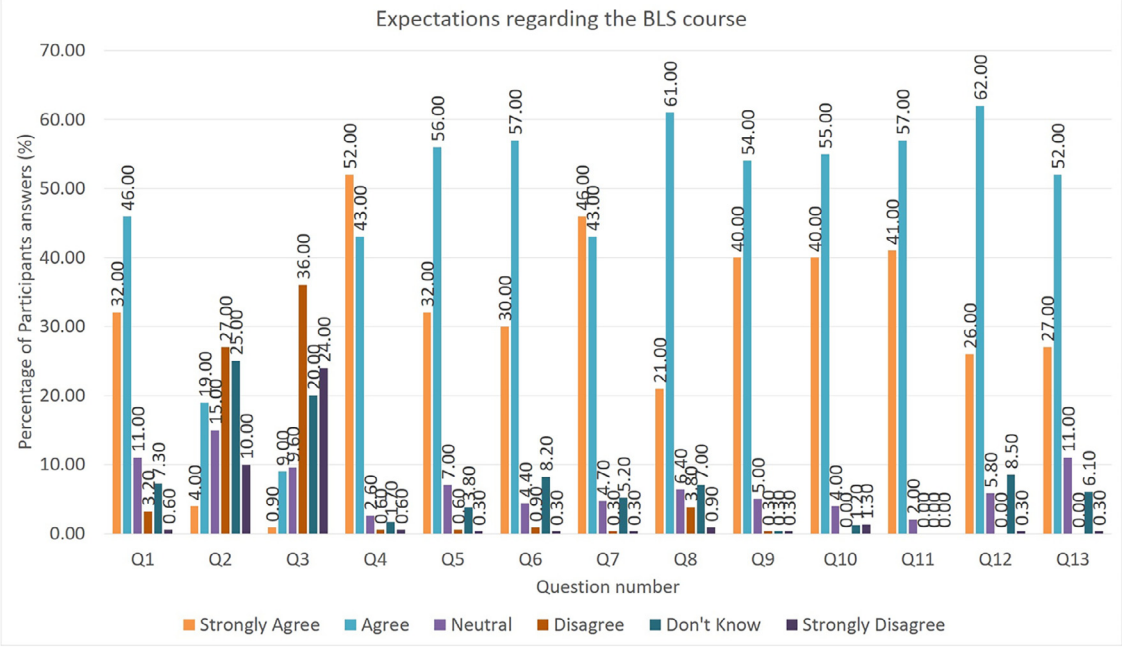

Figure 1 Expectations regarding the BLS course.

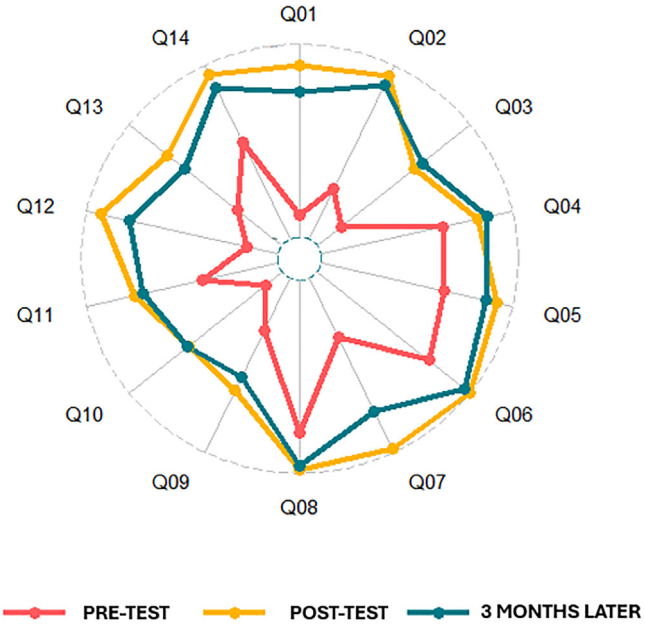

Figure 2 Pattern of correct answers in the pre-test, immediate post-test, and 3-month post-test.

The analysis of the participants' score data was conducted using ANOVA, as it provided better interpretation of the results and allowed for the calculation of effect size. ANOVA showed an intervention effect on participants' scores ($F_{Greenhouse-Geisser}$ [1.95; 657.83] = 998.4, $p < 0.001$, $\eta^2 p = 0.747$). Scheffé's post hoc test indicated a statistical difference between the means of all three points in time ($p < 0.001$), with the pre-test mean of 5.8 with a standard deviation of 2.2; the immediate post-test mean was 11.8 with a standard deviation of 1.6; and the post-test conducted three months after the course showed a mean of 10.9 with a standard deviation of 2.0. Mean score three months later showed a significant difference compared to the immediate post-test (95% CI 0.61 to 1.13, Cohen's $d = 0.354$).

The pattern of correct answers by the participants is shown in Figure 2. After the educational intervention, a notable improvement was observed in participants' correct responses. Furthermore, it is evident that individuals had significantly higher prior knowledge regarding seeking help – knowing which number to call for emergency services (SAMU) and where to find an Automated External Defibrillator (AED) – compared to their understanding of the subsequent steps in managing CA. On the other hand, in the delayed post-test, a correct answer rate of approximately 60% was observed for questions 9, 10, and 13, indicating a possible decline in the retention of knowledge related to the steps to be followed during CA management when compared to performance on the rest of the test.

Figure 3 describes the participants' evaluation and satisfaction regarding the activity after the course. In this questionnaire, emphasis is placed on the combined percentage of those who completely agree and those who simply agree with the statements. When comparing these results to the expectation questionnaire (Fig. 1), it is noted that the participants' motivation remained virtually the same (77%). After the intervention, 70% of students perceived their knowledge as sufficient, 91% regarding the ease of performing CPR maneuvers after the practical class, 92% regarding the ease of executing the step-by-step process to manage a CA after both theoretical and practical classes, and 98% regarding the importance of the manikin simulation in consolidating theoretical knowledge. The students also evaluated the overall organization of the course, as illustrated in Table 2.

Discussion

This work represents a local implementation and replication of school-based CPR training, aligned with ongoing Brazilian initiatives.[2,10] Our findings demonstrate consistent knowledge retention at 3 months, complementing prior Kids Save Lives Brazil programs.[2,10] The study's novelty is in adapting, delivering, and reporting outcomes within a specific school network (Aracaju, Sergipe).

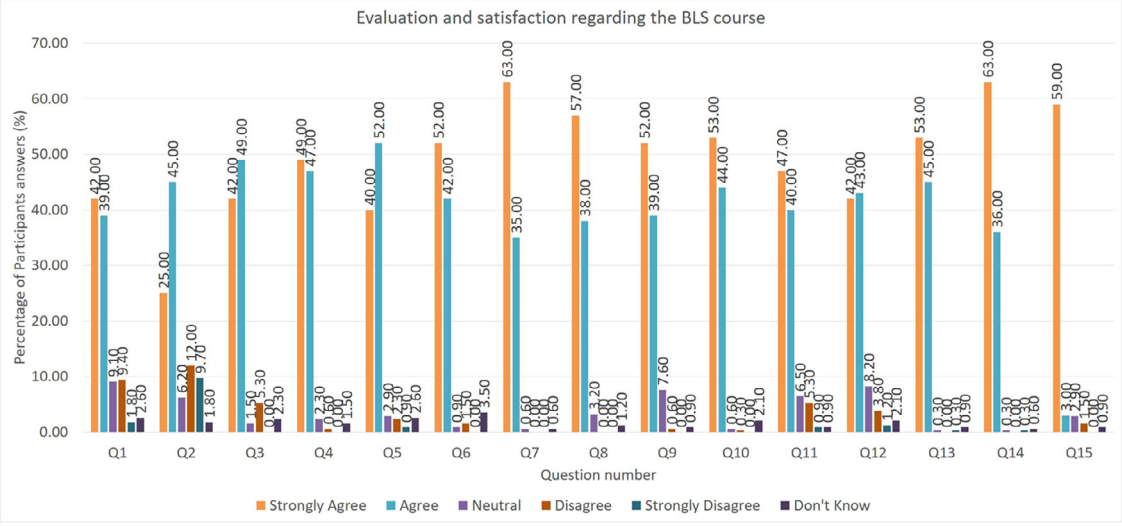

Figure 3 Evaluation and satisfaction regarding the BLS course.

Table 2 Results of evaluation of the BLS course structure.

Statement	Mean (SD)	Median [IQR]	Minimum – Maximum
General organization and course structure	9.3 (0.91)	10 [9 – 10]	**5 – 10**
Teaching staff and tutors (different skills, actions and strategies adopted by teachers and tutors in the development and promotion of the course)	9.4 (0.95)	10 [9 – 10]	**3 – 10**
Assessment system (relevance of theoretical assessment methods for student learning)	**9.3 (1.16)**	**10 [8 – 10]**	**5 – 10**
Materials provided (quality, interest and applicability of materials provided in the course)	9.4 (0.91)	10 [9 – 10]	**5 – 10**
Work methodologies (how the content is worked on in group dynamics)	9.4 (0.91)	10 [9 – 10]	**5 – 10**
Support services (ways of supporting students throughout the course in terms of resolving queries and relating to learning progression)	9.6 (0.81)	10 [9 – 10]	**5 – 10**

The low cost of implementing the CPR program in schools stands out due to the simplicity of the materials required, such as BLS manikins and educational videos. With volunteer instructors, such as local healthcare professionals, conducting the training sessions, costs are further reduced.

The schools selected for this study were strategically chosen to represent the social and educational diversity of the capital city. In the context of this study, the implementation of a 180-minute instructional program, which included the use of intermediate-fidelity manikins in schools, proved to have a significant impact, resulting in substantial improvements in evaluations between the pre-test, immediate post-test, and delayed post-test.[11]

Most students, around 70% of participants, had prior knowledge about the need to seek help in the event of CA. However, only about 15% of students knew how to carry out the initial steps required after recognizing CA. These findings are consistent with the results of a study conducted with second-year high school students in Ceará, which revealed a low accuracy rate in the pre-test regarding the assessment of responsiveness and CPR technique.[11]

The analysis of the results from the present study indicates that the initial intervention was effective in improving participants' knowledge about CPR, as the average score in the immediate post-test was 11.8, corresponding to an 84.3% success rate, while the average score in the pre-test was 5.8, equivalent to about 41.4% accuracy. Similar results were observed in studies conducted with high school students in Saudi Arabia, Jordan, and Brazil. Initially, these studies identified low prior knowledge among students regarding the management of CA. However, following educational interventions, participants demonstrated a significant increase in acquired knowledge and skills.[12–14]

It is worth noting that the results show a slight decrease in the accuracy rates of the questions in the delayed post-test compared to the immediate post-test. However, scores remained substantially higher than baseline despite the small decline over time, indicating a likely retention of learning over the three-month period. When analyzing the post-test question by question, questions 9, 10, and 13 from the test (Fig. 2) showed an accuracy rate of around 60% in the delayed post-test, indicating lower performance compared to the other questions in the same test. However, the outcome for these questions was nearly the same in the immediate post-test. This suggests that more technical questions may present a higher level of difficulty for lay responders. Similarly, an evaluation of a study conducted with second-year high school students in the city of Maceió/AL showed a significant reduction in the percentage of correct answers in the delayed evaluation when the topic was related to the technical aspects of chest compression maneuvers.[11] In this context, considering the nature of the specific questions on the post-test is important, as some questions maintained high accuracy rates, reaching up to 96.5%, possibly due to their association with easily memorized information.

When compared with the existing literature, the results of this study are consistent with previous research showing that CPR knowledge retention can decline over time, even if gradually, following the successful completion of an initial training course.[11] This highlights the importance of continuing education and regular practice to maintain CPR skills. In any case, when comparing the results of the delayed post-test with the pre-test, a considerable improvement in learning can still be observed; however, a study conducted over a longer analysis period is indeed necessary. It is worth noting that several authors have studied this topic, but there is no consensus in the literature regarding the ideal interval between training sessions, which may vary depending on several parameters.[14] Essential skills, like calling for assistance, performing chest compressions, and providing ventilation, tend to deteriorate between three and six months after the initial training. It is important to note that these findings are based on various studies that differ in terms of course duration and format, the characteristics of the instructors and participants, as well as the frequency with which participants are involved in real-life resuscitation situations.[14,15,21] As an example, Berden et al.[15] concluded that for a group of nurses in non-cardiac units, satisfactory maintenance of CPR skills could be achieved with training every six months. However, Woollard et al.,[16] when training lay individuals at an airport in the United Kingdom, suggested that the interval between CPR and AED training sessions should not exceed seven months. On the other hand, Riegel et al.,[17] when studying lay volunteers, found an

adequate level of retention of CPR and AED skills even 17 months after the initial training.

After completing the course, the vast majority of participants reported an increase in their motivation (77%), knowledge about CPR (96%), and confidence in performing CPR maneuvers (91%). It is worth noting that 98% of participants considered the manikin simulation during the practical activity to be essential for consolidating CPR content. Furthermore, most students (60%) stated, prior to the course, that they did not feel confident in managing CA following the CPR protocol. After the course, there was a significant increase in that confidence to 92%. The data obtained in this study support the positive impact of the course and reinforce findings from several studies in the literature.[18,19]

Students gave positive evaluations, with average scores ranging from 9.3 to 9.6, for the overall organization of the course, support services, teaching methodology, and materials provided. These results reflect the importance and the recommendation given by the participants, with 98% stating they would recommend the course to a friend or family member, and 99% considering the course important for society in general. Additionally, 94% of participants agreed that the course should be mandatory in all schools. In this regard, redirecting educational efforts toward the youth population in schools represents an effective strategy to reach a broad social spectrum, given the unique capacity of this environment to bring together a large number of people with the shared goal of learning.[2,6] The main objective of the KSL initiative is to provide BLS education to children of all ages, with a special focus on those over 12 years-old, who generally possess the physical ability required to perform the full BLS protocol.[12] However, even younger children (up to 5 years-old) can be taught CPR concepts, with an emphasis on spreading knowledge or guiding adults on how to perform CPR during a CA, including the use of an automated external defibrillator. Studies have shown that younger children, after repeated exposure to the topic, are capable of retaining and transmitting the information appropriately, effectively playing the role of rescuers or instructors for others.[9,20] Continuous training promotes an increase in confidence and reaction speed, resulting in a significant increase, by 3 to 5 times, in the chances of survival for out-of-hospital CA victims, especially when the event is witnessed.[1,6,7,9]

This study has some limitations that should be acknowledged. First, the sample was limited to five educational institutions in a single Brazilian municipality, which limits the interpretation of the findings to other regions with different socioeconomic and cultural characteristics. Second, the relatively short follow-up period (3 months) does not allow for assessing long-term knowledge and skill retention beyond this timeframe. Longer follow-up periods would be necessary to evaluate whether the observed improvements are sustained over time. Third, the study did not objectively assess the students' ability to perform CPR in a real-life scenario. Finally, the fact that participation was voluntary may have introduced a selection bias, as students who were more motivated or interested in health-related topics might have been more likely to participate, potentially inflating the observed effects of the intervention.

Despite these limitations, the results suggest that school-based CPR training can be feasibly implemented in public school networks, with potential for adaptation in other settings such as rural or low-resource environments. Integration with national education and emergency policies may further reinforce public health outcomes, but further studies with larger, more diverse samples and longer follow-ups are needed.

Conclusion

The teaching of CPR in educational institutions is a valuable strategy for improving CPR knowledge retention at 3 months following the intervention. This finding supports the feasibility of integrating similar programs in Brazilian public and private schools. These initiatives reinforce Brazilian government projects and efforts to teach these concepts in schools and are aligned with well-established international practices. However, there is a clear need for development of studies that evaluate whether teaching these concepts translates into improved and effective care for patients with CA.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistant disclosure

The authors used generative AI tools, including Perplexity AI (Perplexity AI, Inc.) for language editing and clarity improvements, and Gemini (Google LLC) exclusively to enhance image quality without modifying scientific content or underlying data. All manuscript contents, analyses, and conclusions were conceived, verified, and approved by the authors, who take full responsibility for the accuracy and integrity of the work.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844787.

Editor

Liana Azi

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Clinical and sensory evaluation of an instant carbohydrate beverage as a clear liquid in the preoperative period: randomized controlled trial

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Received 3 October 2025; accepted 18 June 2026
Available online 25 June 2026

KEYWORDS
Anxiety;
Carbohydrates;
Coffee;
Enhanced recovery after surgery;
Fasting;
Preoperative care

Abstract

Objective: Preoperative carbohydrate-containing clear liquids are recommended to reduce discomfort associated with prolonged fasting, yet their implementation remains limited in many Brazilian hospitals. This study evaluated the sensory acceptance and clinical effects of an instant coffee-flavored carbohydrate beverage administered during the preoperative period.

Methods: A randomized controlled trial was conducted between March 2022 and December 2024 at a tertiary hospital in Brazil. Adult patients scheduled for elective surgery under general anesthesia were allocated to a test group (200 mL carbohydrate beverage up to two hours before anesthesia induction) or a control group (conventional fasting of approximately 8 hours). Clinical assessments were performed approximately two hours before anesthesia induction. The primary outcome was satiety, assessed using a 0–10 Numerical Rating Scale (NRS). Secondary outcomes included thirst and anxiety. In the test group, palatability, satisfaction, and perceived anxiety control were also evaluated.

Results: The beverage demonstrated good sensory acceptance and was well tolerated. Compared with conventional fasting, participants who received the beverage reported significantly higher satiety scores and lower levels of thirst and anxiety. Among participants with higher baseline anxiety (≥ 7), exploratory descriptive findings suggested favorable perceived anxiety control following beverage intake. No adverse events were observed during the study period; however, the study was not powered to detect rare adverse events.

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https://doi.org/10.1016/j.bjane.2026.844785

Conclusion: Administration of the beverage up to two hours before anesthesia was associated with reduced preoperative discomfort and high patient acceptance. Larger studies are needed to further evaluate clinical outcomes and safety.

Introduction

Preoperative fasting was institutionalized in the 1940s by Curtis Lester Mendelson with the aim of preventing pulmonary complications, vomiting, regurgitation, and aspiration of gastric contents during surgery.[1] For decades, prolonged fasting was considered a standard safety measure. However, beginning in the 1990s, accumulating scientific evidence demonstrated that extended fasting could be detrimental to patients. Consequently, evidence-based perioperative care models such as Enhanced Recovery After Surgery (ERAS) were developed, recommending abbreviation of preoperative fasting as part of a broader multimodal strategy to attenuate surgical stress and accelerate postoperative recovery.[2-4]

In parallel, research has shown that prolonged fasting is associated with significant patient discomfort, including hunger, thirst, and anxiety. Moreover, it contributes to metabolic disturbances such as insulin resistance and impaired glycemic control. Excessive caloric restriction may also predispose vulnerable individuals to nutritional deterioration, thereby negatively affecting clinical outcomes.[5,6] Thus, the traditional "nil per os after midnight" practice has progressively been reconsidered.

Currently, guidelines from the American Society of Anesthesiologists (ASA) permit the intake of clear liquids up to two hours before elective anesthesia.[7] Importantly, adequate preoperative nutritional status has been associated with reductions in morbidity, mortality, and healthcare costs, while targeted nutritional interventions contribute to improved recovery.[8] Furthermore, carbohydrate administration in the preoperative period has been shown to reduce hunger and thirst without increasing the risk of bronchial aspiration.[9,10] From a metabolic perspective, prolonged fasting leads to glycogen depletion, decreased insulin secretion, and increased glucagon levels, thereby exacerbating insulin resistance and amplifying the metabolic stress response to surgery.[11]

Taken together, these physiological and subjective effects, including hunger, thirst, discomfort, nausea, and vomiting, may compromise patient well-being and tolerance to fasting. Therefore, ERAS protocols recommend the use of carbohydrate-rich beverages before various surgical procedures to mitigate the adverse consequences of extended fasting.[7,9] In this context, the present study aimed to develop a fat-free, carbohydrate-enriched instant beverage based on decaffeinated coffee and to clinically evaluate its effects on hunger, thirst, and anxiety during the preoperative period.

Methods

This study was conducted in two distinct phases: 1) Product development and characterization (preclinical phase) and 2) Clinical validation through a randomized controlled trial (clinical phase). The study followed the CONSORT guidelines for reporting randomized clinical trials.

Preclinical phase — instant coffee development and characterization

The instant coffee, free of solids, for the perioperative period was prepared with different concentrations of coffee, maltodextrin, and glucose, resulting in four product Formulations (F1, F2, F3, and F4), all providing 300 kcal per 200 mL serving. Detailed information regarding formulation composition and product development is available in the patent registered with the National Institute of Industrial Property (INPI), n° BR102022022016-6 (https://busca.inpi.gov.br/pePI/servlet/PatenteServletController?Action=detail&CodPedido=1682210&SearchParameter=BR%2010%202022%20022016%206%20%20%20%20%20%20&Resumo=&Titulo=).

For the characterization of the formulations, microbiological analyses for *Salmonella* spp. and *Escherichia coli* were initially performed in accordance with the requirements established by Brazil's Normative Instruction n° 161, dated July 1, 2022, followed by sensory evaluation.[12]

The sensory evaluation aimed to identify the most acceptable formulation based on taste and overall preference and was approved by the Ethics Committee (CAAE 67767223.9.0000.5351). Sample size was defined according to methodological recommendations for preference ranking tests analyzed using the Friedman test (α = 5%; power = 80%), resulting in the inclusion of 45-untrained volunteers of both sexes who were regular consumers of the product category. Panelists received approximately 30 mL of each formulation at 60°C, served in balanced order in containers coded with random three-digit numbers. Mineral water at room temperature was provided for palate cleansing between samples. Sensory preference was evaluated using a ranking test.[13] Panelists were instructed to order the four Formulations (F1–F4) according to overall preference, assigning rank 1 to the most preferred sample and rank 4 to the least preferred. Ranking data were analyzed using the Friedman test to compare differences in mean ranks among formulations. Lower mean rank values were interpreted as indicating higher preference.

The formulation with the highest sensory acceptance was physicochemically characterized for pH, acidity, moisture, protein, lipids, fibers, ash, carbohydrates by difference, energy value, water activity, and instrumental color (L*, a*, and b*), and was subjected to a clinical trial to validate its efficacy. The pH measurement was performed using a pH meter (Digimed, model DM-22, São Paulo, Brazil) calibrated with buffers at 4.0, 7.0, and 10.0. Acidity was determined volumetrically using 0.1 M NaOH solution, and results were expressed in g/100 g on a dry basis. Moisture was determined in a forced-air oven (Fanem 320-SE, São Paulo, Brazil)

using 3.0 g of sample at 105°C until constant weight. Protein content was measured by the Kjeldahl method using a digestion-distillation system (VELP-UDK 126A). Lipids were determined by Soxhlet extraction (Nova Ética®, model NT340) using petroleum ether (Química Moderna® 30–60° C). Ash content was determined by combustion of organic matter in a muffle furnace (Lavoisier, model 400C) at 550°C for 6 hours. Water activity was measured using a water activity analyzer (Novasina, Labtouch), calibrated with deionized water and NaCl solution with 0.819 a_w until stabilization, followed by measurement of the sample's a_w/T (°C). All methodologies followed the Instituto Adolfo Lutz.[14] Total dietary fiber was determined according to method 985.29.[15]

Color was determined using a colorimeter (Minolta Chroma Meter, model CR-400) in the CIELAB color system, including the three components: L* (lightness or brightness), which ranges from 0 (black) to 100 (white), and the chromaticity coordinates a* and b*, which range from -a* (green) to +a* (red) and from -b* (blue) to +b* (yellow), respectively.

Clinical Phase – Clinical validation through a randomized controlled trial

This randomized controlled trial was registered in the Brazilian Registry of Clinical Trials (ReBEC; RBR-5qczxhb; https://ensaiosclinicos.gov.br/rg/RBR-5qczxhb) on May 13, 2025. The study was approved by the Human Research Ethics Committee (CAAE 67767223.9.0000.5351) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

This phase included real adult patients aged 18–65 years who were scheduled for elective surgical procedures at the study hospital (Unimed Erechim Hospital, located in the north of Rio Grande do Sul). The trial was conducted between March 2022 and December 2024. Participants were recruited during routine preoperative evaluation visits. All eligible patients received detailed verbal and written information about the study objectives, procedures, and potential risks before signing the informed consent form. Surgeries were performed according to the hospital's standard schedule (morning or afternoon), and the timing of beverage administration was individually adjusted to ensure ingestion up to two hours before anesthesia induction.

Sample size was calculated based on the primary outcome, defined as the satiety score measured on a 0–10 numerical scale. Assuming a minimum clinically relevant difference of 1-point between groups, a standard deviation of 1.0 (based on pilot data), a two-sided alpha level of 5%, and 80% statistical power, at least 17 participants per group were required. To increase robustness and account for potential losses, 30 participants were included in each group, totaling 60 patients.

Participants were randomly allocated in a 1:1 ratio to either the test group (n = 30), which received the instant coffee-based carbohydrate beverage up to two hours before anesthesia induction, or the control group (n = 30), which followed the standard institutional preoperative fasting protocol. The allocation process is presented in the CONSORT flow diagram (Fig. 1). Due to the nature of the intervention, participant blinding was not feasible.

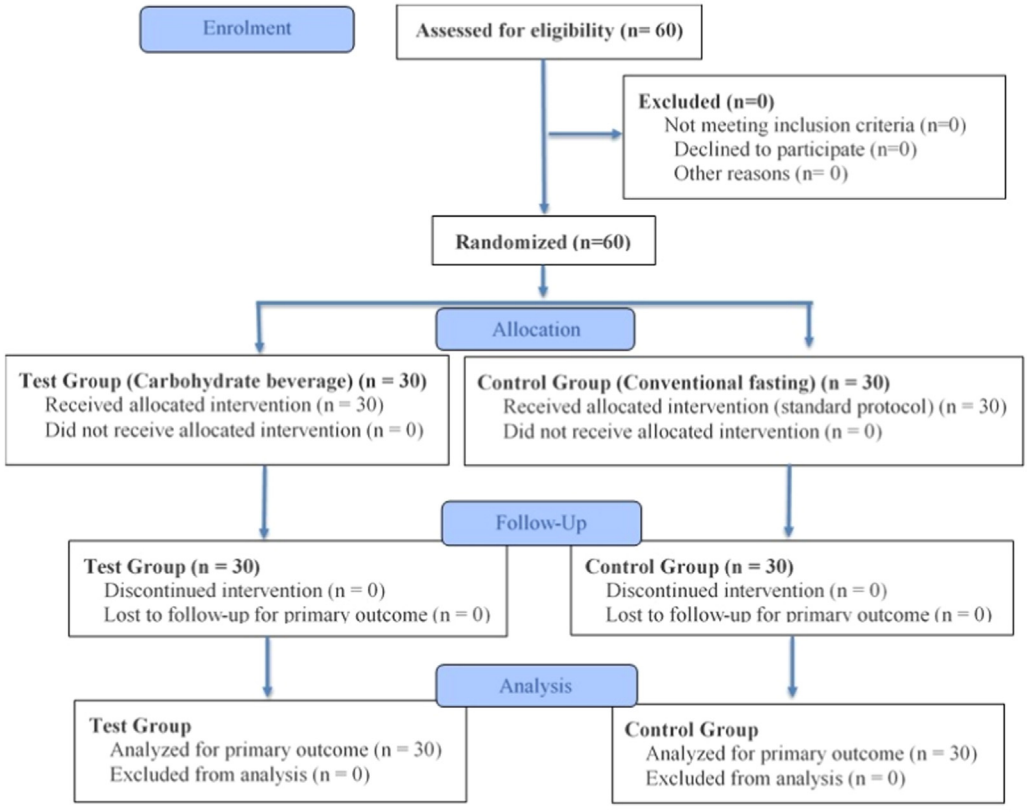

Figure 1 CONSORT flow diagram of the clinical trial on preoperative instant coffee administration, comparing test and control groups.

Eligibility criteria were established a priori. Inclusion criteria comprised adults aged 18–65 years who were candidates for elective surgery and able to understand and complete the study assessments. Exclusion criteria included diabetes mellitus (type 1 or type 2), uncontrolled metabolic or endocrine disorders, gastroparesis, severe gastroesophageal reflux disease, pregnancy, insulin use, use of medications affecting gastric emptying, or increased risk of aspiration as determined by the anesthesiology team. Patients with diabetes were not included in the study.

All surgical procedures were performed under general anesthesia, according to institutional clinical protocols and at the discretion of the attending anesthesiologist. No regional or combined anesthesia techniques were used in this study.

The 200 mL carbohydrate beverage was prepared according to patent BR102022022016-6, following a standardized preparation protocol to ensure consistent dilution, volume, and temperature. The solution was prepared by trained research personnel and administered under supervision in the hospital's preoperative area. Participants allocated to the test group consumed the beverage up to two hours before anesthesia induction, in accordance with ERAS recommendations. The control group followed the institutional standard fasting protocol, which required a minimum of 8 hours of fasting from the last oral intake (including liquids) until anesthesia induction.

Clinical evaluation was performed at a single preoperative time point, approximately two hours before anesthesia induction. Participants were assessed for sensation of hunger, thirst, anxiety, and related perceptions using structured instruments.

Anxiety was assessed using a 0–10 Numerical Rating Scale (NRS), where 0 represented "no anxiety" and 10 represented "maximum anxiety". The NRS is widely used in clinical research and practice because of its simplicity, ease of application, and reproducibility. Thirst was evaluated as a binary outcome (present/absent) based on participants' self-reports at the time of assessment.

Additional evaluations were performed in the test group following beverage consumption. Palatability was rated using a three-category scale ("very good", "good", or "bad"), while overall satisfaction with the intervention was recorded as a yes/no response. Participants also rated their perceived ability to control anxiety after beverage intake on a 0–10 NRS, with higher scores indicating greater perceived anxiety control.

In the test group, additional assessments were conducted after beverage consumption and prior to anesthesia induction. Approximately 20–30 minutes after intake, and still within the preoperative holding area, participants evaluated palatability, satisfaction with the intervention, and perceived anxiety control using structured instruments. All assessments were completed before transfer to the operating room.

The numerical and categorical scales used in this study were simple structured instruments developed by the authors for clinical applicability in the preoperative setting and were not previously validated as formal psychometric tools. However, the 0–10 NRS format is widely accepted and commonly used in clinical research for subjective symptom measurement.

All questionnaires were administered and recorded by trained members of the research team following standardized procedures. Outcomes related to discomfort, hunger, thirst, and anxiety were self-reported by the patients. Sociodemographic and clinical data were collected from medical records and complementary patient interviews.

Potential risks associated with preoperative carbohydrate ingestion, such as delayed gastric emptying or aspiration, were minimized through strict exclusion criteria and adherence to the two-hour fasting interval. All surgeries were performed as scheduled, with no cancellations related to the intervention, and no adverse events associated with beverage ingestion were observed.

Statistical analysis

Data were analyzed using descriptive and inferential statistics as appropriate. The normality of continuous variables was assessed using the Shapiro-Wilk test. As normal distribution assumptions were not satisfied, non-parametric methods were applied for the analysis of clinical outcomes.

Physicochemical analyses (n = 3) were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test, adopting a 5% significance level. Statistical analyses were performed using Statistica version 5.0 (Statsoft Inc., USA).

For the sensory evaluation stage, differences in preference rankings among formulations were analyzed using the Friedman test. In the clinical phase, between-group comparisons for the primary outcome (satiety score) and other continuous variables were performed using the Mann-Whitney *U*-test. Associations between categorical variables were assessed using Fisher's exact test.

An exploratory descriptive analysis was conducted among participants in the test group with baseline anxiety scores ≥ 7, defined as moderate-to-high anxiety on the 0–10 numerical rating scale. Perceived anxiety control after beverage intake in this subgroup was summarized using descriptive statistics only. Owing to the limited number of participants, no inferential statistical testing was performed for this analysis, and findings should be interpreted as exploratory.

Results

Product characterization

Microbiological analyses did not detect the presence of *Salmonella* sp. or *Escherichia coli*, confirming that the product meets food safety standards and can be consumed without health risks.

In the sensory analysis stage, 45 panelists participated. Demographic characterization revealed a predominance of females (75%), a higher concentration in the 18–20 year age range (47%), and a majority educational level corresponding to higher education (56%).

The preference ranking test showed limited variation among formulations with different coffee concentrations. Sample F3 presented the lowest mean rank (2.14), indicating the highest preference among panelists, followed by F4 (2.30), F1 (2.50), and F2 (3.07). Based on these

Table 1 Nutritional information of the instant coffee-flavored product.

Component	Per 100 g	Per serving (78.53 g)	%DV[a]
Energy (kcal)	389.94	306.22	15.31
Total carbohydrates (g)	97.54	76.60	25.52
Glucose (g)[b]	83.44	64.53	–
Maltodextrin (g)[b]	14.10	12.07	–
Protein (g)	0	0	0
Total fat (g)	0	0	0
Saturated fat (g)	0	0	0
Trans fat (g)	0	0	0
Dietary fiber (g)	0	0	0

[a] % Daily Values based on a 2,000 kcal (8,400 kJ) diet.
[b] Carbohydrate distribution according to formulation described in patent BR102022022016-6.

findings, formulation F3 was selected for the clinical phase, considering both sensory performance and technical criteria, including ingredient balance, lower perceived bitterness, and compliance with the patented formulation (BR102022022016-6).

The physicochemical analysis of formulation F3 showed a pH of 5.12 (±0.005), acidity of 9.61% (±0.92), water activity of 0.38 (±0.02), and moisture content of 0.60% (±0.004), indicating stability and low availability of free water. In the instrumental color analysis, the Lightness (L) value was 60.77, classifying it as visually clear with no perceptible residues, making it compatible with the recommendations for clear liquids during preoperative fasting.

The nutritional composition (Table 1), prepared in accordance with RDC n°359 and IN n° 75 (December 23, 2003),[16] indicates that each 78.53 g serving provides 76.6 g of carbohydrates, corresponding to 25.52% of the recommended daily value. According to the formulation, these carbohydrates are composed of 64.53 g of glucose and 12.07 g of maltodextrin per serving. The formulation contains no fat and is designed to provide rapid energy availability.

Thus, considering the sensory acceptability of formulation F3, its physicochemical suitability, and nutritional value, it is configured as a viable alternative for use in clinical interventions during the preoperative period.

Clinical trial

In the clinical phase, the test group consisted of 30 participants (27 females and 3 males; mean age 37.5 ± 11.15 years). The most frequently reported comorbidities were systemic arterial hypertension and controlled hypothyroidism, with no significant differences between groups. In the test group, 8 patients (26.7%) had at least one comorbidity, whereas in the control group, 9 patients (30%) reported comorbid conditions, predominantly hypertension, as shown in Table 2. The use of continuous medications reflected these underlying conditions and did not differ significantly between groups.

Based on the data in (Table 3), most participants in the test group reported complete satiety after consuming the product, and 96% experienced relief from thirst. Palatability was well-rated: 60% described it as "very good" and 40% as "good," with no cases of rejection. Average scores for "anxiety level" and "anxiety control" were 6.33 and 8.23, respectively. Furthermore, all participants expressed satisfaction with the experience, indicating full acceptance of the intervention.

In contrast, the control group showed lower satiety and greater preoperative discomfort, mainly due to hunger and anxiety. When comparing groups, the test group demonstrated significantly higher satiety scores and lower anxiety levels compared to the control group ($p < 0.001$ for both comparisons), as detailed in Table 3 and Figure 2a. Similarly, mean anxiety levels were significantly lower in the test group compared to the group that remained on conventional fasting ($p < 0.001$), demonstrating the positive effect of the nutritional intervention on reducing preoperative anxiety (Fig. 2b).

An additional exploratory analysis was performed among participants in the test group who presented baseline anxiety scores ≥ 7. In this subgroup, the mean perceived anxiety control score after beverage intake was 8.38 on a 0–10 scale, indicating a high level of subjective anxiety control. These findings suggest that even individuals with higher initial anxiety levels reported substantial perceived benefit following the intervention. However, due to the exploratory nature of this analysis and the limited number of participants in this subgroup, these results should be interpreted with caution.

Discussion

Several national and international scientific societies, such as the American Society of Anesthesiologists (ASA) and the Brazilian Society of Parenteral and Enteral Nutrition (SBNPE), recommend the adoption of multimodal ERAS protocols, including the abbreviation of preoperative fasting time.[17,18] However, its practical implementation remains limited in many centers, mainly due to the lack of viable and

Table 2 Baseline demographic and clinical characteristics of participants.

Variable	Control (n = 30)	Test (n = 30)	p-value
Age (years), mean ± SD	39.96 ± 11.38	37.50 ± 11.15	0.39[a]
Female sex, n (%)	16 (53%)	27 (90%)	0.002[b]
Any comorbidity, n (%)	9 (30%)	8 (26.7%)	0.77[b]
Continuous medication use, n (%)	12 (40%)	9 (30%)	0.41[b]

[a] Mann-Whitney test.
[b] Fisher's exact test.

Table 3 Preoperative self-reported outcomes.

Variable	Control (n = 30)	Test (n = 30)	p-value
Satiety (0–10), mean ± SD	6.43 ± 1.07	9.03 ± 0.88	< 0.001[a]
Thirst present, n (%)	29 (96.7%)	1 (3.3%)	< 0.001[b]
Anxiety level (0–10), mean ± SD	9.00 ± 0.87	6.33 ± 1.70	< 0.001[a]
Anxiety control (0–10), mean ± SD	–	8.23 ± 0.97	–

[a] Mann-Whitney test.
[b] Fisher's exact test.

accessible strategies that combine safety, cost-effectiveness, and patient acceptance.

The ERAS protocol is an evidence-based perioperative care approach aimed at improving the management of patients undergoing surgery. Initially applied in colorectal procedures, its use has expanded to various surgical specialties, showing positive outcomes. The adoption of ERAS has proven effective in reducing hospital length of stay, increasing the safety and efficiency of surgical procedures, and contributing to lower hospital costs.[3,19]

In this context, the development of a coffee-flavored, instant-reconstitution product that is safe and palatable represents an alternative to conventional preoperative fasting. Clinical analysis showed that consumption of the product up to two hours before elective surgery was associated with improved satiety and thirst control, symptoms frequently reported by patients subjected to prolonged fasting.[9,20,21] No cases of pulmonary aspiration or other adverse events were observed among participants who consumed the product during the study period. However, these findings should be interpreted descriptively and not as definitive evidence of safety.

Furthermore, a significant reduction in anxiety levels was observed in the test group, reinforcing evidence that carbohydrate administration in the preoperative period can alleviate emotional discomfort and contribute to a more positive perioperative experience.[22-24] An exploratory analysis focusing on participants with higher baseline anxiety levels (≥ 7) demonstrated high perceived anxiety control after beverage intake. Although no inferential statistical analysis was performed due to the limited subgroup size, the descriptive findings suggest that the intervention may offer subjective emotional benefits even in more anxious individuals. Future studies with larger samples and repeated anxiety measurements are needed to better characterize this potential association.

An additional exploratory analysis suggested that participants with higher preoperative anxiety levels tended to report greater perceived anxiety control after consumption of the beverage. A positive trend was observed between baseline anxiety intensity and perceived anxiety control scores, indicating that more anxious individuals may experience greater subjective benefit from the intervention. Although this observation does not allow causal inference and was not subjected to formal statistical testing due to the limited sample size, it supports the hypothesis that abbreviated fasting combined with preoperative carbohydrate administration may contribute not only to the reduction of physical discomfort but also to an improved emotional experience during the preoperative period. These findings are consistent with previous studies reporting that carbohydrate-containing beverages administered before surgery are associated with improvements in subjective well-being, comfort, and patient satisfaction. Future studies using larger samples and validated anxiety assessment instruments are warranted to better characterize the magnitude and clinical relevance of this potential association.

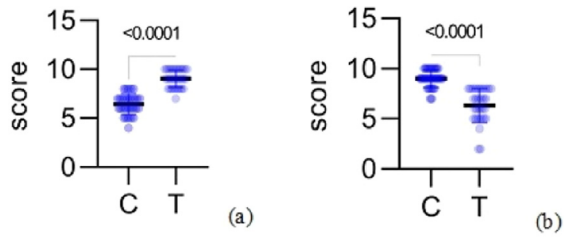

Figure 2 Comparison of satiety between the test group and the control group (a). Comparison of anxiety levels between the test group and the control group (b).

The product's palatability was satisfactory and well accepted by all participants, an essential aspect for adherence to the proposed nutritional strategy.[25,26] In this regard, it is also noteworthy that the majority of volunteers were female, which may be related to a greater willingness among women to accept innovative and participatory approaches in managing their own health.

According to the presented results, the developed product reinforces the potential of the intervention as part of perioperative care protocols. Previous studies have shown that the intake of liquids containing simple carbohydrates not only reduces discomforts such as hunger and thirst, but also attenuates metabolic responses to trauma, decreases insulin resistance, and may promote better clinical outcomes.[3,10,27] Zhang et al.[28] observed that preoperative carbohydrate use was associated with a near-significant reduction in the overall rate of perioperative complications in patients undergoing abdominal surgeries. Furthermore, the administration of an oral carbohydrate load demonstrated benefits for patient well-being, such as relief of thirst and reduced anxiety, as well as a marked decrease in postoperative metabolic and inflammatory responses, promoting a faster recovery after the surgical procedure.

Based on the results of Wang et al.[29], the oral administration of low-concentration carbohydrates before surgery may promote a better quality of postoperative recovery, according to patient self-assessment, as well as reduce the incidence of postoperative hyperglycemia following thyroidectomy.

This study has some limitations that should be acknowledged. First, the control group did not receive a placebo clear beverage. Although standard fasting care was maintained, the

absence of a placebo drink may limit the ability to fully distinguish the specific effects of carbohydrate administration from potential expectancy or hydration effects. Future randomized trials incorporating a placebo-controlled design would strengthen internal validity.

Second, the groups were not fully comparable regarding gender distribution, with a higher proportion of female participants in the test group than in the control group. Although gender is not expected to substantially influence satiety perception under these conditions, this imbalance may represent a potential confounding factor and should be considered when interpreting the findings.

Third, the sample size was relatively small and derived from a convenience sample. Although adequate for detecting differences in the primary outcome (satiety score), the study was not designed or powered to evaluate safety outcomes. This study was not powered to evaluate rare adverse events such as pulmonary aspiration. No adverse events were observed during the study period; however, this finding should be interpreted descriptively and should not be considered definitive evidence of safety. Larger studies specifically designed to assess safety outcomes are needed to further evaluate the safety profile of preoperative carbohydrate beverages.

Conclusion

The instant coffee-flavored carbohydrate beverage was well accepted and was associated with favorable patient-reported outcomes when administered as a clear liquid during the preoperative period. Its intake was associated with reduced perception of hunger, thirst, and anxiety when compared with standard fasting care, contributing to greater patient-reported comfort. The product also demonstrated practical ease of preparation and a composition consistent with current nutritional recommendations. No adverse events were observed during the study period; however, the study was not powered to evaluate rare adverse events, and these findings should not be interpreted as definitive evidence of safety.

Although carbohydrate-containing beverages in the preoperative period are supported by scientific evidence, their implementation remains limited in many Brazilian hospitals. The present findings suggest a potential role for accessible and practical strategies aimed at reducing prolonged fasting and improving the perioperative experience. Broader adoption of evidence-based perioperative practices may help enhance patient-centered care, although larger studies are needed to further evaluate clinical outcomes and safety.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The clinical phase of this study was registered in the Brazilian Registry of Clinical Trials (ReBEC; RBR-5qczxhb — https://ensaiosclinicos.gov.br/rg/RBR-5qczxhb) and approved by the Human Research Ethics Committee (CAAE 67767223.9.0000.5351). The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

Consent for publication

Not applicable.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, grammar correction, readability improvement, and organization of the manuscript. All AI-assisted outputs were critically reviewed, edited, and validated by the authors, who take full responsibility for the accuracy, integrity, and scientific content of the published article.

Authors' contributions

Joice Carla Dorneles Zanin: Methodology; analyses; investigation; validation; writing-original draft. Rosicler Colet: Methodology; analyses; investigation. Marcieli Peruzzolo: Methodology; investigation; validation. Geciane Toniazzo Backes: Conceptualization; investigation; data analysis; writing-review & editing. Jamile Zeni: Conceptualization; investigation; data analysis; writing-review & editing. André Keng Wei Hsu: Conceptualization; methodology; investigation; data analysis; visualization; writing-review & editing; project supervision.

Funding

No specific funding was received for the conduct of this study. However, support for open access publication was provided by the Coordination for the Improvement of Higher Education Personnel (CAPES-ROR: 00 × 0ma614), Brazil.

Conflicts of interest

One or more authors are listed as inventors on the patent deposit BR102022022016-6 related to the beverage formulation evaluated in this study. No financial compensation or commercial licensing agreements are currently in place. All other authors declare no competing interests.

Acknowledgements

This study was financed in part by the National Council for Scientific and Technological Development — Brazil (CNPq), the Coordination for the Improvement of Higher Education

Personnel – Brazil (CAPES), and the Research Support Foundation of the State of Rio Grande do Sul — Brazil (FAPERGS).

Associate Editor

Lorena Ibiapina Mendes de Carvalho

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Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Impact of perioperative clonidine on postoperative respiratory adverse events in children: a post-hoc observational analysis of prospectively collected datasets

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Received 9 January 2026; accepted 23 June 2026
Available online 8 July 2026

KEYWORDS
Clonidine;
Patient Outcome Assessment;
Pediatric Anesthesia;
Perioperative Period;
Postoperative Complications;
Signs and Symptoms, Respiratory

Abstract
Background: Clonidine, an alpha-2-agonist, has several applications in pediatric anesthesia. Sympathetic nervous system-mediated pathways contribute to airway reactivity, suggesting that clonidine could mitigate respiratory adverse events similarly to more selective agents.
Methods: This was a post-hoc analysis of prospectively collected observational datasets from three research projects on children (1–16 years) undergoing elective extracapsular (adeno-) tonsillectomies between January 2018 and November 2021. Patients' study data sheets and medical records were reviewed for clonidine use. The primary outcome was postoperative respiratory events (at emergence from anesthesia or in the post-anesthesia care unit). Post-anesthesia care unit length of stay was also monitored.
Results: The cohort consisted of 512 patients. The tonsillectomies were performed using coblation or electrocautery, local anesthetic infiltration; the airway was managed with a flexible supraglottic airway (97%). In the unadjusted cohort, postoperative respiratory events occurred in 44/306 children receiving clonidine (14%) and 50/203 children not receiving clonidine (25%) (OR = 0.616; 95% CI 0.361—1.047; p = 0.074). After propensity score matching, the between-

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https://doi.org/10.1016/j.bjane.2026.844792

group difference narrowed to 5 percentage points in the complete-case dataset and 4 percentage points in the multiply imputed dataset, with no statistically significant association between clonidine and postoperative respiratory events. Clinically, clonidine use did not prolong stay in PACU, 48.2 minutes (±22.5), compared with 50.0 minutes (±23.5).
Conclusions: This post-hoc analysis found no statistical reduction in postoperative respiratory events associated with perioperative clonidine in pediatric patients following extracapsular (adeno) tonsillectomy and a flexible supraglottic airway. Clonidine use did not prolong time in PACU.

Introduction

Clonidine is a centrally acting alpha-2 agonist and a popular agent in pediatric anesthesia with several applications, including premedication, prevention of emergence delirium, antiemesis, and as an analgesic adjunct, both systemically and in regional anesthesia.[1] Intraoperatively, clonidine reduces sympathetic outflow and attenuates the neurohormonal response to surgical stress.[2] Some evidence suggests that anxiety and sympathetic nervous system-mediated pathways can contribute to airway reactivity.[3-5] Dexmedetomidine, a more selective alpha-2 agonist, has been beneficial in an animal reactive airway model.[6] This introduces the possibility that clonidine might similarly mitigate respiratory complications. Two studies have reported a lower rate of respiratory adverse events following intranasal dexmedetomidine.[7,8]

The 7th National Audit Project of the Royal College of Anaesthetists UK found that severe hypoxemia was the leading cause of cardiac arrest in patients undergoing non-cardiac surgery.[9] Serious respiratory adverse events are a leading cause of closed claims for anesthesia in the United States.[10] Perioperative Respiratory Adverse Events (PRAE) occur from the induction of anesthesia until discharge from the Postoperative Care Unit (PACU). The incidence of PRAE is approximately 15%–30% of pediatric general anesthetics, and it is most frequent in the postoperative phase.[11-13] Tonsillectomy patients are regarded as at a higher risk.[14]

Medications given perioperatively that are active in the early postoperative phase therefore have the potential to reduce adverse respiratory events and improve outcomes. To date, no Randomized Controlled Trials (RCTs) have directly examined the impact of clonidine on adverse respiratory events in children.

The primary aim of this post-hoc analysis of observational datasets was to explore whether the administration of clonidine pre- or intraoperatively reduced the incidence of postoperative respiratory events in children prior to designing a more definitive RCT. A secondary outcome was to assess the effect of clonidine on the time to discharge from the PACU.

Methods

Cohort

Post-hoc analysis of prospectively collected observational datasets from three research projects on children undergoing elective (adeno-) tonsillectomies between January 2018 and November 2021: the Bee Pain Free (Child and Adolescent Health Service Human Research Ethics Committee Approval CAHS HREC RGS0000003325, Australia and New Zealand Clinical Trials Registry ACTRN12619001385134),[15] EMPHASIS (CAHS RGS0000000296; ACTRN12617001379303), and OSATS2 (CAHS RGS0000000014; ACTRN12615001037594)[16,17] trials. The Bee Pain Free trial was an interventional study on postoperative pain, while the other two were observational studies investigating PRAE risk factors. Nearly identical perioperative data were collected for each, allowing for a merged analysis. Our report follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patients between 1 and 16 years old were enrolled from two public and three private centers in Western Australia. The main exclusion criteria were severe cardiopulmonary disease or other significant medical conditions. In all studies, extracapsular tonsillectomy was performed using Coblation™ (Smith Nephew, Watford, UK), BiZact™ (Medtronic PLC, Minneapolis, USA) or bipolar/monopolar electrocautery. Local anesthetic infiltration was usually given by the surgeons, no topical or peri-glottic local anesthetic was used. The indication for surgery in nearly all cases was sleep-disordered breathing. Anesthesia was conducted in accordance with institutional guidelines. Sedative (midazolam or clonidine) premedication was at the discretion of the treating anesthetist, and use was recorded. Induction of general anesthesia was either via incremental inhalation of sevoflurane (up to 8 vol%, with nitrous oxide) or intravenous propofol (> 3 gt; 3 $mg.kg^{-1}$). Sevoflurane was used for anesthesia maintenance in most patients, with a small number receiving a propofol infusion. The airway was managed with a flexible supraglottic airway in the vast majority of children. Deep vs. awake removal of the airway was also recorded.

Analgesia included standardized administration of acetaminophen 15–20 $mg.kg^{-1}$ orally (preoperatively) or Intravenously (IV) intraoperatively and weight-based parecoxib IV. Opioid use was at the discretion of the treating anesthetist and Oral Morphine Equivalent (OME) was calculated, typically fentanyl 1–2 $\mu g.kg^{-1}$, and/or morphine 0.05–0.1 $mg.kg^{-1}$, pethidine 1 $mg.kg^{-1}$ or hydromorphone 10–20 $mcg.kg^{-1}$. In a few children, alfentanil or remifentanil was used as part of total intravenous anesthesia maintenance. In the PACU, intravenous fentanyl 0.25 $\mu g.kg^{-1}$ or morphine 0.25 $mg.kg^{-1}$ was available until tolerating oral medications for acute pain. All patients received dual intraoperative antiemetics.

Exposure

Clonidine was administered at the discretion of the treating anesthetist. When used, it was typically given as premedication

at 2–4 μg.kg^{-1} or intravenously intraoperatively at 1 μg.kg^{-1}. Patients' study datasheets and medical records were reviewed for the presence or absence of pre- and/or intraoperative clonidine.

Primary outcome

The primary outcome was postoperative respiratory events, as defined in previous studies on perioperative respiratory adverse events by our group i.e., measured any PRAE recorded at emergence from anesthesia or in the PACU.[12]

- Laryngospasm: complete airway obstruction with associated muscle rigidity of the abdominal and chest walls, leading to the child's unsuccessful ventilation, unresponsive to simple jaw thrust and CPAP maneuvers.
- Bronchospasm: increased respiratory effort, particularly during expiration and wheeze on auscultation.
- Desaturation: Oxygen saturation < 95% for > 10 secs on pulse oximetry.
- Airway obstruction: the presence of airway obstruction with a snoring noise and/or increased respiratory efforts.
- Severe persistent coughing: pronounced, persistent coughs lasting more than 10 seconds.
- Postoperative stridor: high-pitched sound during breathing in the postoperative period.

Risk factors for PRAE collected in all studies were: history of recurrent wheeze, prior diagnosis or family history of asthma or atopy, Upper Respiratory Tract Infection (URTI) in the past 2 weeks, caregiver smoking, as previously published.[12,17]

Statistical analysis

The incidence of postoperative respiratory events was compared for children who received clonidine and those who did not. However, these raw incidences do not account for baseline differences between the two groups. Propensity Score Matching (PSM) was therefore used to adjust for any systematic differences between patients who were and were not given clonidine. Propensity scores were estimated by fitting a logistic regression model for the probability of being given clonidine pre- or intraoperatively. True confounders (variables related to both treatment with clonidine and the outcome of respiratory events) and variables related to the outcome, except treatment with clonidine, were included in the propensity score estimation model,[18,19] regardless of their statistical significance level. These included respiratory factors (history of respiratory symptoms, recent upper respiratory tract infection, eczema, family history of asthma and/or eczema, exposure to tobacco smoke, history of wheezing), age, ASA category, type of anesthesia induction, maintenance, airway device, timing of removal of airway device, trial, year of surgery, site (public vs. private), and sex. To address missing data, we used Multiple Imputations by Chained Equations (MICE)[20] with m = 100 imputations prior to propensity score matching. The log-odds of estimated propensity scores were matched between the clonidine and no-clonidine groups using a 1:1 nearest neighbor approach without replacement, and with a caliper size of 0.2*Standard Deviation (SD). Covariate balance was assessed by consideration of the Standard Mean Difference and Variance Ratio between the clonidine and no-clonidine groups.

To estimate the effect of clonidine on the incidence of postoperative respiratory events, we fitted logistic regression models to the binary outcome occurrence of respiratory events at emergence and/or PACU for both the multiply imputed and complete case propensity-score-matched datasets.[18,21] Similarly, to estimate the effect of clonidine on the length of stay in PACU, we fitted a linear model to the continuous outcome of PACU stay duration.

All analyses were performed in R.[22] Statistical significance was taken at 5% ($p < 0.05$) unless otherwise stated.

Results

The cohort consisted of a total of 512 patients enrolled in the three included studies (Fig. 1). Baseline characteristics and anesthesia details grouped by clonidine status are presented in Table 1 and risk factors for adverse respiratory events are presented in Table 2; these are broadly comparable between groups. Fourteen percent (44/306) of the clonidine cohort received it preoperatively but the dose was not recorded on the data sheet, with the remaining patients generally receiving 1 μg.kg^{-1} intraoperatively.

In the raw dataset, a total of 94 patients (18%) experienced postoperative respiratory events (during emergence or in the PACU, see Table 3). Severe postoperative respiratory events (bronchospasm and laryngospasm) were uncommon, 9 (2%) patients and similar between groups. None of the 3 patients with missing clonidine data had any type of adverse respiratory event. In this raw data, 25% (50/203) of participants in the no-clonidine group experienced any postoperative respiratory events compared with 14% (44/306) of those who received any clonidine. In patients with only intraoperative clonidine, it was 33/264 (13%).

Propensity score matching, narrowed the difference in postoperative respiratory event incidence between groups. In the complete case dataset, the incidence was 22% in the no-clonidine group and 17% in the clonidine group (OR = 0.732, 95% CI 0.420–1.265), a reduction of 23%, and similarly in the imputed (m = 100) dataset (n = 347.4) of 4 percentage points (22% to 18%). No statistically significant effect of clonidine on the rate of postoperative respiratory events in the matched datasets was observed overall or at emergence or in PACU separately, with Odds Ratios (95% CI) ranging from 0.616 (0.361, 1.047) to 0.757 (0.429, 1.335) across models (Table 4). When included in the propensity score matching model intraoperative OME did not impact the results; this, coupled with the rate of missingness in intraoperative opioid dosing relative to other variables (Supplement Fig. 3) and the similar mean OME between clonidine and no-clonidine groups (Table 1), led to the decision not to include this as a predictor in the final model.

For the matched complete case data, the mean length of stay in PACU was 48.2 minutes (SD $\pm$22.5 minutes), compared with 50.0 minutes (SD $\pm$23.5 minutes) for those receiving clonidine. Based on inspection of residual distributions, the PACU duration was log-transformed before linear modelling. Based on these models, there was no significant difference in the mean duration of stay in PACU between groups in any analysis (Table 4).

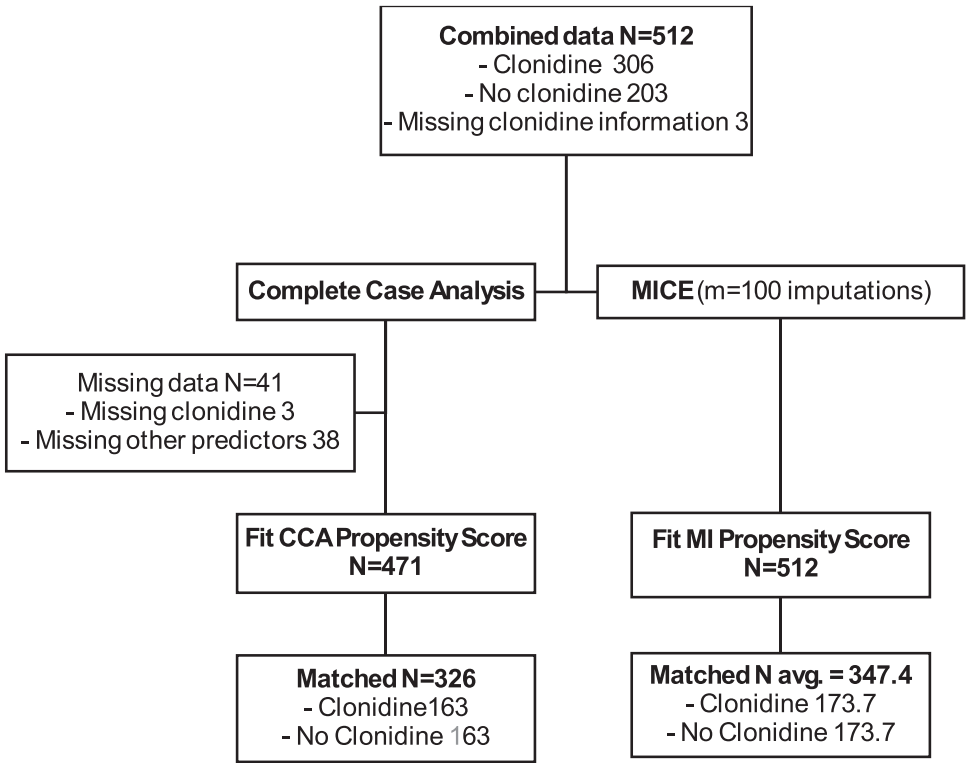

Figure 1 Cohort and propensity score matched datasets. Avg, Average between multiply imputed and matched datasets; CCA, Complete Case Analysis; MI, Multiple Imputation; MICE, Multiple Imputation by Chained Equations.

Discussion

In this post-hoc propensity-matched analysis, pre- or intraoperative clonidine was not associated with a statistically significant reduction in the incidence of postoperative respiratory events in children undergoing adenotonsillectomy. Although a lower incidence of respiratory events was observed in the clonidine group in the raw data (14% vs. 25%), when correcting for baseline differences and accounting for missing data this difference narrowed (18% vs. 22%; OR = 0.757 [95% CI 0.43–1.34]) and remained not significant (Table 4). The overall incidence of postoperative respiratory events reported in our cohort was 18%, which is consistent and at the lower end of studies in the literature.[23-25] This low rate may in part be due to the use of flexible SGAs rather than endotracheal tubes as standard airway management in our institution.[26] In addition, clonidine use did not seem to prolong the time to PACU discharge.

An animal model has shown the potential beneficial effects of alpha-2 agonists on the respiratory system, which may be due to an increased depth of anesthesia, blunting airway reflexes, a reduction in airway reactivity, increased bronchodilation and cough suppression.[27] Importantly, oral clonidine premedication at 4 mcg.kg^{-1} does not seem to attenuate the carbon dioxide response curve in children undergoing sevoflurane anesthesia,[28] which, with its analgesic, anxiolytic and sedative actions, allows sparing or reduction in midazolam, sevoflurane and opioids, perhaps promoting a better wake-up from anesthesia.

Alpha-2 agonists have demonstrated a benefit in those at high risk of adverse respiratory events, for example in those with OSA, reactive or inflamed airways. Shen et al.[8] reported significantly lower respiratory adverse events rates in children, prior to tonsillectomy, receiving premedication with intranasal dexmedetomidine (24%) compared to midazolam (56%) or saline (40%). In their post-hoc analysis, there was an even more pronounced effect in those with URTI in the preceding 4 weeks, 20.0% had respiratory events with dexmedetomidine vs. 64.4% in the midazolam group. Another RCT of children with congenital heart disease and recent upper respiratory tract infection, undergoing cardiac catheterization, showed that intranasal dexmedetomidine more than halved the incidence of adverse respiratory events in those aged less than 3 years.[7] A meta-analysis of dexmedetomidine studies from ten older pediatric studies containing 1,056 patients, with four of the studies in tonsillectomy patients, demonstrated reduced PRAE compared to active comparators and reduced cough, breathing holding and laryngospasm compared to placebo.[29] Preoperative midazolam may be associated with increased PRAE,[12] but was spread evenly across groups.

Our data has several limitations. The retrospective nature of our analysis and merged data from past trials over a four-year period introduce potential biases, particularly reliance on data that was not originally collected for this research question, as well as changes in anesthesia or surgical technique over time. The raw data for the clonidine group (Table 2) had several factors, e.g. more private patients, more patients from the more recent BEE study, more males, less obese patients, higher use of TIVA and SGAs, many of which may be protective for respiratory events[14,30] but were adjusted for in the analysis, and may explain the narrowing in incidence in the matched data set and did not demonstrate benefit. It may be that the sample

Table 1 Baseline and anesthesia characteristics of patients grouped by whether or not they received clonidine pre- or intraoperatively.

Characteristic	No Clonidine (n = 203)	Clonidine (n = 306)
Trial		
BEE	141 (69%)	249 (81%)
EMPHASIS	22 (11%)	35 (11%)
OSATS2	40 (20%)	22 (7%)
Year of Surgery		
2018	14 (6.9%)	18 (5.9%)
2019	36 (18%)	22 (7.2%)
2020	123 (61%)	188 (61%)
2021	30 (15%)	78 (25%)
Site		
Public	185 (91.1%)	198 (65%)
Private	18 (8.9%)	108 (35%)
Age in years, mean (SD)	6.70 (2.97)	6.23 (2.95)
Age range in years		
1 to 5.9	95 (47%)	162 (53%)
6 to 8.9	75 (37%)	99 (32%)
9 and over	33 (16%)	45 (15%)
Weight in KG, median (P25, P75)	22.95 (19.18, 31.60)	21.26 (16.80, 28.25)
Height in CM, mean (SD)	121.9 (17.7)	117.7 (19.9)
BMI z-score for age, mean (SD)	0.54 (1.35)	0.45 (1.49)
BMI Category by Percentile for age		
Underweight (< 5^{th})	11 (6%)	19 (17%)
Healthy Weight (5^{th}–< 85^{th})	119 (60%)	163 (58%)
Overweight (85^{th}–< 95^{th})	22 (11%)	43 (15%)
Obese (95^{th}+)	43 (22%)	49 (17%)
Under 2 years old	3 (2%)	8 (3%)
ASA		
I	81 (40%)	135 (44%)
II	120 (59%)	167 (55%)
III	2 (1%)	4 (1%)
Sex: Male / Female	125 (62%) / 78 (38%)	153 (50%) / 153 (50%)
Induction: IV / Inhalation	28 (14%) / 175 (86%)	31 (10%) / 275 (90%)
Maintenance: Sevoflurane / Propofol TIVA	200 (99%) / 3 (1%)	288 (94%) / 18 (6%)
Airway SGA / ETT	193 (95%) / 10 (5%)	300 (98%) / 6 (2%)
Airway removal timing		
Awake	152 (75%)	246 (80%)
Deep	51 (25%)	60 (20%)
Anesthetic Duration minutes, median (P25, P75)	42.0 (36, 51)	39.50 (34, 47)
Intraoperative opioid use	203 (100%)	306 (100%)
Intraoperative OME ($mg.kg^{-1}$)	0.41 (0.13)	0.40 (0.12)
Fentanyl	129 (64%)	137 (45%)
Morphine	106 (52%)	75 (25%)
Hydromorphone	26 (14%)	25 (9%)
Pethidine	36 (19%)	138 (48%)
Tramadol	0 (0%)	4 (1%)
Remifentanil	0 (0%)	1 (0%)
Alfentanil	0 (0%)	2 (1%)
Premedication Midazolam	21 (10%)	32 (10%)
Premedication Clonidine	0	44 (14%)
Intraoperative Clonidine	0	264 (86%)
Dose in $mcg.kg^{-1}$ (of those who had it)		0.98 (0.87, 1.12)
Unknown dose		22

Note: Clonidine information was missing for n = 3 participants — more information can be found in the Supplementary Material. Two patients received both premedication and intraoperative clonidine. SD, Standard Deviation; Kg, Kilogram; P25, 25^{th} percentile: P75, 75^{th} percentile; Cm, Centimeters; BMI, Body Mass Index; ASA, American Society of Anesthesiologists physical status classification; SGA, Supraglottic Airway; ETT, Endotracheal Tube; TIVA, Total Intravenous Anesthesia.

Table 2 Risk factors for perioperative respiratory adverse events according to clonidine status.

Characteristic	No Clonidine (n = 203)	Clonidine (n = 306)
URTI in 2 weeks preoperatively	31 (15%)	59 (19%)
Nocturnal dry cough	34 (17%)	59 (19%)
Wheeze during Exercise	38 (19%)	33 (11%)
Asthma	36 (18%)	43 (14%)
Hay fever	59 (29%)	87 (28%)
Eczema	52 (26%)	77 (25%)
Asthma — Family History	74 (36%)	94 (31%)
Eczema — Family History	61 (30%)	95 (31%)
Hay fever — Family History	97 (48%)	132 (43%)
Caregiver Smoking	60 (30%)	75 (25%)

Note: Clonidine information was missing for n = 3 participants — more information can be found in the Supplementary Material. URTI, Upper Respiratory Tract Infection.

size available for the adjusted analyses was insufficient to exclude modest effect sizes with precision.

The MICE analysis allowed for missing data and showed a similar result, adding to the statistical reliability of the findings. Despite the propensity score matching and MICE, residual confounding might still play a role, particularly due to patient factors that were not recorded or standardized, for example doses and types of opioids used across studies and

Table 3 Postoperative respiratory events incidence according to clonidine status for the entire cohort without adjustment.

Postoperative Respiratory Event Type	No Clonidine (n = 203)	Clonidine (n = 306)
Bronchospasm	0 (0%)	1 (0%)
Laryngospasm	5 (2%)	3 (1%)
Coughing	23 (11%)	18 (6%)
Desaturation less than 95%	20 (10%)	20 (7%)
Airway Obstruction	20 (10%)	22 (7%)
Respiratory Event Timing		
Emergence	16 (8%)	11 (4%)
PACU	43 (21%)	38 (12%)
Postoperative Severe Respiratory Event	**5 (2%)**	**4 (1%)**
Any Postoperative Respiratory Event	**50 (25%)**	**44 (14%)**

Note: Participants may have had more than one type of respiratory event or at more than one timing. PACU, Post-Anesthesia Care Unit. Severe respiratory events include bronchospasm and laryngospasm.

Table 4 Results from models (logistic regression for the outcome of Perioperative Respiratory Adverse Events (PRAE), linear regression on the log of Post-Anesthesia Care Unit (PACU) length of stay for the outcome of PACU length of stay) for raw complete-case, matched complete-case, and matched multiply imputed datasets.

RAW CCA	No Clonidine, n = 203	Clonidine, n = 306	Model estimate (95% CI)	p-value
PRAE at emergence and/or PACU	50 (25%)	44 (14%)	0.616 (0.361, 1.047)[a]	0.074[a]
PRAE at Emergence	16 (7.9%)	11 (3.6%)	0.466 (0.180, 1.162)[a]	0.104[a]
PRAE at PACU	43 (21%)	38 (12%)	0.675 (0.386, 1.176)[a]	0.166[a]
Time in PACU (mins), median (P25–P75)	44.0 (33.0–58.8)	45.0 (35.0–59.0)	0.023 (-0.05, 0.097)[c]	0.533[a]
Matched CCA	**No Clonidine, n = 163**	**Clonidine, n = 163**		
PRAE at emergence and/or PACU	36 (22%)	28 (17%)	0.732 (0.420, 1.265)[b]	0.266[b]
PRAE at Emergence	11 (6.7%)	9 (5.5%)	0.808 (0.317, 2.006)[b]	0.645[b]
PRAE at PACU	30 (18%)	23 (14%)	0.728 (0.399, 1.314)[b]	0.295[b]
Time in PACU mins, median (P25–P75)	45.0 (34.0–59.0)	45.0 (35.0–57.0)	0.036 (-0.054, 0.126)[c]	0.434[c]
Matched Imputed	**No Clonidine, n = 173.7**	**Clonidine, n = 173.7**		
PRAE at emergence and/or PACU	38.8 (22%)	31.2 (18%)	0.757 (0.429, 1.335)[b]	0.334[b]
PRAE at Emergence	10.5 (6.1%)	8.2 (4.7%)	0.754 (0.275, 2.067)[b]	0.582[b]
PRAE at PACU	34.0 (20%)	27.1 (16%)	0.757 (0.419, 1.368)[b]	0.354[b]
Time in PACU (mins), median (P25–P75)	44.3 (33.9–59.0)	44.7 (34.8–59.1)	0.025 (-0.070, 0.121)[c]	0.601[c]

Notes:
[a] Raw OR and p-values adjusted for significant confounders, including patient characteristics and surgical information via a multivariable model.
[b] Matched OR and p-values for single regression models since confounders are handled in propensity score matching process prior to modelling.
[c] Model estimates and p-values are from linear regression models for log-transformed length of stay, while the medians are reported on the original linear scale.
OR, Odds Ratio; CI, Confidence Interval; Est, Parameter Estimate; CCA, Complete Case Analysis.

documentation of local anesthetic or exact hemostatic technique used by surgeons was not recorded in studies.

This confounding may also include the anesthesiologist's reasons for using clonidine, for example, an anxious child may have a more stormy IV induction without preoxygenation, leading to increased risk of desaturation. Of note, for the 14% receiving preoperative clonidine the dose was not recorded in the original studies, so only a binary analysis of "clonidine or no clonidine" was used; additionally, propensity score matched analysis is only valid for a binary exposure. We did not explore whether variations in clonidine dosing impacted rates of respiratory events differently, due to the post-hoc nature of the analysis. It is possible that different doses or timing of doses could have different effects. That said, looking just at intraoperative intravenous dosing (86% of cases), which was largely consistent at 1 $\mu g.kg^{-1}$, the rate of respiratory events was similar in the raw data to those receiving preoperative dosing, despite the higher doses given. Another limitation is the lack of standardization of anesthesia, including induction technique, drug selection (opioid) and dosing, as well as extubation strategies. All of these differences can affect the incidence of adverse respiratory events,[14,30] but they were also accounted for in the propensity score matched modelling and represent a more "real-world" anesthesia approach. Predominantly, the anesthesia technique was an inhalational induction and maintenance with sevoflurane. Propofol-based TIVA was used slightly more in the clonidine group (6% vs. 1%), which has been associated with fewer adverse respiratory events.[25,31] However, even prior to matching the numbers of propofol, TIVA instances were statistically balanced between clonidine and no-clonidine groups (Supplement Figs. 6 and 8). Of note, in our institutions, a flexible supraglottic airway is commonly used during tonsillectomy, 96.8% of this cohort. The use of supraglottic airway has been shown to reduce the incidence of adverse respiratory events[12,14,30] compared to endotracheal intubation, and was used slightly more in the non-clonidine group. In particular, SGA versus ETT for tonsillectomy in children has shown to nearly halve respiratory adverse events, with Odds Ratio (OR = 0.55 [95% CI: 0.36, 0.82], p = 0.004) but with a similar incidence of laryngospasm (OR = 0.84 [95% CI: 0.39, 1.81]).[26] It is likely that the high use of SGA may have lowered the base incidence rate in both groups. Many institutions use endotracheal tubes as standard for tonsillectomy, which limits generalizability beyond SGA case tonsillectomy. Despite minor variations in anesthesia conduct, the study had patients across four centers, both public and private, with different surgeons and anesthesiologists which adds to the generalizability of the study.

It should also be noted that recent URTI, one of the most important risk factors for adverse respiratory events, was more prevalent in the clonidine group (19% vs. 15%, see Table 2). This was also adjusted for via propensity score matching, resulting in rates of 14% URTI in the matched clonidine group versus 15% in the no-clonidine group. The vast

majority of cases were performed to treat sleep-disordered breathing/snoring — a known risk factor for adverse respiratory events. In particular, the severity of any associated Obstructive Sleep Apnea (OSA) was not known between the groups (apart from the OSATS2 patients), as polysomnography is not routinely performed preoperatively even though OSA severity represents an important confounding risk factor.[32]

While this study focused on clonidine, it is worth considering that dexmedetomidine's greater selectivity for alpha-2-receptors, used at similar dosing (1–2 $\mu g.kg^{-1}$), could account for a superior efficacy in the prior animal and clinical studies.[7,8] A relatively low dose of clonidine (1 $\mu g.kg^{-1}$) was used in most patients, and it may be that a higher dose, such that it approximates an equipotent dose of dexmedetomidine, might be required. While we did not find a significant reduction in postoperative respiratory events, clonidine use did not increase PACU time at this dose. This is of particular importance since clonidine is widely used in clinical practice and is inexpensive. There is a gap for a high-quality prospective randomized controlled trial, preferably using differing doses of clonidine perioperatively, to definitely investigate its role in reducing respiratory adverse events. This is particularly true for research in high-risk subgroups, for example, in those with a recent URTI or proven OSA or at institutions that use predominantly ETTs, since those children might gain more from clonidine.

Conclusion

This post-hoc analysis found no evidence of a difference in postoperative respiratory events when administering perioperative clonidine in pediatric patients undergoing extracapsular (adeno)tonsillectomy with a flexible supraglottic airway. Clonidine at doses used in this cohort did not prolong time in PACU.

Data availability statement

The data for this manuscript are available upon reasonable request and in accordance with institutional ethical and governance requirements.

Trial registration

This post-hoc analysis includes data from three prospective research projects on children undergoing elective (adeno-) tonsillectomies between January 2018 and November 2021: the Bee Pain Free (Child and Adolescent Health Service Human Research Ethics Committee Approval CAHS HREC RGS0000003325, Australia and New Zealand Clinical Trials Registry ACTRN12619001385134), EMPHASIS (CAHS RGS0000000296; ACTRN12617001379303), and OSATS2 (CAHS RGS0000000014; ACTRN12615001037594)

AI-use disclosure

AI has not been used in the preparation of this manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

David Sommerfield: Conceptualization, Funding acquisition, Investigation, Methodology, Writing — original draft, Writing — review & editing. **Bojana Stepanovic:** Investigation, Writing — original draft, Writing — review & editing. **Daisy Evans:** Conceptualization, Data curation, Formal analysis, Methodology, Writing — review & editing. **Andy Jeon:** Investigation, Writing — review & editing. **Anne Louise de Barros Garioud:** Investigation, Writing — review & editing. **Aine Sommerfield:** Conceptualization, Funding acquisition, Project administration, Writing — review & editing. **Neil Hauser:** Conceptualization, Funding acquisition, Methodology, Writing — review & editing. **R. Nazim Khan:** Conceptualization, Formal analysis, Supervision, Writing — review & editing. **Britta S. von Ungern-Sternberg:** Conceptualization, Funding acquisition, Methodology, Investigation, Project administration, Resources, Supervision, Writing — review & editing.

Acknowledgments

We thank the children and their families who participated in the Bee Pain Free, EMPHASIS, and OSATS2 studies for their participation and engagement with these trials.

Funding

BSvUS is part funded by the Stan Perron Charitable Foundation and through a National Health and Medical Research Council Investigator Grant (2009322). Bee Pain Free was funded through a WA Health Research Translation Project 2019 and supported by the Cooperative Research Centre for Honey Bee Products. EMPHASIS was funded through a Society of Paediatric Anaesthesia Australia and New Zealand (SPANZA) Research Grant 2018. OSATS2 was funded via a Telethon Research Fellowship 2018 from Telethon Channel 7.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2026.844792.

Editor

Liana Azi

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Impact of named caps on anesthesia and intensive care team performance: a randomized simulation study

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Received 21 September 2025; accepted 26 July 2026
Available online 4 September 2026

KEYWORDS
Anesthesiology;
Clinical Competence;
Communication;
Patient care team;
Patient safety;
Simulation training

Abstract

Background: Effective communication and team non-technical skills are key points for patient safety in anesthesia and intensive care. Named caps have been proposed as a strategy to enhance team efficiency. However, evidence regarding their impact on objectively assessed team performance remains limited.

Methods: We conducted a prospective, single center, randomized, and experimental study in a high-fidelity simulation setting (SimHU, Nîmes). Anesthesia and intensive care residents, young doctors, and paramedics participated in simulated critical scenarios, alternating between sessions with and without named caps. The primary objective was to compare team performance, assessed by observers using the TEAM score. The secondary objectives were self-reported measures of entitativity, team cohesion and inclusion of self in the group.

Results: A total of 112 participants across 32 simulation sessions were included, which were assessed by 19 instructors. TEAM scores were significantly higher in the named cap group compared to the control group: the 44 points TEAM score (37 ± 7 vs. 33 ± 7; $p = 0.026$) and the total score (45 ± 8 vs. 40 ± 9; $p = 0.020$). Subjective perceptions of entitativity and team cohesion did not differ significantly.

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https://doi.org/10.1016/j.bjane.2026.844812

Conclusions: Named caps were associated with higher team performance in a simulated environment. Their impact on perceived team cohesion and entitativity was not statistically significant under simulation conditions. Further research in clinical settings is needed to determine whether named caps improve teamwork and patient safety.

Introduction

Teams working in anesthesia and intensive care units are complex interprofessional systems composed of individuals with diverse professions, personalities, and skills, all working toward the shared goal of managing critically ill patients through effective collaboration. Directed communication is a major determinant of patient safety during perioperative and critical care management.[1] In the operating room, structured intraoperative briefing involving surgeons, anesthetists and nurses has been associated with reductions in mortality, unplanned reoperations, and hospital length of stay.[2] Beyond interprofessional communication, rapid and accurate identification of team members may also contribute to quality of care. Facilitated identification may promote task coordination and communication among professionals,[3] thereby enhancing teamwork and collective adaptive capacity. Wearing named caps represents a simple and safe strategy to facilitate identification, particularly in operating rooms where conventional identification badges are often concealed by sterile gowns and personal protective equipment. Named caps may therefore support teamwork and improve adaptive team functioning.[4,5]

According to the teamwork model proposed by Gregory et al.,[6] team adaptation depends on the implementation of key performance mediators. Their Input-Mediator-Output (IMO) model highlights that team performance depends on the quality of inputs – such as role clarity, team composition, and context – as well as on effective communication,[7] which supports leadership, shared situational awareness,[8] and other teamwork-related mediators. Haller et al.[9] demonstrated a direct association between poor communication and adverse events, while Schmutz et al.,[10] in a meta-analysis, emphasized the relationship between teamwork processes and clinical performance.

The implementation of the WHO Surgical Safety Checklist has contributed to reducing perioperative morbidity and mortality.[11] As part of this process, team members introduce their names and roles before surgery. Nevertheless, recall of team member identity remains poor, with rates of approximately 30%.[12,13] Tools facilitating identification have been shown to optimize team functioning.[14] The social media initiative #theatercapchallenge, launched in 2018, popularized the use of named caps in operating rooms worldwide. Wearing caps displaying names and professional roles has been associated with improved perceived teamwork and communication,[12] particularly by facilitating directed communication.[15] However, no previous study has objectively evaluated the association between named caps and externally assessed team performance. Assessment of team performance remains challenging. One widely used approach relies on validated behavioral assessment tools evaluating non-technical skills.[16] The TEAM score assesses key domains such as leadership, teamwork, and task management, all of which are known to influence patient safety and quality of care.[17] Beyond observable behavioral processes, team performance may also be influenced by affective and cognitive dimensions such as group entitativity. Introduced by Campbell,[18] entitativity refers to the extent to which a collection of individuals is perceived as a coherent and unified group. It can be measured using dedicated scales such as the GEM scale[19,20] and includes dimensions such as group cohesion (sense of closeness among group members) and self-inclusion within the group (individual's perceived place within the group).[21] We hypothesized that named caps could positively influence these perceptions.

The objective of this study was therefore to assess the association between the use of named caps during simulation sessions and team performance, as well as participants' perceptions of team dynamics, including entitativity, group cohesion, and self-group inclusion.

Methods

Study design and population

This was a prospective, single-center, randomized, controlled, and simulation study. The study protocol was approved by the Nimes University Hospital Institutional Review Board (IRB n° 24-12-03).

Inclusion criteria: All medical and paramedical professionals participating in the simulation sessions as part of their continuing professional development were eligible for inclusion. All participants were adults. This included third- and fifth-year anesthesiology and intensive care residents (recently graduated physicians), as well as ICU and operating theatre nurses and nursing assistants. All participants were affiliated with the Montpellier-Nîmes University Hospital (France) and provided written informed consent before participation. Providing consent was mandatory for study participation and constituted the sole exclusion criterion.

Before the simulation sessions, participants attended a general briefing, visited the simulation rooms, and were familiarized with the equipment, particularly the mannequins. Confidentiality, psychological safety, and the right to make mistakes were emphasized. After completion of the scenario and study procedures, participants received a structured debriefing (Fig. 1).

The instructor group consisted of 19 anesthesiologists and healthcare professionals specifically trained in simulation-based medical education and non-technical skills assessment. The simulation scenarios were developed in accordance with the guidelines of the French Society for Simulation in Healthcare (SOFRASIMS) and consisted of standardized high-fidelity scenarios. Four distinct clinical

	Scenario 1 Day 1	Scenario 1 Day 2	Scenario 2 Day 1	Scenario 2 Day 2	Scenario 3 Day 1	Scenario 3 Day 2	Scenario 4 Day 1	Scenario 4 Day 2
Session1	Group 1 Leader 1A	Group 5 Leader 5A	Group 2 Leader 2A	Group 6 Leader 6A	Group 3 Leader 3A	Group 7 Leader 7A	Group 4 Leader 4A	Group 8 Leader 8A
Session 2	Group 2 Leader 2B	Group 6 Leader 6B			Group 4 Leader 4B	Group 8 Leader 8B	Group 3 Leader 3B	Group 7 Leader 7B
Session 3			Group 1 Leader 1B	Group 5 Leader 5B				
Session 4	Group 3 Leader 3B	Group 7 Leader 7A	Group 4 Leader 4A	Group 8 Leader 8A				
Session 5	Group 4 Leader 4B	Group 8 Leader 8B			Group 1 Leader 1A	Group 5 Leader 5A	Group 2 Leader 2A	Group 6 Leader 6A
Session 6			Group 3 Leader 3B	Group 7 Leader 7B	Group 2 Leader 2B	Group 6 Leader 6B	Group 1 Leader 1B	Group 5 Leader 5B

Figure 1 **Session schedule:** Each leader participated in sessions with (orange) or without (grey) named caps. Each scenario was conducted both with and without named caps. Similarly, each team member participated in sessions with (orange) or without (grey) named caps. Sessions 1, 2, and 3 were conducted in the morning, whereas sessions 4, 5, and 6 took place in the afternoon.

situations were simulated: cardiogenic shock requiring extracorporeal life support, trauma, obstetric anesthesia, and pediatric anesthesia.

Simulation teams consisted of three or four members, including a medical team leader, a resident, a specialized nurse, and, for intensive care scenarios, a nursing assistant. All scenarios had previously been tested at our simulation center (SIMHU, Nîmes University Hospital) using similar team compositions.

Randomization

Each session was randomized in a 1:1 ratio to either the "named cap" group or the control group. Randomization was stratified by training day and by team. Consequently, each team participated in an equal number of named cap and control sessions. Team composition and scenario order were determined independently and blinded to the randomization process, while the randomization list was prepared by S.G.

Eight groups were constituted, each composed of two leaders and two paramedical teams (one for anesthesia sessions and one for intensive care sessions). Each leader worked with both paramedical teams, and each paramedical team worked with both leaders. Each group participated in four scenarios (Fig. 1).

Interventions and data collection

The intervention consisted of wearing an identification cap displaying the participant's name and profession during the named-cap sessions (Material Supplementary Picture 1). In the control sessions, participants either wore plain caps or remained bareheaded. Each team member participated in an equal number of sessions with and without named caps. Sessions without named caps constituted the control group, whereas sessions with named caps constituted the intervention group.

Data were collected at the end of each session, immediately before the debriefing (Fig. 2). This included TEAM score assessments completed by instructors and team members, as well as participant questionnaires. The TEAM score is a 44 points scale composed of 12 items assessing different domains of non-technical skills, including leadership, teamwork, and task management. In addition, an overall performance 10-point score was recorded.

The observers were not informed of the study objectives. TEAM score assessment was presented as an educational performance evaluation tool intended to support the debriefing process.

Outcomes

The primary outcome was collective performance, assessed using the TEAM score by simulation instructors, with a focus on non-technical skills.

Secondary outcomes evaluated participants' perceptions of the team using three self-reported scales: Entitativity, from 0 to 28;[19] Self-inclusion in the group, using the IOS scale (0—7);[21] Team cohesion, assessed with an adapted version of the GEM scale (0—7).[20]

Statistical analysis

No a priori sample size calculation was performed. The sample size was determined pragmatically based on the number of simulation sessions conducted during the study period, and on a previous similar study.[22] Descriptive statistics were used to summarize participant characteristics, using means and standard deviations or medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Gaussian distribution of variables was checked graphically. Analyses were performed on complete case basis.

The primary unit of analysis was the simulation session, as TEAM scores were assessed at the session level. We used mixed-effects linear regression models to assess the effect of cap versus control group because the outcome (TEAM score) is continuous and the data have a hierarchical structure, with potential non-independence of observations due to repeated participation of teams across simulation sessions. These models included random intercepts to account

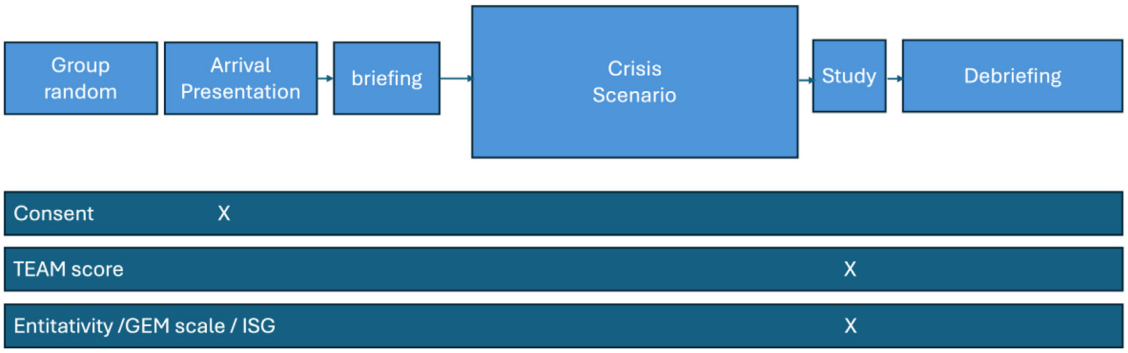

Figure 2 **Study design:** The TEAM score is a validated score for the assessment of non-technical skills.[17] The GEM scale is a validated scale to evaluate the entitativity of a group.[20] ISG, Inclusion of Self in the Group.

for clustering of observations. No additional covariates were included in the model.

Specifically, a random intercept was included for the team, allowing us to account for within-cluster correlation arising from repeated participation across sessions. Instructor-level clustering was not explicitly modeled given the completely anonymous nature of data collection, as no linkage of individuals between sessions could be performed. Model assumptions were assessed by visual inspection of residuals, including Q—Q plots for normality and plots of residuals versus fitted values to evaluate homoscedasticity.

A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using R software (version 4.0.0; R Core Team, Vienna, Austria).

Results

In January 2025, a total of 112 participants were included, completing 32 simulation sessions involving 15 different leaders. The 19 instructors provided 58 assessments, with 29 assessments in each group, corresponding to one or two evaluations per session. There were two missing data points in the control group and one in the named cap group.

The simulation sessions were conducted over two days. Eight groups were formed, each comprising two leaders, one ICU team, and one anesthesia team. Each team participated in two sessions led by different leaders – one session with named caps and one without. Similarly, each leader participated in one session with caps (intervention group) and one without caps (control group).

In one group, given only a single leader was available, the same leader conducted all four scenarios, including two sessions with caps and two without.

The questionnaire response rate was 107/112 (95.5%). The characteristics of the study population are detailed in Table 1.

Primary outcome: team performance assessment (Fig. 3)

The TEAM score was significantly higher in the intervention group than in the control group, both for the 44-point TEAM score (37 ± 7 vs. 33 ± 7; $p = 0.026$) and for the total score (45 ± 8 vs. 40 ± 9; $p = 0.020$). Detailed results are presented in Table 2.

A similar difference was observed for the overall performance rating (7.9 ± 1.54 vs. 6.86 ± 1.76; $p = 0.035$) and for the teamwork domain (23.7 ± 4.3 vs. 21.1 ± 4.4; $p = 0.031$) (Fig. 3).

No statistically significant differences were observed in the leadership ($p = 0.12$) or task management ($p = 0.13$) domains.

Secondary outcomes: participants' perceptions of team functioning

No significant differences were observed between the control and intervention groups regarding perceived entitativity (difference = 0.35 [-1.4; 2.1]; $p = 0.8$), group cohesion (difference = 0.38 [-0.11; 0.87]; $p = 0.4$), or self-inclusion in the group (difference = 0.21 [-0.19; 0.61]; $p = 0.2$) (Table 3).

Table 1 Characteristics of the study population: ECLS, Extracorporeal Life Support.

Characteristic	Named-cap Group (n = 16)	Control Group (n = 16)
Scenarios		
Extracorporeal Life Support (ECLS), n	4	4
Traumatology, n	4	4
Pediatrics, n	4	4
Obstetrics, n	4	4
Participants		
Young doctors, n	15	15
Women/Men	7/8	7/8
Third-year residents, n	17	17
Women/Men	9/8	9/8
Nurses, n	16	16
Women/Men	10/6	10/6
Nursing assistants, n	9	9
Women/Men	5/4	5/4
Completed questionnaires	52	55
Young doctors, n	16	16
Third-year residents, n	16	16
Nurses, n	16	16
Nursing assistants, n	4	7
Instructors' assessments	29	29

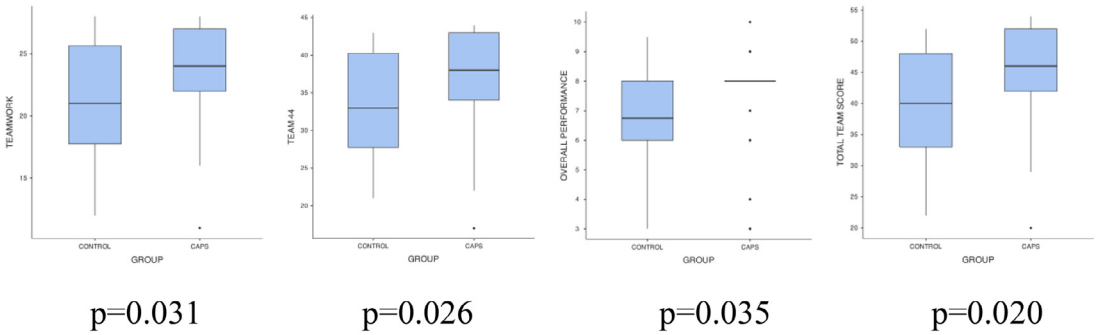

Figure 3 Comparison for TEAM score between the named-cap and control groups:[17,23] Boxplots show the median, interquartile range (Q1−Q3), minimum, and maximum values. Points represent outliers.

Discussion

Optimizing teamwork is a major goal for critical care teams and a key mediator of quality of care and patient safety. Healthcare simulation enables teams to be tested and assessed in different contexts. The scenarios used involve critical situations requiring optimal teamwork and are therefore particularly suitable for analyzing team performance. In this study, using named caps was associated with higher team performance, as assessed by the TEAM score, a validated measure of non-technical skills performance.[17,23] Although no difference was observed in the leadership domain, significantly higher scores were observed for both teamwork and overall performance. The TEAM score has excellent inter-rater reliability and good construct validity, allowing discrimination between

Table 2 Team performance assessment by instructors using the TEAM score.[17,23]

Assessment	Overall (n = 58)	Control group (n = 29)	Named-cap Group (n = 29)	Mean Difference [95% CI]	p-value
Leadership				0.79 [-0.04, 1.6]	p = 0.12
Mean ± SD	6.37 ± 1.60	5.98 ± 1.67	6.77 ± 1.44		
Median (Q1−Q3)	6.0 (5.5−8.0)	6.0 (4.0−8.0)	7.0 (6.0−8.0)		
Range	3.0−8.0	3.0−8.0	3.0−8.0		
Missing data, n	1	0	1		
Teamwork				2.6 [0.26, 4.9]	p = 0.031
Mean ± SD	22.5 ± 4.5	21.1 ± 4.4	23.7 ± 4.3		
Median (Q1−Q3)	23.0 (19.5−26.0)	21.0 (17.8−25.6)	24.0 (22.0−27.0)		
Range	11.0−28.0	12.0−28.0	11.0−28.0		
Missing data, n	1	1	0		
Task Management				0.64 [-0.12, 1.4]	p = 0.13
Mean ± SD	6.25 ± 1.46	5.93 ± 1.58	6.57 ± 1.28		
Median (Q1−Q3)	7.0 (5.0−7.0)	6.0 (5.0−7.0)	7.0 (6.0−8.0)		
Range	2.0−8.0	2.0−8.0	3.0−8.0		
Missing data, n	0	0	0		
TEAM Score (/44)				4.2 [0.60, 7.9]	p = 0.026
Mean ± SD	35 ± 7	33 ± 7	37 ± 7		
Median (Q1−Q3)	35 (31−41)	33 (28−40)	38 (34−43)		
Range	17−44	21−43	17−44		
Missing data, n	2	1	1		
Overall Performance (/10)				1.0 [0.16, 1.9]	p = 0.035
Mean ± SD	7.39 ± 1.72	6.86 ± 1.76	7.90 ± 1.54		
Median (Q1−Q3)	8.0 (6.0−8.0)	6.75 (6.0−8.0)	8.0 (8.0−8.0)		
Range	3.0−10.0	3.0−9.5	3.0−10.0		
Missing data, n	1	1	0		
Total TEAM Score (/54)				5.4 [0.85, 9.9]	p = 0.020
Mean ± SD	43 ± 9	40 ± 9	45 ± 8		
Median (Q1−Q3)	44 (38−51)	40 (33−48)	46 (42−52)		
Range	20−54	24−52	20−54		
Missing data, n	3	2	1		

Table 3 Participants' perceptions of team functioning according to study group: Entitativity, inclusion of self in the group, and group cohesion scores are presented as mean ± standard deviation and median (Q1–Q3).

	Overall (n = 107)	Control Group (n = 55)	Named-cap Group (n = 52)	Mean Difference [95% CI]	p-value
Entitativity Score				0.35 [-1.4, 2.1]	p = 0.8
Mean ± SD	22 ± 5	21 ± 4	22 ± 5		
Median (Q1–Q3)	23 (19–25)	22 (18–24)	23 (20–25)		
Inclusion of Self in the Group (ISG)				0.21 [-0.19, 0.61]	p = 0.4
Mean ± SD	6 ± 1	6 ± 1	6 ± 1		
Median (Q1–Q3)	6 (5–6)	6 (5–6)	6 (5–6)		
Group Cohesion (GEM)				0.38 [-0.11, 0.87]	p = 0.2
Mean ± SD	5 ± 1	5 ± 1	5 ± 1		
Median (Q1–Q3)	5 (4–6)	5 (4–6)	6 (5–6)		

different levels of expertise among simulation teams.[17,23,24] As hypothesized, our findings suggest that named caps may be associated with higher observed team performance in this simulation setting and with the ability of groups to function effectively as teams. Previous studies have suggested an association between wearing named caps and improved communication or self-assessed teamwork efficiency,[12,25] and the present study was designed to provide objective and quantitative support for this hypothesis. This represents an important step forward because teamwork assessment tools have only been validated for external evaluation, and limited data are available regarding their use for self-assessment and their validity in this context.[26,27] Even though participants introduced themselves and their roles before each simulation session, prior studies have shown that name retention remains poor and that tools facilitating identification can further improve direct communication and role recognition.[4,5,12] Theoretical models of teamwork, particularly the model proposed by Gregory et al.,[6] emphasize that communication not only directly influences performance but also facilitates the activation of other performance mediators. Improved performance could therefore be expected through enhanced identification and communication. However, the healthcare simulation context – characterized by small groups, general pre-briefing, and individual session debriefing within a psychologically safe environment – already facilitates identification and may optimize performance.[2,28] In most cases, each role is assigned to a single individual, and reduced role ambiguity is a well-established factor promoting teamwork and performance, as observed in the sports setting.[29] Identification may be particularly important in inexperienced, newly formed teams, such as those included in our study, especially in critical situations. The magnitude of the effect observed here, corresponding to an approximately 10% increase in TEAM score, is consistent with previous studies using TEAM,[30] as well as with simulation studies evaluating the impact of positive communication,[22] cognitive aids use,[31] and structured role allocation on team performance during critical situations.[28]

Self-assessment by team members did not reveal any effect of named caps on group entitativity, which was high in both groups, or on its two components: inclusion within the group and group cohesion. The concept of entitativity, introduced by Campbell,[18] refers to the extent to which a collection of individuals is perceived as a unified entity or a "real" group. Groups with high entitativity are considered as having greater capacity for collective action.[32] Key drivers of entitativity include a shared goal, interdependence, effective communication, and shared values such as benevolence and security,[33] all of which are fostered by the healthcare simulation environment. Conversely, factors such as the duration of group membership and the intensity of shared group experience also enhance group identity. These were absent in our transient teams, which had no previous or future collective experience. Entitativity is linked to two dimensions in social psychology: group cohesion and individual self-inclusion within the group. These two dimensions were assessed separately in our study and were high in both groups, with no significant differences. Although this separation remains debatable, as these metrics are traditionally assessed together, our findings suggest that respondents meaningfully differentiated between these two dimensions, supporting the validity of this analytical approach. Assessing these dimensions in clinical settings within established care teams could, therefore, be of interest.

Self-inclusion reflects individuals' perceived position within the group. In our study, participants reported a high level of integration, although the study design and limited sample size did not allow further analyses according to professional category. Nevertheless, the higher performance observed in teams wearing named caps was not associated with different perceptions among team members, reinforcing the hypothesis that named caps may improve non-technical skills rather than reflecting differences in team commitment.

Moreover, the implementation of performance mediators, as measured by the TEAM score, may lead to performance adaptation through affective, behavioral, and cognitive mechanisms. In this study, we hypothesized that the intervention would promote affective effects, including a sense of cohesion, entitativity, and inclusion within the team, but it was unable to demonstrate such effects. However, the simulation context, particularly repeated exposure to critical situations, may have reinforced these feelings in both groups, resulting in a ceiling effect. Another explanation is that performance may involve other affective

mechanisms not assessed here, such as stress, as well as behavioral and cognitive mechanisms. For example, named caps promote the use of first names,[4] which may help capture attention.[34,35] Finally, implicit processes, such as interpersonal synchrony or co-representation, may also be involved,[36,37] but could not be assessed in this study.

The main limitation of our study was that participants could not be fully blinded to the intervention, as wearing named caps inherently revealed the study objective. Although all instructors were qualified assessors, and their primary role was educational, the presence of caps may have influenced their perception, leading to observer bias. Observer-based assessments of team performance remain subjective and prone to bias and noise.[38] This raises broader questions regarding the evaluation of team performance by external observers, particularly when the intervention is highly visible, as in the present study. Automated systems, such as those already integrated into operating room "black boxes" and using artificial intelligence, may help standardize and streamline such evaluations in the future.[39] Experimental studies also suggest that analysis of inter-individual synchrony, including inter-brain, behavioral, and physiological synchrony, could contribute to the assessment of team performance.[37] Team performance assessment remains a major challenge for understanding the determinants of performance and helping teams improve, particularly through simulation training. The teams studied were formed specifically for the simulation training session. Therefore, it was not possible to measure the prior level of knowledge within each team. Similarly, prior team experience with the clinical situations presented in the scenarios was not assessed. These factors may represent potential confounders. However, since all leaders were junior physicians with no prior experience acting as senior physicians within those paramedical teams, and since they had the same level of academic training, the impact of these confounders may have been limited. The simulated setting also ensured optimal support and psychological safety. Therefore, our results are valid only within such an environment, which specifically allows the use of first names in communication. Named caps should be considered as part of a broader human factor strategy.[40] In this study, cap tolerance was not specifically assessed. However, no discomfort or adverse effects were reported.

The effect of named caps may also have been enhanced by the fact that teams were newly formed and leaders relatively inexperienced. Their impact should therefore be assessed in other circumstances, particularly among experienced teams and in ecological clinical settings. Conversely, the teams studied here were small and composed of members with clearly defined roles. Future studies could test this intervention in larger teams with higher turnover.

We also could not account for clustering at the instructor level, which may have introduced residual dependence in our analyses. Finally, the absence of an a priori sample size calculation is a limitation, as the study may have been underpowered to detect small but clinically relevant differences.

Overall, these findings highlight the need for larger-scale evaluation under real-life conditions, such as in operating rooms and/or intensive care units, to confirm the impact of improved identification on team performance in both critical and routine situations, and to determine whether this intervention can ultimately improve patient outcomes.

Conclusion

Facilitated identification of team members using named caps was associated with higher observed team performance in this simulation study. No statistically significant effect was observed on perceived group cohesion, self-inclusion, or group entitativity. These findings should be validated in larger real-life clinical settings before conclusions can be drawn regarding patient outcomes.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistance disclosure

The authors used ChatGPT (OpenAI) to improve the English language and readability of the manuscript. The authors reviewed and edited the output and take full responsibility for the content.

Study registry

Not applicable — Not a clinical study.

Authors' contributions

Study design: SG, LB, CR, GB. Recruitment of participants: SG, CR, LMa. Randomization: SG. Data acquisition: SG, CR, LMa. Interpretation of results: SG, CR, CS. Statistical analyses: CS. Writing of the first version of the article: SG, CR, LMu. Critical revision of the article for intellectual content: GB, LB, PC, NB, SB. Final approval of the version to be published and acceptance of responsibility for all aspects of the work, thus ensuring that questions related to the accuracy or integrity of any part of the work are properly investigated and resolved: All authors.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844812.

Editor

Liana Azi

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Relative hematocrit declines at the time of transfusion and postoperative outcomes after coronary artery bypass grafting: a retrospective cohort study

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Received 27 October 2025; accepted 26 July 2026
Available online 7 August 2026

KEYWORDS
Blood transfusion;
Cardiac surgical procedures;
Coronary artery bypass;
Hematocrit;
Postoperative complications

Abstract

Background: Despite advances in patient blood management, the optimal hemoglobin threshold for Red Blood Cell (RBC) transfusion remains controversial. This observational study evaluated the association between the relative decline in Hematocrit (HCT) at the time of transfusion and postoperative outcomes in patients undergoing Coronary Artery Bypass Graft (CABG) surgery.

Methods: We conducted a retrospective cohort study of 629 patients who underwent CABG and received a transfusion at Tehran Heart Center Hospital, Iran, between March 2018 and December 2021. Based on the relative hematocrit reduction at the time of transfusion, patients were divided into two groups: Group A (≥ 40% change) and Group B (< 40% change). Early postoperative outcomes were compared between groups. Primary outcomes included mortality, hospital length of stay, intensive care unit length of stay, and intubation time. The composite secondary outcome comprised postoperative infection, renal failure, tamponade, and reoperation due to bleeding.

Results: There were no significant differences in primary outcomes, except hospital length of stay ($p = 0.02$). However, after adjustment for potential confounders, this difference was no longer significant ($p = 0.32$). Composite secondary outcomes were comparable between the two groups, with no significant difference observed ($p = 0.85$).

Conclusion: In patients undergoing CABG surgery, this study did not identify a significant difference in early postoperative outcomes between two transfused patient groups stratified by a 40% change in HCT. Further prospective studies are needed to determine clinical relevance of

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https://doi.org/10.1016/j.bjane.2026.844813

relative hematocrit decline at the time of transfusion as a potential adjunct to conventional transfusion triggers.

THC institutional review board: IR.TUMS.THC.REC.1402.070.

Introduction

After extensive research in the field of blood transfusion, the ideal trigger for transfusion has still not been clearly defined. Some believe that blood transfusion based solely on a fixed threshold is not clinically desirable. Although restrictive transfusion strategies are widely endorsed, they may overlook the unique needs of certain patient populations.[1] Therefore, some studies have suggested using the percentage change in hemoglobin levels instead of a fixed threshold. In fact, some studies in surgical patients showed that if the percentage change in hemoglobin was 50% or greater, the risk of complications, such as ischemic events, was higher.[2] The primary objective of transfusion is improving oxygenation. Beyond general physiological responses to anemia, such as increased iron absorption, distribution, and mobilization, and organ adaptation, cellular adaptation plays a key role in chronic anemia.[3] Alongside other cellular adaptation mechanisms in response to cellular hypoxemia, such as alterations in transcription, translation, and post-translational pathways, and modifications to metabolite-dependent activity, mitochondrial adaptation plays a major role in both acute and chronic cellular hypoxia.[4] These regulatory mechanisms vary with the chronicity and severity of changes, thereby affecting cells' ability to respond adequately to various levels of stress, including hypoxia caused by anemia. Hypoxia-Induced Factor-1 (HIF-1α) is one example of an acute cellular adaptation that increases oxygen delivery and decreases oxygen consumption, whereas in chronic settings, HIF-2α is a major determinant of organ adaptation.[5]

Logically, a patient with a preoperative hemoglobin level of 17 g.dL^{-1} would require significant blood loss to reach a postoperative level of 7 g.dL^{-1}. It does not seem prudent to assume that another patient with a baseline hemoglobin of 10 g.dL^{-1} would experience the same stress responses to anemia with a current post-bleeding hemoglobin of 7 g.dL^{-1}. Several studies have evaluated clinical outcomes according to the magnitude of hemoglobin decline from baseline at the time of transfusion. In the study by Spolverato G and colleagues, mortality and ischemia-specific complications in patients undergoing major gastrointestinal surgery, as well as relative hemoglobin reduction, were evaluated. Patients with a relative hemoglobin reduction of $>$ 50% whose nadir hemoglobin remained $\geq$ 7 g.dL^{-1} were more likely to develop postoperative complications.[6] Another study reported that among transfused patients, outcomes worsened with a substantial hemoglobin decline, regardless of nadir hemoglobin levels.[7] These findings raise questions regarding reliance solely on an absolute hematocrit threshold, prompting us to perform a retrospective study evaluating whether the percentage change in hematocrit observed at the time of transfusion was associated with early postoperative outcomes. The percentage change in Hematocrit (ΔHCT) was calculated using the formula: $\Delta HCT = [\,(baseline\ HCT - transfusion - time\ HCT)\ /\ baseline\ HCT] \times 100$.

We assessed whether postoperative outcomes differed by the magnitude of hematocrit decline at the time of packed red blood cell transfusion.

Methods

This single-center, retrospective, observational study compared the early postoperative outcomes of patients who received packed red blood cells (PRBCs) and were subsequently divided into two groups based on the relative change in hematocrit levels (ΔHCT). The study population included all adult patients who underwent coronary artery bypass grafting (CABG) at Tehran Heart Center between March 2018 and December 2021, had documented pre- and postoperative hematocrit changes, and received blood transfusions. Data were collected by evaluating patients' medical records, the hospital database, and intensive care unit (ICU) flow sheets. A total of 1,800 patient records were screened, of which 629 patients were included in the final analysis. The exclusion criteria included: age less than 18, history of pathological bleeding in the three previous months, recent myocardial infarction (MI), history of receiving blood in the past two weeks, blood dyscrasias, renal failure, and hepatic failure. All CABG procedures were included, including those combined with other cardiac operations (e.g., valve repair). Cases without CABG were excluded. To maintain analytical rigor and enhance patient homogeneity, off-pump patients were excluded from this study. This exclusion was required due to the limited number of cases in this subgroup and the significant confounding effects of cardiopulmonary bypass (CPB) on critical physiological parameters, including hemodynamics, coagulation, and hematocrit, which influence transfusion requirements. The primary objective was to evaluate early postoperative outcomes, including ICU length of stay, intubation time, 30-day in-hospital mortality, and total hospital length of stay. Secondary outcomes included the incidence of postoperative infections, atrial fibrillation (AF), acute kidney injury (AKI), postoperative encephalopathy, and reoperation due to bleeding. For the assessment of secondary outcomes, a composite endpoint was defined as the occurrence of postoperative infection, cardiac tamponade, reoperation due to bleeding, or renal failure.

Infections included pneumonia, mediastinitis, and wound infections. Acute kidney injury was defined according to the acute kidney injury network (AKIN) criteria as an abrupt decline in renal function occurring within 48 hours after surgery, identified by an increase in serum creatinine of $\geq$ 0.3 mg.dL^{-1}, an increase to $\geq$ 1.5 times the baseline serum

creatinine, or a urine output of < 0.5 mL.kg^{-1}.h^{-1} for more than 6 hours.[8] Postoperative renal failure was defined as renal failure diagnosed during the index hospitalization by the consulting nephrologist. In patients with suspected postoperative renal dysfunction, a nephrology consultation was requested, and the diagnosis was established based on the consulting nephrologist's clinical assessment. Postoperative encephalopathy was diagnosed by the hospital neurologist and encompassed patients who experienced delirium, coma, or seizures at any point during the three-day postoperative period. Figure 1 presents the patient flow diagram, categorized according to the established patient selection criteria.

Anesthesia was performed according to the standard protocol for CABG, and extubation was performed based on the established ICU protocol. The administration of PRBCs is typically guided by absolute hemoglobin levels and follows our hospital's protocol, which aligns with the transfusion practices of most centers – generally based on hemoglobin thresholds of 7–8 g.dL^{-1}. However, this guideline was occasionally overridden at the discretion of the surgical team, depending on specific intraoperative or clinical considerations. We identified patients who received transfusions and subsequently evaluated the change in hematocrit at the time of transfusion. The baseline hematocrit was defined as the mean hematocrit within the 3 days preceding surgery. The hematocrit value at the time of PRBC transfusion – whether in the operating room or the intensive care unit – was documented as the transfusion-time HCT. The percentage change in hematocrit (ΔHCT) was calculated using the formula: $(\Delta HCT) = [(baseline\ HCT - transfusion - time\ HCT) / baseline\ HCT] \times 100$.

Based on the magnitude of the ΔHCT, we categorized the patients into two groups. The first group consisted of patients whose hematocrit had declined by 40% or more at the time of transfusion (group A), while the second group included those whose hematocrit had declined less than 40% at the time of transfusion (group B).

This study was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences (Approval n° IR.TUMS.THC.REC.1402.070). Written informed consent for the use of clinical data was obtained as part of the routine admission process at Tehran Heart Center.

Statistical analysis

Continuous variables are presented as mean ± SD (Standard Deviation) or median (Interquartile Range boundaries; IQR). Categorical variables are expressed as frequencies and percentages. Quantitative variables were compared using the Student's *t*-test or the Mann–Whitney *U*-test, as

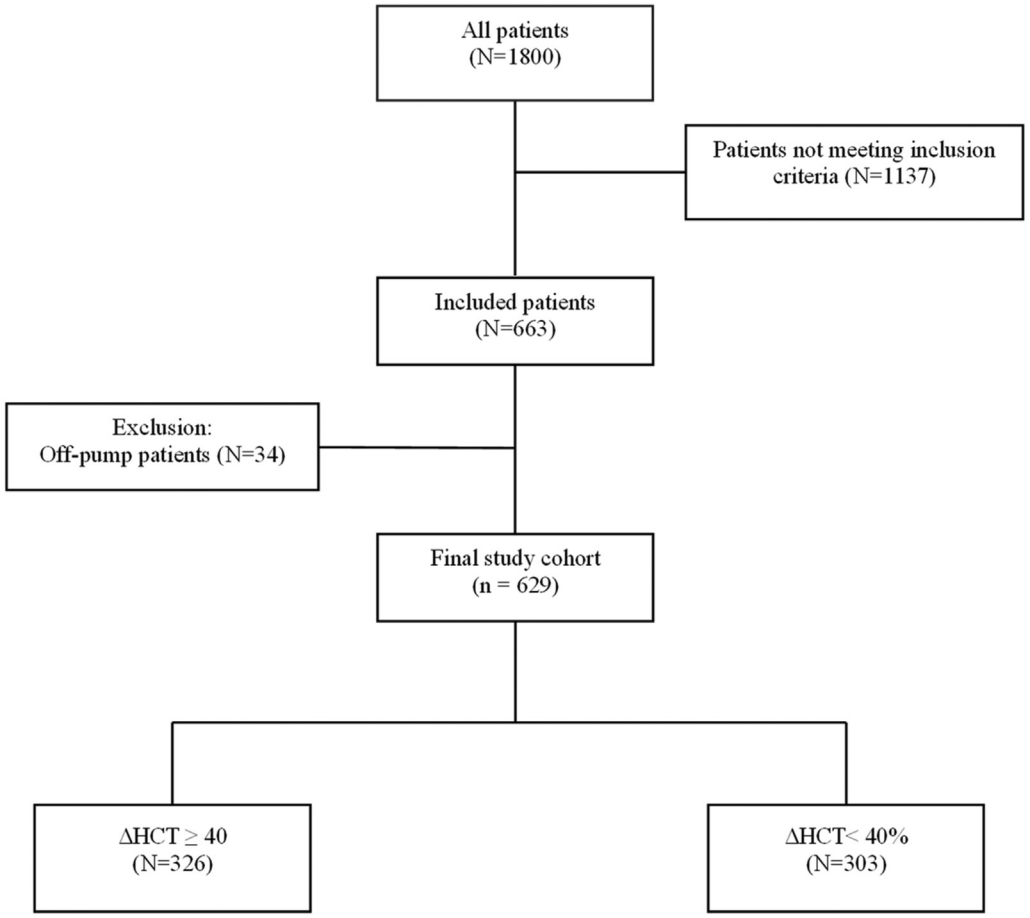

Figure 1 Flow diagram of patient selection for the study. Among 1,800 reviewed records, 663 coronary artery bypass grafting (CABG) patients met the inclusion criteria. After excluding 34 off-pump cases, 629 patients were included in the final analysis, with 326 experiencing relative hematocrit declines ≥ 40% and 303 with relative hematocrit declines < 40%.

appropriate. In contrast, categorical variables were compared using the Chi-Squared or Fisher's exact test as required. A restricted cubic spline (RCS) with three knots at the 25th, 50th, and 75th percentiles was employed to determine the turning point of the ΔHCT variable that changed its effect on secondary composite outcomes. Based on the optimum proposed cut-off, the ΔHCT variable was divided into two levels (Fig. 2 and Supplementary Fig. S1). Linear and logistic regression models, adjusted for literature-identified confounders using stabilized inverse probability weighting (sIPW), were applied to analyze ΔHCT levels. The standardized mean difference (SMD) served as the metric for assessing covariate balance through graphical representation in Supplementary Figure S2. The association between the exposure and primary outcomes [hospital length of stay (hospital LOS), intensive care unit length of stay (ICU LOS), and intubation time] and a composite secondary outcome (postoperative infection, renal failure, reoperation due to surgical bleeding, and tamponade) was examined using linear and logistic regression analyses. These models were adjusted using stabilized inverse probability weighting. The results were presented as beta and odds ratio (OR), with 95% confidence intervals (95% CIs). To evaluate the robustness of the findings to missing data, a sensitivity analysis was performed, and the results are presented in Supplementary Table S1. All p-values were two−tailed, and a $p < 0.05$ was considered to be statistically significant. Analyses were conducted using the R Statistical language (version 4.3.0; R Core Team, 2023)[9] using the packages Weight It (version 1.4.0; Greifer N, 2025)[10] and plotRCS (version 0.1.5; Huo R, 2025).[11,12]

Results

Initially, 1800 CABG patients were screened, of whom 663 met the study inclusion criteria. After the exclusion of 34 patients due to off-pump surgical procedures, 629 patients comprised the final analytical cohort. Within this cohort, 48% had a ΔHCT below 40%, whereas 52% had a ΔHCT of 40% or greater at the time of transfusion. The patient cohort exhibited a mean age of 63 ± 8 years. Baseline hematocrit levels averaged 38.8% ± 4.4%, while the mean HCT at the point of transfusion was 23.2% ± 3.4%. While age did not differ significantly between the groups (p = 0.60), statistically significant variations were evident in the latter two parameters. The average change in Hematocrit (ΔHCT) across the patient population was 15.65% ± 3.8%. Table 1 illustrates the basic characteristics and clinical data of the two groups.

Baseline creatinine levels, body mass index (BMI), hypertension, and EuroSCORE II exhibited no statistically significant differences between the two groups (p = 0.79, p = 0.82, p = 0.06, and p = 0.06, respectively). Conversely, significant inter-group variations were observed in gender distribution, history of chronic obstructive pulmonary disease (COPD), ejection fraction, and incidence of diabetes mellitus ($p \leq 0.01$, 0.02, 0.01, and 0.02, respectively). Isolated CABG was the most common surgical procedure, accounting for 78.7% of all cases. The remaining patients underwent combined procedures, including aortic valve replacement (AVR), mitral valve repair, or tricuspid valve repair in conjunction with CABG. There was no statistically significant difference between the two groups with respect to the distribution of surgical types (p = 0.78). The majority of procedures were

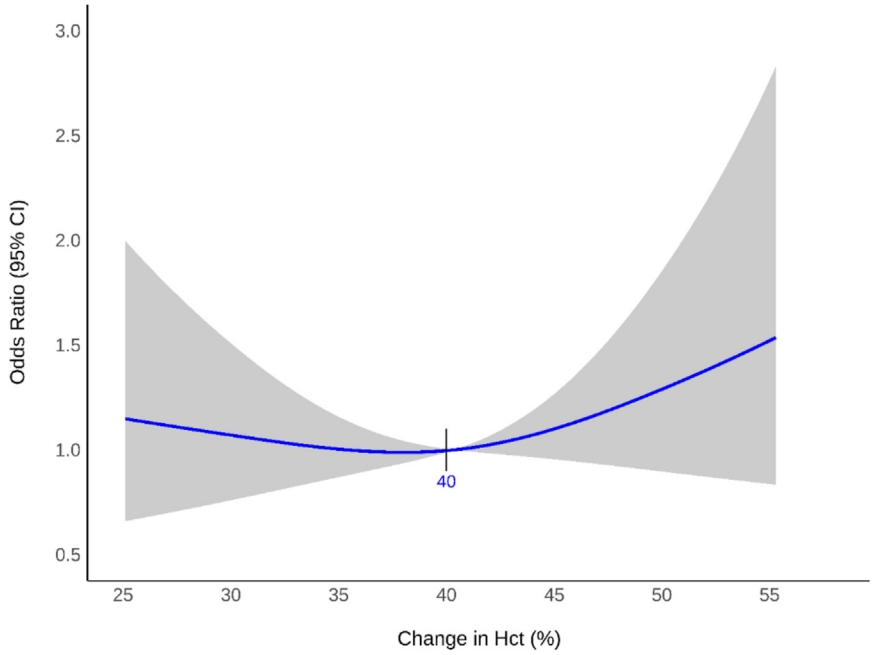

Figure 2 Restricted cubic spline (RCS) analysis showing the association between change in hematocrit (ΔHCT) and the odds of the study outcome. The solid blue line represents the estimated odds ratio, and the shaded area indicates the 95% confidence interval. A ΔHCT of 40% was used as the reference value (OR = 1.0). The spline suggests a nonlinear relationship, with increasing odds at higher ΔHCT levels.

Table 1 Baseline characteristics and perioperative variables according to relative HCT reduction in CABG patients.

Variables	Overall (n = 629)[a]	Relative HCT reduction		p-value[b]
		≥ 40 (n = 326)[a]	< 40 (n = 303)[a]	
Age, years	63.58 ± 8.51	63.83 ± 8.37	63.31 ± 8.66	0.604
Male sex, n (%)	377 (59.9%)	164 (50.3%)	213 (70.3%)	< 0.001
BMI, $kg.m^{-2}$	27.47 ± 4.20	27.43 ± 4.22	27.51 ± 4.19	0.823
Diabetes Mellitus, n (%)	313 (49.8%)	177 (54.3%)	136 (44.9%)	0.018
Hypertension, n (%)	436 (69.3%)	237 (72.7%)	199 (65.7%)	0.056
Hyperlipidemia, n (%)	358 (56.9%)	199 (61.0%)	159 (52.5%)	0.030
Smoking, n (%)	233 (37.0%)	111 (34.0%)	122 (40.3%)	0.107
COPD, n (%)	36 (5.7%)	12 (3.7%)	24 (7.9%)	0.022
Pre-op HCT, %	38.86 ± 4.42	39.74 ± 4.22	37.92 ± 4.44	< 0.001
HCT before transfusion, %	23.21 ± 3.40	21.53 ± 2.72	25.02 ± 3.12	< 0.001
LVEF, %	50.0 (40.0, 55.0)	50.0 (40.0, 55.0)	45.0 (40.0, 55.0)	0.007
Baseline Creatinine, $mg.dL^{-1}$	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	0.794
EuroSCORE II	1.8 (1.2, 4.4)	2.0 (1.2, 5.1)	1.6 (1.1, 4.2)	0.056
CAG, n (%)				0.849
SVD	38 (6.0%)	20 (6.1%)	18 (5.9%)	
2VD	88 (14.0%)	48 (14.7%)	40 (13.2%)	
3VD	503 (80.0%)	258 (79.1%)	245 (80.9%)	
Operation, n (%)				0.785
Isolated CABG	495 (78.7%)	253 (77.6%)	242 (79.9%)	
CABG + Valve	55 (8.7%)	30 (9.2%)	25 (8.3%)	
CABG + Valve + Other	39 (6.2%)	23 (7.1%)	16 (5.3%)	
CABG + Other	40 (6.4%)	20 (6.1%)	20 (6.6%)	
Surgery, n (%)				0.384
Elective	583 (92.7%)	305 (93.6%)	278 (91.7%)	
Emergent/urgent	46 (7.3%)	21 (6.4%)	25 (8.3%)	
Cross Clamp Time, min	46.5 (37.0, 60.0)	47.0 (38.0, 60.0)	45.0 (36.0, 60.0)	0.223
CPB Time, min	83.0 (65.0, 110.0)	86.0 (70.0, 110.0)	80.0 (63.0, 110.0)	0.115
Post-op Systolic BP mean, mmHg[c]	134.1 ± 15.7	136.2 ± 15.2	137.2 ± 12	0.120
Post-op Diastolic BP, mmHg[c]	78 ± 4.3	79 ± 5.4	75 ± 8.3	0.113
Heparin, I/U	29,765.50 ± 7,557.60	29,438.65 ± 7,125.31	30,117.16 ± 7,993.60	0.213
Protamine, mg	350.0 (300.0, 400.0)	350.0 (300.0, 400.0)	400.0 (300.0, 400.0)	0.191
Transamin, gr	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.649
Blood drainage, mL[d]	450.0 (350.0, 550.0)	450.0 (350.0, 550.0)	450.0 (350.0, 550.0)	0.427
PRBC, units[e]	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	< 0.001
Urine in OR, mL	1,800 (1,500.0, 2,300.0)	1,900.0 (1,500.0, 2,300.0)	1,800.0 (1,350.0, 2,200.0)	0.035
Urine in ICU, mL[f]	3,521.54 ± 934.20	3,463.49 ± 901.13	3,583.99 ± 966.11	0.171

[a] n (%); Mean ± SD; median (IQR).
[b] p-values calculated using an Independent Sample *t*-test for continuous variables and Pearson's Chi-Square test or Fisher's exact test for categorical variables.
[c] Mean blood pressure in postoperative time until extubation.
[d] Mean chest drainage in first 24 hours in the ICU.
[e] The units of PRBC transfused during ICU and OR.
[f] The amount of urine in first 24 hours in the ICU.
BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAG, coronary angiography; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; Cr, creatinine; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HCT, hematocrit; ICU, intensive care unit; LVEF, left ventricular ejection fraction; OR, operating room; PRBC, packed red blood cells; Pre-op, preoperative; Post-op, postoperative; SVD, single-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease.

performed electively (92.7%), with no significant intergroup difference in elective case frequency (p = 0.38).

No statistically significant differences were observed between the two study groups regarding cardiopulmonary bypass duration and aortic cross-clamp time (p = 0.11 and p = 0.22, respectively). The median number of PRBC units transfused in the operating room and during the initial six days of ICU stay was 2.0 (1.0–2.0). Despite a statistically significant difference in the number of PRBC units transfused between the two groups (p < 0.01), the observed variation

Table 2 Comparison of postoperative clinical outcomes between patients with relative HCT reduction ≥ 40% and < 40%.

Variables	Overall (n = 629)[a]	Relative HCT Reduction		p-value[b]
		≥ 40 (n = 326)[a]	< 40 (n = 303)[a]	
Primary outcomes				
Mortality, n (%)	8 (1.3%)	6 (1.8%)	2 (0.7%)	0.289
LOS ICU, hours	65.0 (26.0, 97.0)	66.0 (40.0, 109.0)	64.0 (24.0, 96.0)	0.236
Intubation time, hours	16.0 (12.0, 22.0)	16.0 (12.0, 22.0)	16.0 (12.0, 22.0)	0.214
LOS hospital, days	7.0 (6.0, 10.0)	7.0 (6.0, 10.0)	7.0 (5.0, 9.0)	0.025
Secondary outcomes				
Composite, n (%)	164 (26.1%)	84 (25.8%)	80 (26.4%)	0.856
Infection, n (%)	53 (8.4%)	25 (7.7%)	28 (9.2%)	0.478
Renal failure[c], n (%)	12 (1.9%)	9 (2.8%)	3 (1.0%)	0.105
Reoperation, n (%)	113 (18.0%)	60 (18.4%)	53 (17.5%)	0.766
Tamponade, n (%)	38 (6.0%)	16 (4.9%)	22 (7.3%)	0.216
Post-op AF, n (%)	126 (20.0%)	73 (22.4%)	53 (17.5%)	0.125
Post-op encephalopathy, n (%)	57 (9.1%)	28 (8.6%)	29 (9.6%)	0.668
Post-op AKI, n (%)	65 (10.3%)	34 (10.4%)	31 (10.2%)	0.935
Post-op Creatinine, $mg.dL^{-1}$	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	0.598
Relative HCT reduction (ΔHCT), %	40.02 ± 7.74	45.73 ± 4.60	33.87 ± 5.36	< 0.001
Absolute HCT change, percentage points	-15.65 ± 3.86	-18.20 ± 2.89	-12.90 ± 2.71	< 0.001
Absolute pre- to post-transfusion HCT difference, percentage points	5.22 ± 3.33	6.35 ± 3.36	4.00 ± 2.84	< 0.001
Post-transfusion HCT, %	28.43 ± 3.32	27.88 ± 3.34	29.02 ± 3.20	< 0.001

[a] n (%); Mean ± SD; median (IQR).
[b] p-values calculated using an independent *t*-test for continuous variables and Chi-Square test or Fisher's exact test for categorical variables.
[c] Two patients in the Relative HCT reduction ≥ 40% group received dialysis.
Absolute HCT change, absolute difference (percentage points) between baseline and transfusion-time HCT; HCT, hematocrit; ICU, intensive care unit, Intubation time: time from ICU admission to tracheal tube extubation; LOS hospital, time from surgery to hospital discharge, LOS ICU, length of stay in intensive care unit, Post-op, postoperative, Post-op AF, postoperative atrial fibrillation, Post-op AKI: postoperative acute kidney injury, Post-op HCT, postoperative hematocrit, Relative HCT Reduction: relative reduction (%) in HCT from baseline to transfusion time.

does not appear to be clinically meaningful. There were no statistically significant differences between the groups regarding intraoperative or postoperative bleeding within the ICU (p = 0.43). Furthermore, comparative analyses revealed no significant differences in the administered doses of protamine (p = 0.19), tranexamic acid (p = 0.65), or heparin (p = 0.21) between the cohorts (Table 1).

Table 2 details patients' outcomes in each group. With respect to the primary outcomes, neither intubation time nor ICU length of stay differed significantly between the groups (p = 0.21 and p = 0.24, respectively). Although hospital length of stay was initially longer in the ΔHCT ≥ 40% group (p = 0.02), the difference was no longer statistically significant after adjustment. Conversely, although the 30-day mortality difference did not reach statistical significance (p = 0.29), it may nonetheless be of clinical importance. Consistent with these findings, adjusted regression analyses showed no significant association between ΔHCT and any of the primary outcomes (Table 3).

The composite secondary outcomes did not differ significantly between the two groups in unadjusted analysis (p = 0.82). Consistent with these findings, adjusted logistic

Table 3 Unadjusted and inverse probability weighting-adjusted linear regression analyses of the association between relative hematocrit reduction and primary outcomes.

Outcomes	Unadjusted			Adjusted		
	Beta	95% CI	p-value	Beta	95% CI	p-value
Log hospital LOS	-0.08	-0.15, -0.01	**0.018**	-0.06	-0.13, 0.00	0.320
Log ICU LOS	-0.11	-0.23, 0.02	0.099	-0.06	-0.18, 0.07	0.392
Intubation time	-3.1	-9.4, 3.3	0.342	-0.82	-6.6, 4.9	0.779

Thirty-day mortality was not included in the regression analyses because only 8 deaths occurred during the study period
CI, confidence interval; ICU, intensive care unit; Intubation time, time from ICU admission to tracheal tube extubation; Log, logarithm; LOS hospital, length of stay in hospital; LOS ICU, length of stay in intensive care unit.

Table 4 Unadjusted and IPW-adjusted associations between relative hematocrit reduction and secondary postoperative outcomes.

Outcome	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Composite of secondary outcomes	0.96	0.67, 1.38	0.825	1.07	0.74, 1.55	0.707

Composite secondary outcomes include the incidence of infections, tamponade, renal failure, and reoperation due to bleeding.
CI, confidence interval; IPW, inverse probability weighting; OR, odds ratio.

regression analysis demonstrated no significant association between ΔHCT and the composite secondary outcome (OR = 1.07; 95% CI 0.74−1.55; p = 0.71) (Table 4).

Additionally, the incidence of postoperative encephalopathy, post-op AF and AKI did not differ significantly between the two study groups (p = 0.67, p = 0.12, and p = 0.93, respectively).

Sensitivity analyses yielded findings consistent with the primary analyses, with no significant associations observed between ΔHCT and hospital length of stay, ICU length of stay, or intubation time (Supplementary Table S1).

Discussion

In this retrospective, single-center, and observational study, patients who received packed red blood cells were analyzed. They were subsequently categorized into two groups based on the relative change in hematocrit (ΔHCT) to compare early postoperative outcomes. Using a restricted cubic spline model, a 40% decline in hematocrit was identified as a potential threshold, dividing patients into two cohorts: those with ΔHCT < 40% and those with ΔHCT ≥ 40. Our findings showed no statistically significant differences in key early postoperative outcomes, including duration of intubation, ICU stay, and overall hospital stay, between the two groups after adjustment for confounders. Secondary outcomes, including the incidence of AF, infection, reoperation due to surgical bleeding, and elevated serum creatinine, were also similar across cohorts. These results suggest that the magnitude of ΔHCT observed at the time of transfusion was not independently associated with early postoperative outcomes, and that other factors, such as surgical complexity, hemodynamic management, and comorbidities, may play a more dominant role in determining outcomes.

The concept of relative hematocrit change remains elusive and appears to be grounded in the notion that both gross and subcellular adaptations can substantially influence physiological responses to changes in hematocrit. Anemia results in a form of hypoxemia known as anemic hypoxia. In response to hypoxia, the body activates several physiological adaptations to preserve tissue oxygenation, including an increase in cardiac output and an enhanced oxygen extraction ratio by organ tissues. In contrast, it is believed that there are no comparable compensatory mechanisms – such as the ability to significantly elevate hemoglobin concentration or oxygen saturation beyond normal physiological limits – to mitigate the reduction in oxygen delivery associated with decreased cardiac output.[1]

Most recent studies have focused on comparing restrictive versus liberal blood transfusion strategies and their impact on clinical outcomes. Although findings have been somewhat inconsistent, the overall body of evidence tends to support restrictive transfusion approaches, given their association with lower mortality rates and reduced postoperative complications.[13-15] However, relatively very few studies have evaluated the impact of changes in hemoglobin levels (ΔHb) on postoperative outcomes in surgical patients. In a retrospective study, Spolverato G and colleagues reviewed mortality, ischemia-specific complications, and ΔHb in patients undergoing major gastrointestinal (GI) surgery.[6] In contrast to our study, they found that a decrease in Hb ≥ 50%, independent of whether the nadir Hb remained ≥ 7 $g.dL^{-1}$, was significantly associated with increased postoperative morbidity, including ischemic events. Their findings highlighted that the magnitude of relative hemoglobin decline, not just the absolute nadir hemoglobin value, plays a critical role in predicting adverse outcomes, suggesting that current transfusion practices that rely solely on nadir thresholds may overlook clinically relevant anemia-related risks.

Another study investigated the relationship between the degree of hemoglobin decline and clinical outcomes – specifically mortality and the need for urgent therapeutic endoscopy – in patients with GI bleeding.[7] Nadir hemoglobin alone was not significantly associated with adverse outcomes such as in-hospital mortality or urgent endoscopy. However, a relative hemoglobin drop of 30%−40%, combined with moderate nadir Hb levels (8−9 $g.dL^{-1}$), was associated with higher adverse event rates. Among transfused patients, outcomes were worse when hemoglobin drop was substantial, regardless of nadir hemoglobin levels.

In a recent retrospective observational study, Lei Du and colleagues examined the association between varying degrees of hemoglobin change (ΔHb) and early postoperative outcomes in patients undergoing cardiac surgery.[16] The study demonstrated a non-linear association between ΔHb and adverse outcomes, modulated by preoperative anemia status and transfusion volume. In anemic patients, a ΔHb ≥ 30% was linked to increased risk; in non-anemic patients, risk increased at ΔHb ≥ 50%. Transfusion effects varied: in non-anemic patients, small transfusions were protective at high ΔHb, while large transfusions increased risk regardless of ΔHb. In anemic patients, small transfusions reduced risk at lower ΔHb, but only high-volume transfusions increased risk at higher ΔHb. While the majority of patients in that study underwent valvular surgery, our investigation focused primarily on individuals undergoing CABG, with most receiving isolated CABG procedures. It is reasonable to assume that more complex surgical procedures and greater blood loss necessitate higher transfusion volumes, which may predispose to hemodynamic instability and adverse outcomes. By narrowing our cohort to a less complex surgical population with reduced procedural complexity and heterogeneity, we

aimed to minimize confounding. We hypothesize that, in routine clinical practice, most transfusions are not massive. Supporting this, most randomized controlled trials (RCTs) evaluating transfusion thresholds have employed a one-unit transfusion strategy and demonstrated no additional benefit from administering more blood than necessary.[17] Furthermore, to eliminate the confounding influence of cardiopulmonary bypass, patients undergoing off-pump procedures were excluded from the analysis. In addition, we used the EuroSCORE II system to enhance group comparability by accounting for overall clinical status and comorbidities, including variables such as ejection fraction, surgical risk, pulmonary hypertension, and other key factors.[18]

The Lei et al. study categorized patients based on the presence of preexisting anemia but did not clearly differentiate between its chronic and acute forms. In contrast, we excluded individuals with recent transfusions or ongoing anemia treatment, thereby minimizing confounding factors that could influence physiological responses. Transfusion thresholds were similar between studies, with red blood cell transfusions initiated at an HCT of $\leq$ 21% during cardiopulmonary bypass and 21%–24% throughout the perioperative period. While the prior investigation examined hemoglobin declines of 30% and 50%, we employed a 40% ΔHCT threshold for cohort stratification. Intergroup differences in the earlier study were primarily observed in the context of significant drops in hemoglobin and increased transfusion rates. However, critical clinical data such as bleeding volume, hemodynamic stability, and surgical complexity were not reported, despite their relevance to transfusion requirements. On the contrary, our study found no significant differences in blood drainage volumes in the operating room or ICU between Group A and Group B (p = 0.427). Moreover, perioperative PRBC usage in our study was lower than the one reported in the previous study.

Our primary outcomes included early postoperative parameters – duration of intubation, ICU stay, and total hospital stay – which were not evaluated in the earlier study. After adjustment for ΔHCT, no significant differences were observed between groups for these outcomes. Secondary endpoints such as incidence of AF, reoperation due to surgical bleeding, postoperative encephalopathy, and AKI were likewise comparable. These findings suggest that postoperative outcomes may be more closely associated with factors reflecting clinical severity, particularly hypoxemic hypoxia secondary to circulatory dysfunction, than with the magnitude of hematocrit decline observed at the time of transfusion.

Although the observed difference in mortality (1.8% vs. 0.7%) did not reach statistical significance (p = 0.29), the absolute difference may still be clinically meaningful and warrants further investigation in larger, well-powered studies.

Study limitations

This study has several limitations that should be acknowledged. First, its retrospective design inherently limits the ability to establish causality and is subject to potential selection bias and unmeasured confounding. Second, the relatively small sample size and single-center setting may limit the generalizability of our findings; this limitation is partly due to the specific focus of our study population, as we included only patients who underwent CABG, although a very small subset also underwent combined valve procedures. Third, the database lacked certain physiologic parameters – such as arterial blood gas indices and central or mixed venous oxygen saturation ($ScvO_2$/SvO_2) – which would have enabled a more comprehensive assessment of tissue oxygenation and oxygen extraction ratios, providing further insight.

Conclusion

In this retrospective cohort study, postoperative outcomes did not significantly differ between patients with a relative hematocrit decline of $\geq$ 40% and those with a decline of $<$ 40% at the time of transfusion. A relative decline of 40% or more at the time of transfusion was not associated with differences in early outcomes after adjustment. These findings indicate that the degree of hematocrit reduction preceding transfusion may not be independently associated with early postoperative recovery following CABG. Rather, factors such as surgical complexity, perioperative hemodynamic stability, and underlying patient comorbidities may play a more pivotal role in determining clinical outcomes. These observations underscore the need for further studies to determine the clinical relevance of a relative hematocrit decline at the time of transfusion and its relationship to postoperative outcomes following CABG.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI assistance disclosure

The authors did not use generative artificial intelligence in the preparation of this manuscript.

Authors' contributions

Fatemeh Sadr: Data collection; Literature review.
Arash Jalali: Statistical analysis; Interpretation of results, and critical revision of the manuscript.
Ahmad Vakili-Basir: Statistical analysis; Visualization; Designed and created all tables and figures.
Mina Pashang: Data collection.
Khosro Barkhordari: Conceptualization; Supervision; Project administration; Manuscript revision.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844813.

Associate Editor

Luís Vicente Garcia

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Brazilian Journal of Anesthesiology 2026;76(5): 844817

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Enhanced recovery after surgery for cesarean delivery: a systematic review and meta-analysis of randomized trials with trial sequential analysis

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Received 18 February 2026; accepted 31 July 2026
Available online 14 August 2026

KEYWORDS
Cesarean section;
Enhanced recovery after surgery;
Length of stay;
Maternal health;
Perioperative care;
Postoperative care

Abstract
Background: Enhanced Recovery After Surgery (ERAS) protocols have improved perioperative care across multiple surgical specialties. In obstetrics, ERAS pathways for cesarean delivery have been increasingly adopted; however, their comparative effectiveness versus standard care remains uncertain. Therefore, we conducted a systematic review and meta-analysis with trial sequential analysis to compare ERAS protocols with standard perioperative care in cesarean delivery.
Methods: We systematically searched MEDLINE, Embase, Web of Science, and Cochrane databases for Randomized Clinical Trials (RCTs) comparing ERAS and standard care in parturient undergoing cesarean delivery. Statistical analyses were performed using R software (version 4.2.2). We conducted subgroup analyses based on cesarean category (elective vs. emergency) and national income level. A Trial Sequential Analysis (TSA) was also performed.
Results: We included 13 RCTs comprising 1,809 parturient. ERAS was associated with a significant reduction in hospital Length of Stay (LOS) compared with standard care (MD = -17.05 hours, 95% CI -25.08 to -9.02 hours, I^2 = 98.2%, n = 1,128, $p < 0.01$), with similar effects across elective

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https://doi.org/10.1016/j.bjane.2026.844817

and emergency cesarean deliveries. Greater reductions were observed in low- and middle-income countries, whereas no significant difference was identified in upper-middle-income settings, albeit formal subgroup test was not significant. ERAS was associated with lower postoperative pain at 24 and 48 hours, reduced wound infection, and higher maternal satisfaction, with no differences in readmission and postoperative nausea and vomiting. TSA suggested that the accrued sample size was adequate for hospital LOS; however, this should be interpreted cautiously given the substantial clinical and methodological heterogeneity.
Conclusion: This systematic review and meta-analysis suggest that ERAS protocols may be associated with reduced hospital stay and improved maternal recovery after cesarean delivery.

Introduction

Surgical care is a fundamental component of global health, as almost one-third of the global disease burden requires surgical intervention.[1] The demand for surgical procedures, particularly cesarean deliveries, has risen substantially worldwide. By 2030, cesarean deliveries are projected to account for about 30% of all births, totaling approximately 38 million procedures. Most of these procedures are expected to occur in Low- and Middle-Income Countries (LMIC), compared with 11.7% in high-income countries.[2] This trend raises public health concerns, as cesarean delivery outcomes are a key indicator of maternal health system performance.

Enhanced Recovery After Surgery (ERAS) protocols are perioperative care pathways designed to improve patient experience and surgical care. First introduced in 2001, ERAS has become widely adopted across multiple surgical specialties and has consistently demonstrated benefits in safety and clinical outcomes.[3] In obstetrics, Enhanced Recovery After Cesarean (ERAC) pathways were introduced in 2013,[4] and updated evidence-based perioperative care recommendations for cesarean delivery were published by the ERAS Society in 2025.[4-6] Standardization of these pathways has been associated with improvements in quality of care, patient safety, and cost-effectiveness in healthcare systems.[1] Therefore, ERAS may represent a potential strategy to strengthen surgical systems in resource-limited settings without requiring substantial additional resources. Although high-quality evidence remains limited, several ERAS components appear to be low risk, demonstrate favorable clinical outcomes, and align with maternal preferences, particularly due to their association with shorter hospital stays.[7]

Previous meta-analyses have assessed the impact of ERAS implementation on cesarean delivery.[8-11] However, their conclusions were limited by the inclusion of observational studies, the absence of stratification by country income level and cesarean type, and the lack of Trial Sequential Analysis (TSA) and Minimal Clinically Important Difference (MCID) assessments. Therefore, we conducted an updated systematic review and meta-analysis of Randomized Controlled Trials (RCTs) with TSA to compare ERAS protocols with standard perioperative care in patients undergoing cesarean delivery.

Methods

This study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions recommendations.[12,13] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under identifier CRD420251152114 on October 23, 2025.

Eligibility criteria

We included studies that met the following eligibility criteria: 1) Were RCTs, 2) Compared ERAS protocols with standard care, and 3) Included patients aged 18 years or older undergoing cesarean delivery. We excluded studies with overlapping populations, studies not written in English, and studies assessing modified or isolated pharmacological or nutritional interventions that did not constitute a comprehensive ERAS protocol.

Study selection and data extraction

We systematically searched the MEDLINE, Cochrane, Embase, and Web of Science databases on November 17, 2025. A detailed search strategy is available in Supplementary Table S1. Study selection was performed by two independent reviewers using the Rayyan software (rayyan.ai), with disagreements resolved by consensus with a third author. The reference lists of included articles were manually screened to identify additional studies ("backward snowballing" technique). After selection, data were recorded using a piloted, standardized extraction form. Two authors independently extracted quantitative variables, and three authors extracted qualitative data. Data were extracted for the following variables: author and year of publication; country; sample size in the ERAS and standard care groups; gestational age; type of cesarean section (elective, emergency, or mixed); definitions of outcomes; and details of the ERAS protocol implemented across the preoperative, intraoperative, and postoperative phases. For each RCT, information on primary and secondary outcomes was retrieved, along with measures of variance, timing of assessment, and scale type. Discrepancies were resolved by another author when necessary. If clarification was required, the corresponding authors of the original studies were contacted by email.

Quality and risk of bias assessment

The Cochrane Risk of Bias 2 (RoB 2) tool[14] was utilized to assess the studies' risk of bias based on the five domains:

1) Randomization process, 2) Deviations from intended intervention, 3) Missing outcome data, 4) Measurement of the outcome, and 5) Selection of the reported result. Risk of bias figures were generated using the RobVis visualization tool.[15]

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence and the level of recommendation for each outcome in the meta-analysis.[16] This tool accounts for several domains, including risk of bias, imprecision, inconsistency (heterogeneity), indirectness, and publication bias. Any disagreements regarding the certainty of evidence and risk of bias assessments were resolved by a third author.

Endpoints and subgroup analysis

The primary endpoint was hospital Length Of Stay (LOS), defined as the duration of postoperative hospitalization until discharge or fulfillment of institutional discharge criteria. Secondary endpoints were postoperative pain scores at 24 and 48 hours (at rest), Postoperative Nausea and Vomiting (PONV), readmission rate, wound (surgical site) infection, and overall maternal satisfaction. Definitions for all endpoints are provided in Supplementary Table S2.

Maternal satisfaction was assessed using standardized tools, including a five-point Likert scale, the Patient Satisfaction with Nursing Care Quality Questionnaire (PSNCQQ), and the Visual Analogue Scale (VAS). Additionally, studies that used non-standardized methods based on a 0—10 numeric rating were also included. For quantitative synthesis, all satisfaction scores were rescaled to a common 0—10 scale; higher scores indicated greater satisfaction. Postoperative pain scores were also standardized using the 0—10 VAS (0 = no pain; 10 = worst pain).

We conducted two prespecified subgroup analyses. Trials were stratified by national income level as LMIC versus Upper-Middle-Income Countries (UMIC) based on the World Bank classification for the trial's country.[17] Studies were also stratified by cesarean category as emergency, elective, or mixed cohorts.

Data synthesis and analysis

Continuous outcomes were synthesized using the inverse variance method with a random-effects model and are reported as Mean Differences (MD) or Standardized Mean Differences (SMD) with 95% Confidence Intervals (95% CI). Dichotomous outcomes were pooled using the Mantel-Haenszel method with a random-effects model and are presented as Risk Ratios (RR) with 95% CI. Forest plots were generated to illustrate treatment effects. Outcomes reported by at least three trials including more than 100 participants were quantitatively synthesized, whereas the remaining outcomes were described qualitatively. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. When studies reported medians with interquartile ranges or minimum and maximum values, data were converted following Wan's method.[18]

Heterogeneity was assessed using Cochran's *Q*-test and the I^2 statistic, with the DerSimonian-Laird method. The degree of heterogeneity was interpreted using the Cochrane thresholds: low (0 to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%).[13] All statistical analyses were performed under a random-effects model using the R software (packages *meta*, *metafor*, and *dmetar*).[19,20]

We performed TSA for the primary endpoint to assess the risks of type I and type II errors and estimate the required sample size for the outcome. We set the thresholds for the *Z*-score with the O'Brien-Fleming alpha spending function and applied a random-effects model using the DerSimonian-Laird method, which allowed a type I error of 0.05 and a type II error of 0.20 (power = 80%). All calculations were performed using software TSA 0.9.[21]

To explore inconsistencies among studies, we also performed a sensitivity analysis by omitting each study individually for each endpoint (leave-one-out technique) using a random-effects model.

Interpretation of results

Pain scores were interpreted using a broader perspective, as our analysis included emergency cesarean sections. As there is no MCID specific to post-cesarean pain assessment, we referred to evidence from gynecologic surgery, specifically hysterectomy, as the closest comparable context. In this context, we considered evidence suggesting that a change of approximately 1.5 on the VAS typically reflects the MCID in acute postoperative pain.[22]

For maternal satisfaction, a 0.7—1.1-point difference on a 0—10 patient VAS, equivalent to a 7—11 mm change on the original 100-mm scale, was considered the MCID threshold for a perceptible improvement in satisfaction.[23]

Results

Study selection and characteristics

Our search strategy identified 1,199 studies, of which 13 trials including 1,809 parturient ultimately met the inclusion criteria.[24-36] The full details of the study selection process are shown in Figure 1. A list of excluded studies and reasons for exclusion is available in Supplementary Table S3. Three trials were rated low risk of bias[25,27,28] while the remaining ten were assessed as having some concerns.[24,26,29-36] Overall, the included trials were judged to present a moderate risk of bias (Supplementary Fig. S1).

Among the 13 included RCTs, 908 parturient (50.19%) were allocated to the ERAS group. Nine studies enrolled parturient undergoing elective cesarean delivery (n = 1,207),[26-31,33-35] three enrolled parturient undergoing emergency cesarean delivery (n = 402),[24,25,32] and one included both elective and emergency cases (n = 200).[36] Eight trials (61.54%) were conducted in LMIC.[24,25,27-29,31,32,34] ERAS protocols varied across studies, and details of the intervention and study characteristics are summarized in Table 1.

Main endpoint — Hospital length of stay

Eight RCTs, including 1,128 participants, reported hospital LOS.[24,25,29,32-36] ERAS protocols significantly shortened LOS compared with standard care (MD = -17.05 hours, 95% CI

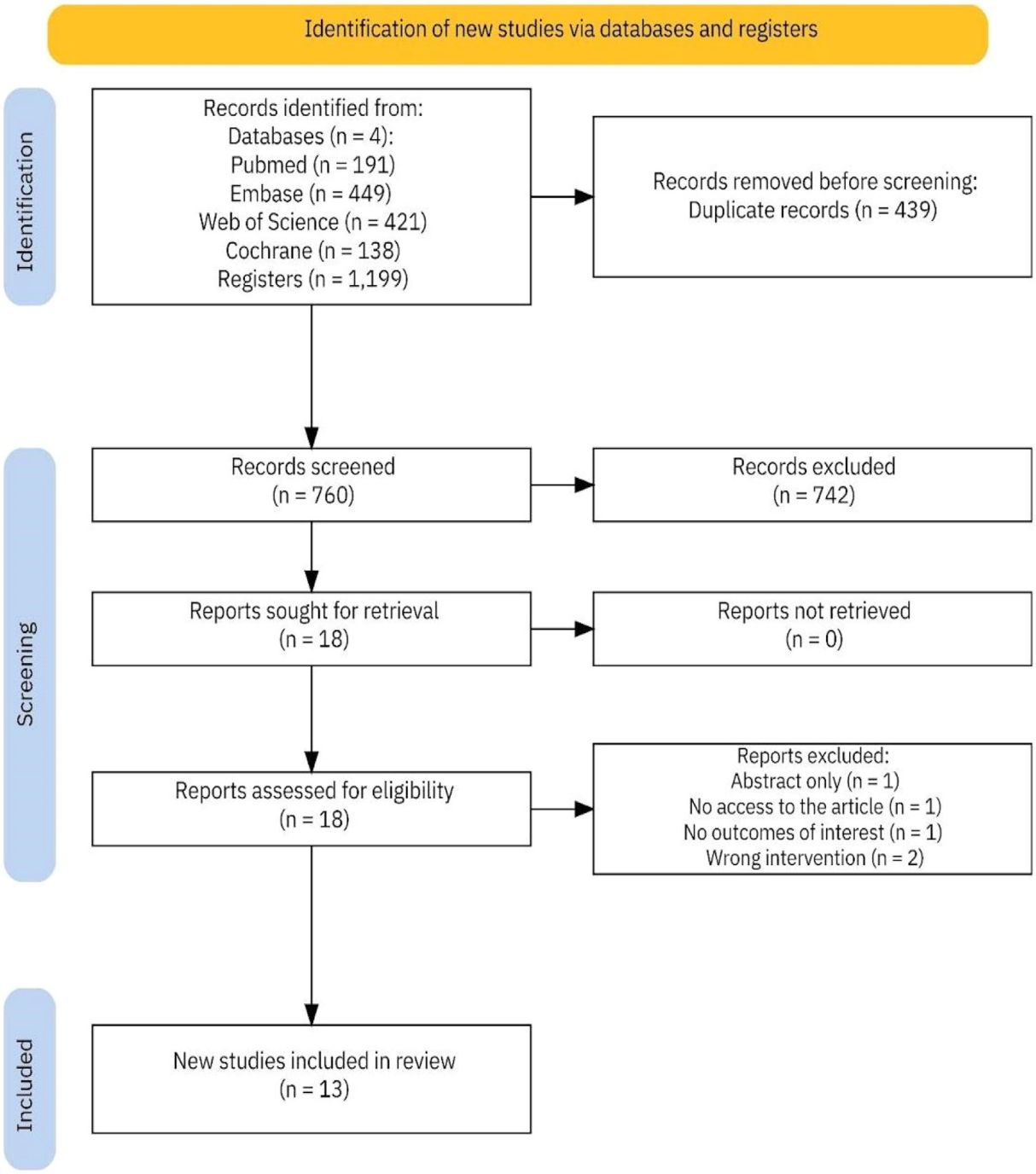

Figure 1 PRISMA flow diagram of study screening and selection.

-25.08 to -9.02 hours, I^2 = 98.2%, p < 0.01, Fig. 2). Due to the high heterogeneity observed in the pooled analysis, a leave-one-out sensitivity analysis showed that the pooled effect remained stable after sequential exclusion of each study (Supplementary Fig. S2). We rated the overall GRADE certainty of the evidence as very low, primarily because of inconsistency and risk of bias (Supplementary Table S4).

Subgroup analysis by cesarean type indicated a reduction in hospital LOS across all categories (emergency: MD = -29.04 hours, 95% CI -42.34 to -15.74, I^2 = 93.6%, p < 0.01; elective: MD = -5.9-hours, 95% CI -11.2 to -0.6 hours, I^2 = 94%, p = 0.03; Supplementary Fig. S3), with significant differences between subgroups (p < 0.01). When stratified by country income level, ERAS significantly reduced hospital LOS in LMIC (MD = -22.81 hours, 95% CI -33.66 to -11.96 hours, I^2 = 96.5%, p < 0.01, Fig. 2).[24,25,29,32,34] In contrast, no statistically significant difference was observed in UMIC (MD = -8.21 hours, 95% CI -23.78 to 7.35 hours, I^2 = 99.1%, p = 0.3; Fig. 2),[33,35,36] although the test for subgroup differences did not achieve significance to show substantial variability between groups (p = 0.13).

Table 1 Baseline characteristics of the included studies.

Author, year	Country	Sample size (n) ERAS vs. Standard Care	Gestational age [mean (SD)]	Type of cesarean	ERAS protocol		
					Preoperative	Intraoperative	Postoperative
Abilashini, 2025	India	50 vs. 50	36.2 (1.44)	Emergency	Education; hydration optimization; early mobilization.	Multimodal analgesia; minimally invasive techniques; normothermia.	Oral intake and mobilization within 6h; emphasis on non−opioid analgesia for pain.
Baluku, 2020	Uganda	80 vs. 80	NA	Emergency	Education; no fasting (solids and liquids); antibiotic prophylaxis; prophylaxis against postoperative NV and pulmonary aspiration.	Spinal hyperbaric bupivacaine and 100 μg of ITM; restrictive fluid administration; continuous adrenaline infusion; normothermia (warm IV fluids); local wound infiltration; rectal diclofenac and misoprostol.	Carbohydrate drink and cessation of IV fluids within 1h; early breastfeeding; oral single fixed-dose (ibuprofen, acetaminophen); IV pethidine (breakthrough pain); early mobilization; early urethral catheter removal; oral antibiotics.
Birden, 2025	Turkey	78 vs. 78	38.33 (1.41)	Elective	Clear liquids until 2h before surgery; light meal up to 6h before surgery; oral carbohydrate supplementation 2h before CD; IV antibiotics within 1h before the skin incision.	Warming devices (hypothermia); euvolemia is prioritized; fluid preloading, IV phenylephrine or ephedrine, and lower limb compression to reduce hypotension and perioperative NV; multimodal antiemetic agents.	Chewing gum after CD; multimodal analgesia (regular nonsteroidal anti-inflammatory drugs and paracetamol); multimodal bowel regimen; regular diet within 2h after CD; tight control of capillary blood glucose; pneumatic compression stockings (prevent thromboembolic disease); early mobilization; urinary catheters removed immediately after CD.
Darwish, 2022	Egypt	150 vs. 150	NA	Elective	Preparatory phase of detailed explanation of the objective of ERAS; breastfeeding education; stop solid food at least 6–8h and clear oral fluid at least 2h before CD; prophylactic antibiotics; thromboprophylaxis measures.	Proper fluid balance: active warming (preheated IV fluids and cotton blankets); gum chewing; delayed cord clamping; NV prophylaxis; immediate skin-to-skin contact/ breastfeeding.	Continuous gum chewing; NV prophylaxis; early oral intake; parenteral analgesics regularly; early mobilization; removal of Foley's catheter 2h after CD; early removal of dressing; meticulous monitoring of vital signs; lactation consultation interview; community support (midwives visit; physiotherapists) and opportunity to go home on day one.

Table 1 (*Continued*)

Author, year	Country	Sample size (n) ERAS vs. Standard Care	Gestational age [mean (SD)]	Type of cesarean	ERAS protocol		
					Preoperative	Intraoperative	Postoperative
Emelinda, 2024	Cameroon	21 vs. 21	NA	Elective	Information on the procedure, pain management plan, necessity of early feeding and mobilization, lactation, and discharge criteria; sweetened fluids up to 2h and solid foods up to 6h before surgery; standard regional anesthetic technique (spinal anesthesia).	Cefuroxime 60 min before incision; Dexamethasone 8 mg + 8 mg Ondansetron for NV; 50 mg Ranitidine; pre−load of fluids + intermittent ephedrine boluses; covering of patient's chest and crystalloid warming (to 37°).	Balanced analgesia with NSAIDs and Paracetamol; Chewing of gum; regular feeding within 2h from surgery; compression stockings and heparin for thromboprophylaxis; early mobilization; sitting 2h after surgery, and walking 6h after removal of urinary catheter; removal of the urinary catheter 6h after CD.
Kanabar, 2024	India	46 vs. 46	39.64 (1.08)	Elective	ERAS education; oral glucose-rich clear fluid 2h before CD; prophylactic antibiotics; 8 mg of IV dexamethasone, 4 mg IV ondansetron for NV prophylaxis; prophylaxis against pulmonary aspiration (40 mg of IV pantoprazole and 10 mg of IV metoclopramide).	Single-shot spinal anesthesia with hyperbaric bupivacaine and 15 μg of preservative-free fentanyl; restrictive fluid to ensure normovolemia; 6 mg intravenous boluses of mephentermine (hypotension); warm IV fluids and warm clothing cover.	Bilateral TAP block; diclofenac 100 mg (rectal); oral carbohydrate drink and cessation of IV fluids within 1h; early breastfeeding (30-min); fixed-dose 400 mg of ibuprofen and 500 mg of acetaminophen every 8h, IV tramadol (breakthrough pain); early mobilization at 8h; Early urethral catheter removal at 6h; oral antibiotics.
Klangprapan, 2022	Thailand	22 vs. 21	38.7 (0.5)	Elective	Education; 50 mL of water with 50 g of glucose at 6 a.m. on the day of surgery.	Standardized spinal anesthesia; cefazolin prophylaxis (both groups); metoclopramide 10 mg IV after spinal; euvolemia and hypothermia prevention.	Oral fluids/food $\geq$ 2h once stable; scheduled multimodal analgesia; early ambulation; catheter out at 6h.

Table 1 (*Continued*)

Author, year	Country	Sample size (n) ERAS vs. Standard Care	Gestational age [mean (SD)]	Type of cesarean	ERAS protocol		
					Preoperative	Intraoperative	Postoperative
Kulshrestha, 2025	India	70 vs. 70	37.4 (2.07)	Elective	Counseling in 3rd trimester and on admission; fasting 6h solids, clear fluids 2−3h pre-op (carb-rich allowed); prophylactic antibiotics; aspiration prophylaxis (ranitidine + metoclopramide).	Standardized spinal anesthesia; TAP block after closure; crystalloids co-load; prophylactic phenylephrine infusion; chlorhexidine-alcohol skin prep; normothermia; immediate skin-to-skin; delayed cord clamping; PONV prophylaxis.	Scheduled multimodal analgesia; ondansetron prophylaxis; oral fluids 2h, regular diet same day; gum chewing; mobilization on the first day; breastfeeding < 1h; catheter removal < 12h; IV fluids stopped in ward.
Mundhra, 2024	India	71 vs. 71	37.91 (1.90)	Emergency	NA	Standardized spinal anesthesia; goal-directed fluids; normothermia.	Oral fluids at 2h, normal diet at 8h, gum chewing; early mobilization, catheter removal 6−12h; ceftriaxone + cefixime, metronidazole; multimodal analgesia; incentive spirometry; dressing off at 24h.
Pan, 2020	China	112 vs. 104	38.99 (0.90)	Elective	Education and counseling, reduced fasting (6h solids, 2h fluids), antibiotics, aspiration prophylaxis.	CSEA; prophylactic phenylephrine 50 μg; active warming with warm-air blower; oxytocin infusion; carboprost if needed.	Early oral intake (2h), early mobilization (6h turning, ambulation on the first day), skin-to-skin, breastfeeding < 1h, scheduled PCEA with 6 mg morphine (vs. 6−7 mg in controls), multimodal antiemetic prophylaxis, ondansetron/tropisetron.
Rajendran, 2025	India	50 vs. 50	NA	Elective	Patient education on pain, feeding, mobilization, lactation, discharge, and follow-up. Clear fluids up to 2h before surgery.	Spinal anesthesia with 0.5% bupivacaine heavy (10 mg) + buprenorphine (60 μg). Prophylactic phenylephrine (100 μg) to prevent hypotension. Granisetron for PONV prophylaxis. Normothermia actively maintained (forced-air warming, pre-warmed bed, fluid warmer). Standard uterotonics and antibiotics.	TAP block with ropivacaine 0.5% (20 mL each side) + dexamethasone (4 mg). Oral paracetamol; tramadol (breakthrough pain). Oral intake within 2h, early mobilization at 6h, immediate skin-to-skin, breastfeeding within 1h.

Table 1 (*Continued*)

Author, year	Country	Sample size (n) ERAS vs. Standard Care	Gestational age [mean (SD)]	Type of cesarean	ERAS protocol		
					Preoperative	Intraoperative	Postoperative
Teigen, 2020	USA	58 vs. 60	39.13 (0.27)	Elective	Standard institutional prophylaxis (antibiotics, surgical preparation). All patients received neuraxial anesthesia (spinal, epidural, or CSEA).	Standard cesarean technique per attending surgeon. No difference in anesthesia between groups.	Chewing gum (xylitol) to reduce ileus; scheduled IV ketorolac for 24h; early oral intake (clear liquids in PACU, regular diet within 30-min); early urinary catheter removal at 12h; dressing removal at 6h; early mobilization at 12h; incentive spirometry every 8h.
Xu, 2025	China	100 vs. 100	NA	Mixed	Reduced fasting (6h solids, 2h clear liquids); oral ranitidine, antacids, acetaminophen; prophylactic antibiotics (IV cefazolin ± oral azithromycin); alcohol-based chlorhexidine/iodine; group education on diet, exercise, and glucose monitoring.	Neuraxial anesthesia; local wound infiltration; goal-directed fluid therapy; active warming (blankets + warmed IV fluids); IV insulin if glucose > 8.25 $mmoL.L^{-1}$; 10% glucose infusion.	Early oral intake (sips of water within 2h, full diet within 8h); chewing gum every 8h; early mobilization (sitting within 8h, ambulation by 24h); urinary catheter removal at 8—12h; early physiotherapy; multimodal analgesia including intermittent IV morphine.

a.m., Ante meridiem; CD, Cesarean Delivery; CSEA, Combined Spinal and Epidural Anesthesia; ERAS, Enhanced Recovery After Surgery; g, Grams; h, Hour(s); ITM, Intrathecal Morphine; IV, Intravenous; mg, Milligrams; μg, Micrograms; mL, Milliliters; min: minutes; $mmoL.L^{-1}$, Millimoles per Liter; NA, Not Available; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; NV, Nausea and Vomiting; PACU, Post-Anesthesia Care Unit; PCEA, Patient-Controlled Epidural Analgesia; PONV, Postoperative Nausea and Vomiting; SD, Standard Deviation; TAP, Transversus Abdominis Plane.

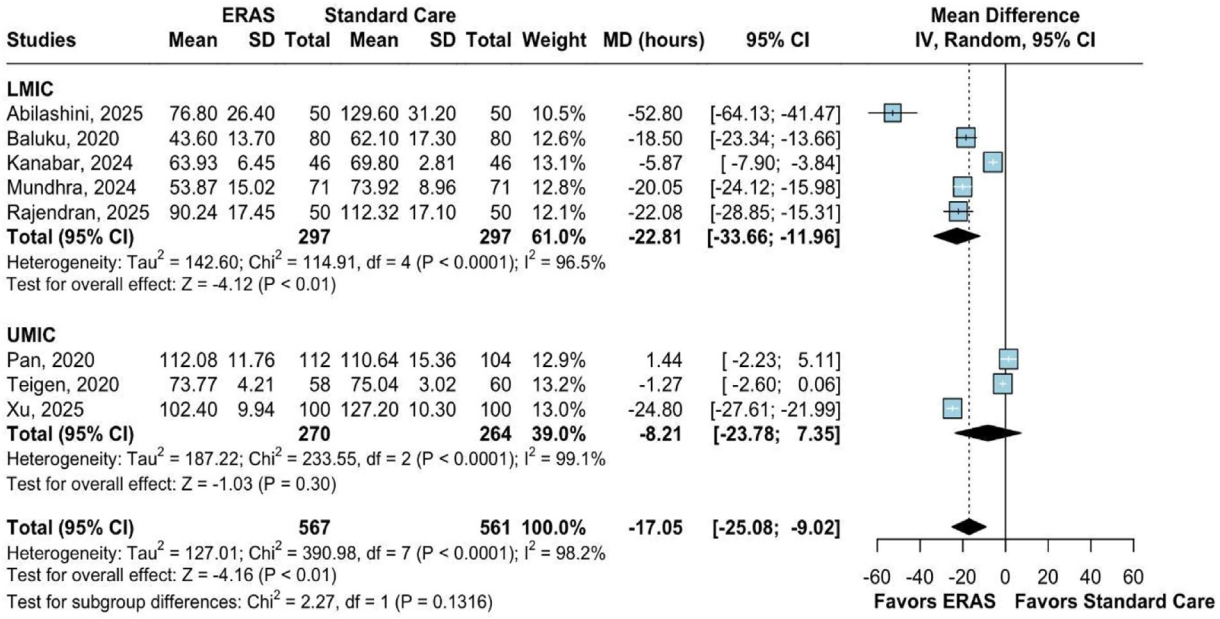

Figure 2 Forest plot depicting the endpoint of hospital length of stay, stratified by country income level. The plot displays mean differences with 95% Confidence Intervals for each included study and subgroup-specific pooled random-effects estimates. Abbreviations: ERAS, Enhanced Recovery After Surgery; SD, Standard Deviation; CI, Confidence Interval; MD, Mean Difference; LMIC, Low- and Middle-Income Countries; UMIC, Upper-Middle-Income Countries.

TSA for hospital LOS showed that the cumulative Z-curve crossed the monitoring boundaries, indicating low risks of type I and type II errors (Fig. 3) and suggesting that the pooled sample size was sufficient to draw reliable conclusions for this outcome.

Secondary endpoints

Pain score

Analysis of pain scores showed lower scores with ERAS protocol at rest at both 24 hours (MD = -1.32 points, 95% CI -2.27 to -0.37, I^2 = 98.9%, p < 0.01, n = 1,097; Fig. 4)[24,26,30–34,36] and 48 hours (MD = -0.83-points, 95% CI -1.56 to -0.09, I^2 = 95.2%, p = 0.03, n = 798; Fig. 5).[31-34,36] The GRADE certainty of evidence for both time points was rated as very low due to risk of bias, inconsistency, and imprecision (Supplementary Table S4). Using an MCID of about 1.5 VAS points,[22] the reductions at 24 hours and 48 hours did not meet the threshold for clinical relevance. The leave-one-out sensitivity analysis at each time point demonstrated that the direction and significance of the effect remained consistent across trials, even after the exclusion of the two studies that incorporated a transversus abdominis plane block (Supplementary Fig. S2).[31,34]

Wound infection

Pooled data from four RCTs showed that ERAS significantly reduced wound infections compared with standard care (RR = 0.23, 95% CI 0.07 to 0.73, p = 0.01, I^2 = 0%, n = 727; Supplementary Fig. S4).[25-27,35] The result remained consistent in the leave-one-out sensitivity analysis (Supplementary Fig. S2). The GRADE certainty of evidence was rated as moderate, downgraded by one level due to the small number of studies contributing to this outcome (Supplementary Table S4).

Readmission

Five RCTs assessed readmission.[25,26,28,32,35] A pooled analysis found no statistically significant difference between ERAS protocols and standard care groups (RR = 0.59, 95% CI 0.23 to 1.55, p = 0.29, I^2 = 13.2%, n = 611; Supplementary Fig. S5). Sensitivity analyses yielded similar results (Supplementary Fig. S2). The GRADE certainty of evidence was rated very low, downgraded for risk of bias, imprecision, and publication bias (Supplementary Table S4).

PONV

Pooled analysis of five RCTs showed that ERAS protocols were not associated with a significant reduction in PONV compared with standard care (RR = 0.65, 95% CI 0.36 to 1.19, I^2 = 0%, p = 0.16, n = 667; Supplementary Fig. S6).[25,26,28,33,34] Sensitivity analyses demonstrated a consistent direction of effect (Supplementary Fig. S2), and the GRADE certainty of the evidence was rated as very low due to risk of bias, imprecision, and potential publication bias (Supplementary Table S4).

Maternal satisfaction score

The pooled analysis of five studies demonstrated a statistically significant improvement favoring ERAS protocols (SMD = 1.02, 95% CI 0.33 to 1.72, I^2 = 94.9%, p < 0.01, n = 756; Supplementary Fig. S7).[24,31,33,34,36] Leave-one-out sensitivity analysis demonstrated the stability of the pooled effect (Supplementary Fig. S2). The observed improvement was clinically meaningful, as point estimates consistently exceeded the MCID of approximately 0.7–1.1 points on a 0–10 VAS, corresponding to a 7–11 mm change on the original 100 mm scale.[23] However, due to substantial heterogeneity, concerns about risk of bias, and the limited number of trials reporting this outcome, the GRADE certainty of the evidence was rated as very low (Supplementary Table S4).

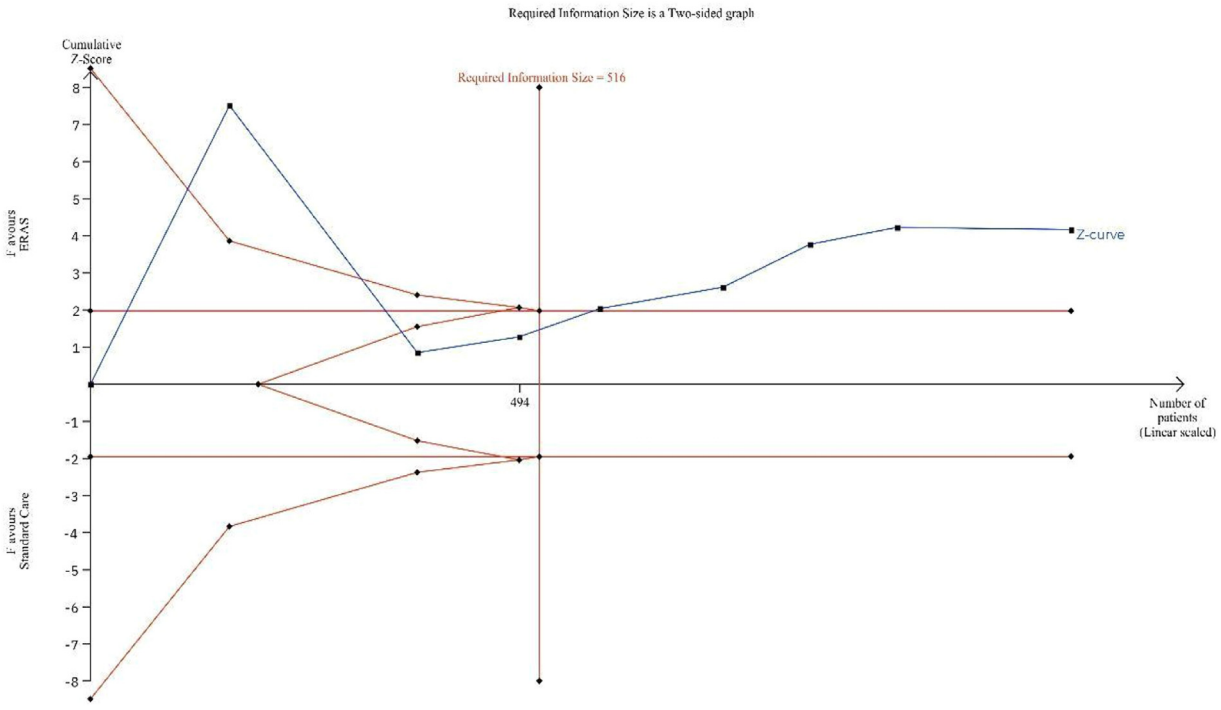

Figure 3 Trial sequential analysis for the hospital length of stay. ERAS, Enhanced Recovery After Surgery.

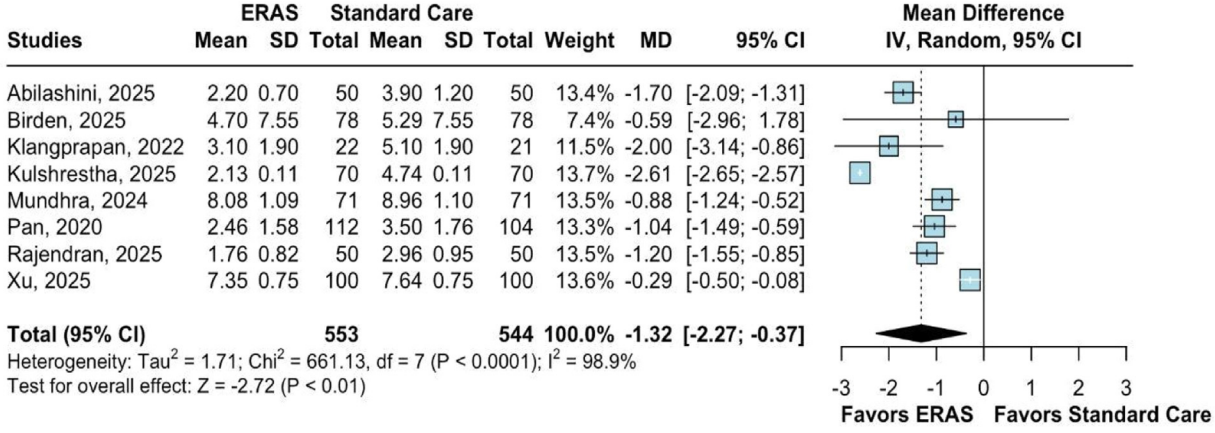

Figure 4 Forest plot for the outcome of pain scores at rest at 24 hours. The plot displays mean differences with 95% Confidence Intervals for each included study and the pooled random-effects estimate. ERAS, Enhanced Recovery After Surgery; SD, Standard Deviation; CI, Confidence Interval; MD, Mean Difference.

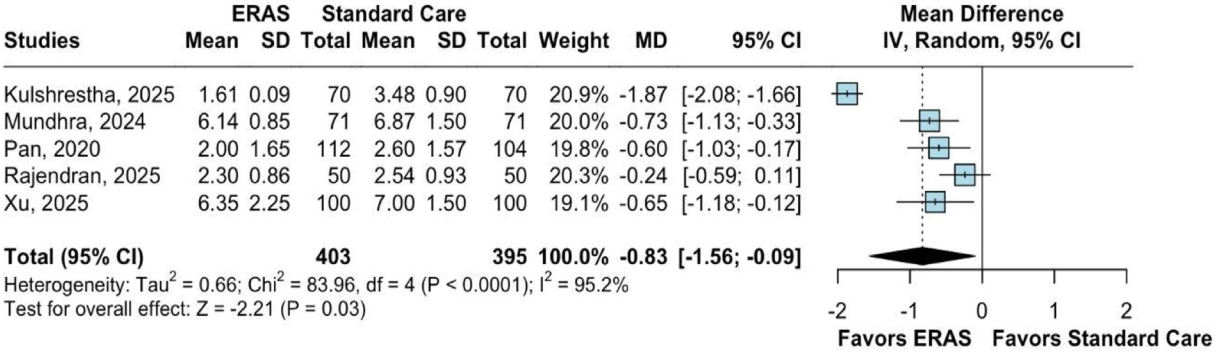

Figure 5 Forest plot depicting the endpoint of pain scores at rest at 48 hours. The plot displays mean differences with 95% Confidence Intervals for each included study and the pooled random-effects estimate. ERAS, Enhanced Recovery After Surgery; SD, Standard Deviation; CI, Confidence Interval; MD, Mean Difference.

Discussion

In this systematic review and meta-analysis of 13 RCTs including 1,809 parturients and comparing ERAS protocols with standard perioperative care for cesarean delivery, we found that ERAS protocols were associated with a statistically significant reduction in hospital LOS, lower postoperative pain scores at rest at both 24 and 48 hours, lower incidence of wound infection, and higher maternal satisfaction. No significant differences in readmission rates or PONV were found.

ERAS protocols were introduced in 1997 by Henrik Kehlet, and over the years, the literature has emphasized that the implementation of multiple evidence-based elements can markedly improve perioperative outcomes.[37] Several components of ERAS protocols, including early mobilization, standardized prophylactic antibiotics, and multimodal analgesic regimens, promote early ambulation and accelerate recovery, which ultimately prepare the patient for earlier discharge.[3,38,39]

Our meta-analysis showed a mean reduction in hospital LOS of -17.05 hours with ERAS compared with standard care. This reduction possibly reflects earlier discharge and improved patient experience,[3,40] and aligns with previous meta-analyses reporting reductions of 12—14 hours, although they also showed similar high heterogeneity between included studies.[10,11] Shorter hospital stays can improve hospital efficiency and resource optimization, and reduced LOS is widely used as a benchmark of institutional performance across diverse healthcare settings.[41,42] Importantly, the reduction in hospital LOS was not associated with higher readmission rates, consistent with prior evidence.[8,10,11] Nonetheless, discharge policies may vary across institutions, and we could not conclusively address resource utilization or cost-effectiveness due to limited reported data.

Pain management remains a critical factor in postoperative recovery, as it influences the quality of recovery and affects mother-newborn bonding in the postpartum period.[43-47] Our pooled analysis suggests that ERAS may reduce pain at rest after cesarean delivery, with mean decreases of 1.32-point at 24 hours and 0.83-point at 48 hours, approaching the lower threshold of clinical significance. Although some studies suggest that the MCID for pain reduction on the VAS may be approximately 1.0-point (10 mm) on a 100 mm scale,[48,49] in our analysis, we adopted a more conservative threshold of approximately 1.5-point based on evidence from gynecologic surgery. These findings are consistent with previous meta-analyses, in which the implementation of the ERAS protocol resulted in statistically significant reductions in postoperative pain and opioid consumption after cesarean delivery[8]; nonetheless, our results should be interpreted with caution, since this MCID value was extrapolated from hysterectomy studies due to a lack of a specific post-cesarean MCID in the current literature.

Wound infection after cesarean delivery is a major concern in clinical practice, as it is associated with increased maternal morbidity, delayed recovery, and hospital readmissions.[50,51] In our meta-analysis, ERAS protocols were associated with a 77% relative reduction in wound infection risk. This finding is consistent with ERAS recommendations that emphasize evidence-based measures such as glycemic control in patients with diabetes, smoking cessation support, intravenous prophylactic antibiotics, chlorhexidine-alcohol skin preparation, prevention of intraoperative hypothermia, and early mobilization, all of which are directly related to lower surgical site infection rates.[5]

Maternal satisfaction is a multidimensional endpoint that captures the patient's perception of care. It reflects the mother's experience and influences postpartum mental health and quality of care.[52-55] Despite high variability among measurement tools, we found that maternal satisfaction was significantly higher among patients managed under ERAS protocols than among those under standard care. Beyond clinical recovery through multimodal analgesia and early mobilization, ERAS pathways may also improve communication, reduce anxiety, and strengthen trust between patients and clinicians.[56,57] Together, these findings suggest that ERAS benefits may extend to both clinical and patient-centered outcomes; nonetheless, we had to pool different measurement tools into a common scale for synthesis, and the heterogeneity among scales may not adequately translate into comparable conclusions across studies.[23]

Emergency cesarean deliveries are associated with higher rates of maternal complications, longer recovery, and prolonged hospitalization.[58] In our subgroup analysis by cesarean categories, ERAS protocols were associated with a significant reduction in hospital LOS for both elective and emergency procedures, with the largest effect observed in emergency cases (MD = -29.04 hours). This finding could be clinically relevant because emergency cesarean deliveries must meet tight decision-to-delivery intervals, limiting opportunities for preoperative optimization and structured perioperative preparation, which may contribute to longer recovery and increased hospital LOS in these higher-acuity cases.[59] Our findings suggest that integrating ERAS pathways into perioperative care could possibly help streamline postoperative recovery and reduce unnecessary hospital stays in these higher-risk scenarios.

A larger reduction in length of stay was observed in LMIC (MD = -22.81 hours), whereas no significant effect was detected in UMIC. While this could reflect more established perioperative pathways and baseline efficiency in these settings, the test for subgroup differences did not achieve statistical significance, possibly due to the smaller number of included studies within the UMIC classification, which hinders any conclusive result. Nonetheless, in resource-constrained health systems, where surgical services are frequently limited by hospital overcrowding and a backlog of untreated surgical conditions, efficiency improvements that reduce hospital stay may enhance patient flow and access to surgical care.[1] Albeit not directly addressed in our study, such improvements could have particular implications given that cesarean-related maternal mortality is nearly 100 times higher in LMIC than in high-income countries.[60] Thus, the implementation of standardized ERAS pathways could possibly impact LMIC by improving efficiency and expanding safe surgical capacity, although further studies are necessary to draw solid evidence, given the lack of subgroup statistical significance in our analysis.

Still, the reliability and interpretability of our pooled estimates were substantially limited by the high heterogeneity observed across key outcomes, particularly hospital LOS (I^2 = 98.2%), pain at 24 hours (I^2 = 98.9%), pain at 48

hours (I^2 = 95.2%), and maternal satisfaction (I^2 = 94.9%). Accordingly, the GRADE certainty of the evidence was rated as very low for most outcomes given such heterogeneity. Our findings should therefore be interpreted as suggestive rather than definitive, since several factors likely contribute to this variability. As shown in Table 1, ERAS protocols differed considerably across trials in their composition, timing, and intensity within all three perioperative phases: preoperative fasting thresholds were heterogeneous, analgesic regimens varied from intrathecal morphine to TAP blocks and multimodal oral regimens, and postoperative mobilization targets differed in onset time. The definitions of "standard care" were similarly heterogeneous, reflecting local institutional practices rather than a uniform comparator. Discharge criteria and LOS measurement also varied, as some studies defined LOS as time to actual discharge, while others used fulfillment of institutional discharge criteria. Pain and satisfaction assessments also lacked standardization across studies, as previously discussed. Taken together, these sources of clinical and methodological heterogeneity represent an intrinsic limitation of this meta-analysis, in which data from diverse ERAS protocols were pooled for statistical purposes. Therefore, ERAS should be interpreted as a flexible framework of perioperative care rather than a single, standardized intervention. Accordingly, the effect estimates should be understood as averages across diverse implementations that may not be generalizable to any specific protocol or healthcare setting, although the overall direction of effect suggests benefit.

Limitations

Our meta-analysis has several limitations. We observed considerable variation in the ERAS protocols across the included trials, which prevented the identification of a universally standardized obstetric ERAS pathway (Table 1). Similarly, "standard care" was inconsistently defined and largely dependent on local institutional practices, contributing to high heterogeneity and lowering the overall certainty of the evidence in the GRADE assessments. Incomplete reporting of perioperative elements in several RCTs limited the assessment of protocol adherence and its impact on key outcomes, including hospital LOS, which could be influenced by institutional discharge policies as well as by the ERAS protocol.

The definition of 'emergency cesarean' was not explicitly reported, limiting the interpretation of the clinical severity of included cases. Variability in the assessment of pain and maternal satisfaction, including differences in timing, scales, and interpretation, likely introduced measurement bias and reduced comparability across studies, contributing to the high heterogeneity observed for these outcomes. For example, the MCID was derived from studies of gynecologic surgery since there is no standard value for a post-cesarean MCID, and this may not fully reflect a clinically meaningful difference for parturients; the conversion of satisfaction measures into a single scale may also not fully reflect clinical similarities. Moreover, none of the trials reported data on cost-effectiveness, staff workload, or resource utilization, limiting our evaluation of ERAS as a potential system-strengthening intervention in resource-limited settings.

Finally, most included studies were judged as having some concerns regarding risk of bias, consistent with the GRADE assessment, which indicated low certainty of evidence for most outcomes, with only one outcome rated moderate. To evaluate the robustness of these findings, we conducted leave-one-out sensitivity analyses and TSA, which supported the stability of the results. However, these analyses do not reduce the clinical and methodological heterogeneity among included studies, and the findings should be interpreted considering the very low certainty of the evidence for most endpoints.

Conclusion

This systematic review and meta-analysis provides updated, albeit still heterogeneous, evidence suggesting that ERAS protocols may provide additional benefits for women undergoing cesarean delivery, including shorter hospital LOS, lower postoperative pain scores at 24 and 48 hours, reduced wound infection rates, and higher maternal satisfaction, although conclusions across different healthcare settings were limited. Importantly, ERAS represents a flexible framework that can be adapted to local needs and clinical contexts. Future research should focus not only on demonstrating efficacy but also on achieving sustainable implementation through multidisciplinary education, local adaptation, and cultural integration within diverse health systems.

Data availability statement

This study was based on data extracted from previously published trials. The authors do not have access to patient-level data from individual publications. All data supporting the findings of this study are available within the article and its Supplementary Material. On July 27, 2026, all included trials and key cited references were checked for retractions, corrections, withdrawals, and expressions of concern in PubMed and on the corresponding journal or publisher websites. No included study or key reference was found to have been retracted or flagged.

Authors' contributions

Tauãna Terra: Conceptualization, Methodology, Investigation, Visualization, Writing-original draft, Writing-review & editing. Vanessa Tapioca: Conceptualization, Investigation, Writing-original draft, Writing-review & editing. Eduardo Pereira: Conceptualization, Formal analysis, Visualization, Writing-original draft, Writing-review & editing. Bruna Ferreira: Investigation, Visualization. Tamiris Soares: Investigation, Visualization, Writing-original draft. Sara Amaral: Conceptualization, Methodology. Maria Luisa Assis: Investigation, Visualization. Gabriel Carvalho: Investigation, Writing-review & editing. Julio S. Curi: Investigation. Kamal Kumar: Writing-original draft, Writing-review & editing, Supervision. Agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved: all authors.

All authors (1) read and approved the final version, (2) met the ICMJE criteria for authorship, (3) believe the paper

represents honest work, and (4) are able to verify the validity of the results reported.

Declaration of Artificial Intelligence (AI) use

The authors did not use AI or AI-assisted technologies at any stage of this work, including data extraction, statistical analysis, reference checking, figure preparation, preparation of the supplementary material, and language editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

PROSPERO registry

CRD420251152114 (October 23, 2025).

Disclosures

This manuscript is an original work; it has not been presented as a conference abstract or submitted to other journals.

Conflicts of interest

The authors declare no have conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844817.

Associate Editor

Edmundo Pereira Souza Neto

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Brazilian Journal of Anesthesiology 2026;76(5): 844820

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Efficacy and safety of preoperative intranasal dexmedetomidine in adults: a systematic review and meta-analysis of randomized controlled trials

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Received 17 March 2026; accepted 31 July 2026
Available online 3 September 2026

KEYWORDS
Administration, Intranasal;
Adult;
Anesthesia;
General;
Dexmedetomidine;
Hemodynamics;
Meta-analysis as topic

Abstract Background: Airway manipulation during General Anesthesia (GA) can produce sympathetic activation and hemodynamic instability. Intravenous (IV) dexmedetomidine attenuates these responses but may cause bradycardia or hypotension. Intranasal (IN) administration is a noninvasive alternative with uncertain evidence in adults. We evaluated preoperative IN dexmedetomidine in adult patients undergoing GA.

Methods: We performed a PROSPERO-registered (CRD420251250492) systematic review and meta-analysis of randomized trials. MEDLINE, Embase, CENTRAL, and CDSR were searched from inception to November 26, 2025. IN dexmedetomidine versus control and IN vs. IV dexmedetomidine were assessed separately. Random-effects models pooled continuous outcomes as MDs/SMDs and adverse events as RRs. Risk of bias was assessed using RoB2 and certainty of evidence using GRADE.

Results: Across 25 trials including 1,968 patients, IN dexmedetomidine was associated with deeper sedation (SMD = 0.76; 95% CI: 0.18−1.34) and reduced heart rate and mean arterial pressure at induction, intubation, and during the early intraoperative period compared with control (MD range: -12.7 to -13.4 bpm and -7.8 to -10.7 mmHg, respectively). Rates of bradycardia and hypotension were similar between IN dexmedetomidine and control groups. Compared with IV dexmedetomidine, IN administration resulted in lighter sedation (SMD = -0.54; 95% CI: -1.08 to -0.01), with similar hemodynamic effects, while bradycardia and hypotension occurred less frequently.

Abbreviations: BMI, Body Mass Index; ENT, Ear Nose and Throat; GA, General Anesthesia; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HR, Heart Rate; IN, Intranasal; IV, Intravenous; MAP, Mean Arterial Pressure; MD, Mean Difference; PACU, Post-Anesthesia Care Unit; PONV, Postoperative Nausea and Vomiting; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized Controlled Trial; REML, Restricted Maximum Likelihood; RR, Risk Ratio; SMD, Standardized Mean Difference.

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https://doi.org/10.1016/j.bjane.2026.844820

Conclusion: Preoperative IN dexmedetomidine may improve sedation and blunt peri-induction hemodynamic responses compared with controls, with broadly similar hemodynamic effects and fewer observed cardiovascular adverse events versus IV administration. However, certainty was low or very low for several efficacy outcomes, and larger well-designed trials are needed.

Introduction

Perioperative sympathetic activation during induction of General Anesthesia (GA) and tracheal intubation remains a major contributor to hemodynamic instability, myocardial stress, and perioperative complications.[1] Excessive tachycardia and hypertension during airway manipulation are associated with increased myocardial oxygen demand, while excessive anesthetic depth or aggressive pharmacologic attenuation can precipitate hypotension and bradycardia.[2] Given the vulnerability of surgical patients to perioperative neurocognitive disorders, achieving adequate anxiolysis and blunting of stress responses without compromising hemodynamic or respiratory safety remains a central challenge in anesthetic practice.[3]

Dexmedetomidine, a selective α2-adrenergic receptor agonist, has emerged as a useful adjunct due to its sedative, anxiolytic, and sympatholytic properties.[4] Unlike many commonly used sedatives, it produces effective sedation with limited respiratory depression, making it particularly appealing during the peri-induction period.[4] Intravenous (IV) dexmedetomidine has been studied extensively, demonstrating efficacy in attenuating hemodynamic responses to laryngoscopy and intubation, reducing perioperative Heart Rate (HR) and blood pressure variability, and improving perioperative sedation quality.[5–7] IV administration is associated with clinically significant bradycardia and hypotension, and may be undesirable or impractical in select perioperative settings or in patients with needle-related anxiety.[8,9]

Intranasal (IN) administration of dexmedetomidine represents a noninvasive alternative, offers relatively high bioavailability, and provides pain-free gradual systemic absorption.[10] Absorption across the nasal mucosa bypasses first-pass hepatic metabolism, yielding a bioavailability of approximately 65% in adults with a more gradual rise in plasma concentration than the IV route.[11] This pharmacokinetic profile can minimize reflex bradycardia and hemodynamic instability associated with IV bolus administration. Peak sedative effect following IN dexmedetomidine occurs approximately 45 to 60 minutes after administration,[11] aligning with typical preoperative holding periods and supporting its use as preanesthetic medication. While IN dexmedetomidine is well established in pediatric anesthesia and procedural sedation,[12,13] robust evidence in adults remains limited, and clinical adoption in adult practice has lagged accordingly.[14–16] To date, the safety profile of IN versus IV dexmedetomidine in adult surgical patients has not been directly compared in a meta-analysis, despite the differing pharmacokinetic behavior of the two routes.

The objective of this systematic review and meta-analysis of Randomized Controlled Trials (RCTs) was to evaluate preoperative IN dexmedetomidine in adults having surgery under GA, compared with IV dexmedetomidine and control, across various clinically relevant domains: depth of sedation, attenuation of the hemodynamic response to intubation, postoperative analgesic requirements, and adverse events.

Methods

This systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251250492) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The two pairwise comparisons, IN dexmedetomidine versus control and IN versus IV dexmedetomidine, were prespecified in the PROSPERO protocol. The protocol also prespecified the relevant outcome domains, including perioperative hemodynamics, sedation, opioid consumption, postoperative nausea and vomiting, and adverse events such as bradycardia and hypotension. The protocol did not explicitly classify outcomes as primary or secondary. For the present report, depth of sedation, perioperative hemodynamics, bradycardia, and hypotension were prioritized as primary outcomes because they directly reflect the intended premedication effects and principal cardiovascular safety concerns of dexmedetomidine. Propofol consumption, postoperative opioid consumption, Post-Anesthesia Care Unit (PACU) time, and postoperative nausea and vomiting (PONV) were considered secondary outcomes. The protocol included additional outcome domains, but they were not pooled due to insufficient data.

Literature search strategy

A comprehensive literature search was conducted by an information specialist (MFE) using the Ovid platform, encompassing MEDLINE, MEDLINE ePubs and In-Process Citations (daily), Embase Classic and Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Searches were completed from inception to November 26, 2025. The search strategy was developed in accordance with the Cochrane Handbook,[18] and the Methodological Expectations for Cochrane Intervention Reviews (MECIR).[19] Preliminary scoping searches and full-text reviews were undertaken to identify relevant keywords and controlled vocabulary, including MeSH terms for MEDLINE and EMTREE terms for Embase. The Yale MeSH Analyzer was used to assist in the identification of appropriate subject headings and text-word terms.[20] The final search strategy combined controlled vocabulary and text-word terms related to preoperative IN dexmedetomidine, inpatient surgery, general anesthesia, perioperative or postoperative outcomes, and RCT study designs. Searches were limited to

studies published in English involving adult human populations, and conference abstracts and other non-peer-reviewed materials were excluded. The MEDLINE search strategy is provided in Table S1. For eligible studies where full texts were unavailable, corresponding authors were contacted to request access.

Study selection criteria

The inclusion criteria were: 1) Adults (≥ 18 years) having inpatient surgery under GA; 2) Preoperative IN dexmedetomidine administered; and 3) RCTs that included a comparator arm, defined as either a control group (placebo or standard care) or an IV dexmedetomidine group. The exclusion criteria included non-randomized study designs, case reports, case series, and cross-sectional studies.

Two independent reviewers (LT, TT) performed title and abstract screening on Covidence. Further, two reviewers (ME, LT) conducted full-text screening independently. Conflicts were resolved by a third reviewer (VV). No automation tools were used in the study selection process. On July 26, 2026, the publication status of all included studies and key references was checked in PubMed, where indexed, the Retraction Watch Database, Crossmark/Crossref, and the relevant journal or publisher websites. No retractions, withdrawals, expressions of concern, or published corrections were identified.

Data extraction

Four independent reviewers (VV, LT, TT, SY) extracted data in duplicate into a standardized form. Discrepancies were resolved by a fifth reviewer (ME). The extraction form included study-level information (year of publication, title, country, type of surgery, sample size for each group IN dexmedetomidine vs. IV dexmedetomidine vs. control, dexmedetomidine dose, and time of administration) and demographics (age, Body Mass Index BMI, and male percentage). Outcomes were recorded regarding depth of sedation, perioperative Hemodynamics (HR and MAP), adverse events (bradycardia, hypotension, and PONV), postoperative opioid consumption, PACU time, and propofol consumption.

Risk of bias assessment

The risk of bias of studies included in the pooled analysis was independently evaluated by two reviewers (ME, VV) using the Revised Cochrane Risk of Bias tool for randomized trials (RoB2).[21] Risk of bias was evaluated across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. For each study, individual domains were classified as low, some concerns, or high risk of bias. The overall risk of bias for each study was determined by the highest concern level across the domains. Disagreements in risk-of-bias judgments were resolved by a third reviewer (LT).

Statistical analysis

Continuous outcomes (sedation scores, HR, and MAP) were pooled as Mean Differences (MD) or Standardized Mean Differences (SMD) using Random−Effects Models (REML). Sedation scales with inverse directionality were harmonized prior to analysis so that positive SMD represented deeper sedation with IN dexmedetomidine. Binary adverse outcomes (bradycardia, hypotension) were analyzed as Risk Ratios (RR). A minimum of two studies was required for meta-analysis. Estimates were presented with 95% confidence intervals, pooled heterogeneity (I^2, τ^2), Cochran's Q, and random-effects p-values. All analyses were conducted using the meta[22] and metafor[23] packages in R (4.5.1); p-value of < 0.05 was considered statistically significant. Sensitivity analyses using leave-one-out procedures were performed for all outcomes with at least three studies. Subgroup analyses by type of surgery, dexmedetomidine dose or timing, and outcome measurement scale were prespecified in the protocol. However, the number of studies contributing to each pooled outcome was insufficient to support meaningful subgroup analysis, and these were therefore not performed.

GRADE appraisal of evidence

The certainty of evidence for each outcome was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines.[24] Certainty was evaluated across five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. The summary table was created using the GRADEpro Guideline Development Tool.[25]

Results

Study selection

The literature search identified 439 records. After removal of 91 duplicates, 348 records were screened by title and abstract. Of these, 293 records were excluded. Full-text review was conducted for 55 studies, of which 30 were excluded. A total of 25 RCTs[14−16,26−47] met eligibility criteria and were included in the systematic review and meta-analysis. Figure 1 presents the PRISMA flow diagram of study selection.

Study characteristics

The 25 included RCTs enrolled 1,968 adult surgical patients undergoing a range of inpatient procedures. Fourteen studies compared IN dexmedetomidine with control,[14−16,26,27,29,31,33,37,38,41,45−47] nine compared IN with IV dexmedetomidine,[28,32,34−36,39,40,43,44] and two studies included both IN and IV dexmedetomidine arms alongside a control group.[30,42] Among trials with a control arm, comparators were placebo controls, usually intranasal or nebulized 0.9% saline, except for one trial that used oral alprazolam as an active control.[41] Individual study sample sizes ranged from 29 to 159 participants (Table 1). Mean age and BMI across studies were 49 ± 16 years and 25 ± 5 $kg.m^{-2}$, respectively. The proportion of male participants varied across studies, ranging from 0% in a gynecologic surgery population to 78% in an Ear, Nose, and Throat (ENT) surgery population. The included studies were predominantly conducted in India

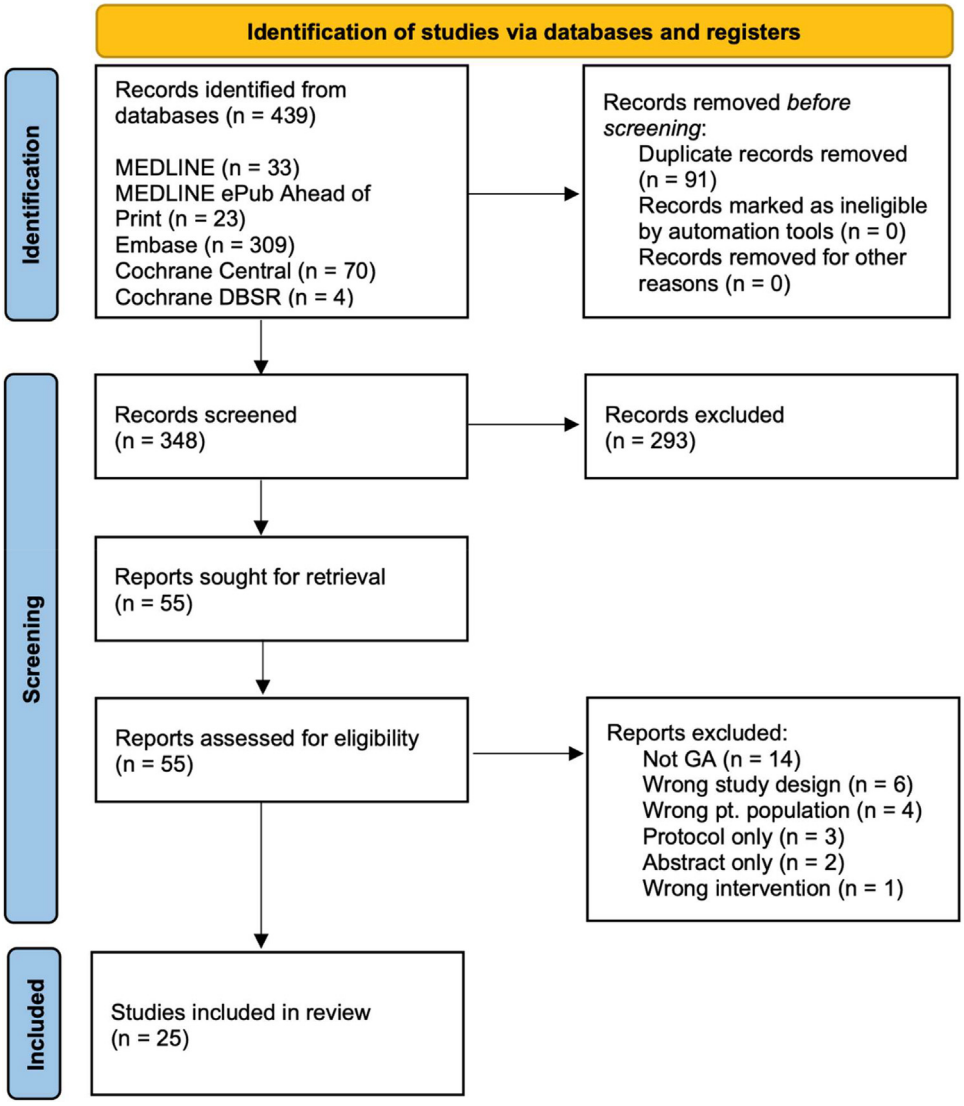

Figure 1 PRISMA flow diagram.

(n = 12), followed by China (n = 10), with fewer studies originating from Egypt (n = 2) and Iran (n = 1).

Surgical procedures included Ear, Nose, and Throat (ENT), neurological, spine, orthopedic, cardiac, gynecologic, bariatric, suspension laryngoscopy, and mixed elective surgery. IN dexmedetomidine dosing strategies varied. Most trials administered 1 $\mu g.kg^{-1}$, while others used lower weight-based doses (0.3–0.75 $\mu g.kg^{-1}$), higher doses up to 2–2.5 $\mu g.kg^{-1}$, or fixed dosing regimens ranging from 50 to 100 μg. Tables 2 and 3 provide a summary of all pooled effects.

Clinical effects of IN dexmedetomidine compared with control

Compared with control, IN dexmedetomidine administration was associated with deeper sedation in five studies (SMD = 0.76; 95% CI: 0.18 to 1.34, p = 0.010; I^2 = 87.6%; Fig. 2A).[14,15,29,30,41] Baseline HR and MAP did not differ statistically between groups. At intubation, seven studies demonstrated lower HR with IN dexmedetomidine versus control, although heterogeneity was substantial (MD = -12.73 bpm, 95% CI: -17.66 to -7.80, p < 0.001; I^2 = 86%; Fig. 3A).[14–16,37,41,42–45] Similarly, MAP appeared lower with IN dexmedetomidine compared with control, with high heterogeneity (MD = -10.44 mmHg, 95% CI: -15.37 to -5.52, p < 0.001; I^2 = 85%; Fig. 3C).[14–16,37,41,42,45]

At induction, HR and MAP were also lower with IN dexmedetomidine than control (HR MD = -13.37 bpm, p < 0.001; MAP MD = -10.65 mmHg, p < 0.001).[15,42] Similar reductions were observed at 10 minutes into surgery (HR MD = -13.15 bpm, p < 0.001; MAP MD = -7.77 mmHg, p = 0.025).[16,37,42,45]

Safety outcomes

The risk of bradycardia was similar between IN dexmedetomidine and control (RR = 1.15, 95% CI: 0.64 to 2.04, p = 0.645; I^2 = 0%).[14,26,27,29,30] Hypotension rates were comparable between IN dexmedetomidine and control

Table 1 Characteristics of included studies.

Study	Sample Size	Mean Age (y)	Mean BMI ($kg.m^{-2}$)	Male %	Surgery Type	Intranasal Dexmedetomidine Dose	Primary Comparator	Administration Device
Gupta 2025, India	75	31.7 ± 9.1	NR	56.0	Laparoscopy	1 $\mu g.kg^{-1}$	Control and IV	Nasal drops
Singh 2025, India	120	42.4 ± 12.1	24.9 ± 2.9	58.3	Neurosurgery	1 $\mu g.kg^{-1}$	IV	Nasal drops
Wang 2025, China	159	48.7 ± 18.5	23.6 ± 2.6	61.6	ENT	75–100 μg	Control	Nasal spray (metered)
Choudhary 2024, India	120	NR	NR	31.7	Mixed	0.75 $\mu g.kg^{-1}$	IV	Nasal drops
Fang 2024, China	100	67.5 ± 3.9	23.7 ± 3.0	59.0	Cardiac	0.3 $\mu g.kg^{-1}$	Control	Nasal drops
He 2024, China	80	68.8 ± 2.9	22.1 ± 1.9	0.0	Gynecology	1.5 $\mu g.kg^{-1}$	Control	Nasal drops
Kohaf 2024, Egypt	60	44.3 ± 11.0	25.6 ± 2.7	78.3	ENT	1 $\mu g.kg^{-1}$	IV	Nasal drops
Mohammed 2024, Egypt	70	40.6 ± 10.7	26.0 ± 3.9	54.3	ENT	1 $\mu g.kg^{-1}$	IV	Nasal drops
Rani 2024, India	90	41.5 ± 11.7	25.3 ± 2.9	54.4	NR	1 $\mu g.kg^{-1}$	Control	Nebulizer
Yang 2024, China	60	50.7 ± 5.2	23.1 ± 2.6	38.3	NR	2.5 $\mu g.kg^{-1}$	Control	Nasal drops
Kaila 2023, India	80	35.4 ± 7.9	NR	53.8	Mixed	1 $\mu g.kg^{-1}$	Control	Nebulizer
M 2023, India	106	39.8 ± 12.3	NR	NR	Mixed	1 $\mu g.kg^{-1}$	IV	Nasal drops
Niu 2023, China	99	70.4 ± 6.5	24.2 ± 4.2	47.5	Spine	1 $\mu g.kg^{-1}$	IV	Nasal drops
Safavi 2022, Iran	59	41.89 ± 13.97	NR	32.9	NR	1 $\mu g.kg^{-1}$	Control	NR
Singh 2022, India	120	41.7 ± 10.4	25.0 ± 3.5	51.7	Mixed	1 $\mu g.kg^{-1}$	IV	Nebulizer
Suryawanshi 2022, India	60	43.4 ± 13.3	NR	51.7	Mixed	1 $\mu g.kg^{-1}$	Control	Nebulizer
Wu 2022, China	29	41.6 ± 12.2	22.1 ± 1.9	44.8	ENT	1 $\mu g.kg^{-1}$	IV	MAD
Zeng 2022, China	72	39.3 ± 11.3	22.2 ± 2.1	40.3	NR	2.5 $\mu g.kg^{-1}$	Control	Nasal drops
Kochhar 2021, India	60	34.5 ± 11.6	NR	55.0	Mixed	1 $\mu g.kg^{-1}$	Control	Nasal drops
Niyogi 2019, India	70	41.4 ± 11.7	22.9 ± 2.1	58.6	Spine	100 μg	IV	Nasal drops
Niyogi 2018, India	70	41.4 ± 11.7	22.8 ± 1.7	58.6	Spine	1 $\mu g.kg^{-1}$	Control	Nasal drops
Lu 2016, China	81	44.7 ± 9.7	22.7 ± 4.2	35.8	Suspension Laryngoscopy	1 $\mu g.kg^{-1}$	Control	Nasal drops
Qiao 2016, China	60	49.0 ± 12.3	23.4 ± 3.3	60.0	ENT	2 $\mu g.kg^{-1}$	Control	MAD
Wu 2016, China	80	47.3 ± 4.7	NR	0.0	Gynecology	1 $\mu g.kg^{-1}$	Control and IV	NR
Jayaraman 2013, India	40	NR	46.9 ± 7.0	NR	Bariatric	1 $\mu g.kg^{-1}$	Control	Nasal drops

ENT, Ear Nose and Throat; IV, Intravenous; MAD, Mucosal Atomization Device; NR, Not Reported.

Table 2 Pooled effects for outcomes in intranasal dexmedetomidine compared with control.

Outcome	Effect on IN Group (95% CI)	n studies (patients)	p-value	I^2	GRADE Certainty of Evidence
Sedation Score	SMD **0.76 Higher** (0.18–1.34)	5 (393)	0.010	87.6%	Low
HR					
Baseline	MD **0.38 Lower** (−2.57–1.80)	8 (568)	0.730	50.8%	Low
Induction	MD **13.37 Lower** (−18.36 to -8.39)	2 (110)	< 0.001	9.2%	High
Intubation	MD **12.73 Lower** (−17.66 to -7.80)	7 (508)	< 0.001	86%	Very Low
10 Minutes	MD **13.15 Lower** (−18.02 to -8.27)	4 (249)	< 0.001	77.4%	Low
MAP					
Baseline	MD **1.05 Higher** (-0.97–3.08)	7 (508)	0.309	42.9%	Moderate
Induction	MD **10.65 Lower** (−16.56 to -4.75)	2 (110)	< 0.001	60.3%	Moderate
Intubation	MD **10.44 Lower** (−15.37 to -5.52)	7 (508)	< 0.001	85.3%	Very Low
10 Minutes	MD **7.77 Lower** (−14.56 to -0.98)	4 (249)	0.025	87.5%	Very Low
Bradycardia Incidence	RR **1.15** (0.64–2.04)	5 (433)	0.645	0%	High
Hypotension Incidence	RR **1.09** (0.61–1.96)	6 (493)	0.769	7.9%	High

IN, Intranasal Dexmedetomidine; HR, Heart Rate; MAP, Mean Arterial Pressure; SMD, Standardized Mean Difference; MD, Mean Difference; RR, Risk Ratio; CI, Confidence Interval; I^2, Heterogeneity statistic; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

(RR = 1.09, 95% CI: 0.61 to 1.96, p = 0.769; I^2 = 7.9%).[14,26,27,29–31]

Clinical effects of IN compared with IV dexmedetomidine

Compared with IV dexmedetomidine, IN administration was associated with lighter sedation in four studies (SMD = -0.54, 95% CI: -1.08 to -0.01, p = 0.047; I^2 = 79%; Fig. 2B).[30,32,34,44] Baseline HR and MAP did not differ statistically between groups. At intubation, no statistically significant differences in HR (MD = 2.44 bpm, 95% CI: -1.08 to 5.96, p = 0.174; I^2 = 62%; Fig. 3B)[36,40,42,43] or MAP (MD = 1.83 mmHg, 95% CI: -0.02 to 3.68, p = 0.052; I^2 = 40%; Fig. 3D)[35,36,40,42,43] were observed between IN and IV dexmedetomidine. No significant differences between IN and IV dexmedetomidine were observed at induction,[35,36,40,42,43] nor at 10 minutes.[34–36,39,40,42,43]

Safety outcomes

Bradycardia occurred significantly less frequently with IN compared with IV dexmedetomidine (RR = 0.31, 95% CI: 0.11 to 0.87, p = 0.026; I^2 = 0%, Fig. S4).[30,32,36,44] Limited data from two studies suggested a lower risk of hypotension with IN compared with IV dexmedetomidine administration (RR = 0.15, 95% CI: 0.03 to 0.79, p = 0.026).[32,36]

Secondary outcomes

Propofol consumption

Across four studies comparing IN dexmedetomidine with control, three reported a significant reduction in propofol consumption in the IN group,[14,15,30] while one study found no significant difference.[33] When comparing IN with IV dexmedetomidine, one study demonstrated a significant

Table 3 Pooled effects for outcomes in intranasal dexmedetomidine compared with intravenous dexmedetomidine.

Outcome	Effect on IN Group (95% CI)	n studies	p-value	I^2	GRADE Certainty of Evidence
Sedation Score	SMD **0.54 Lower** (−1.08 to -0.01)	4 (303)	0.047	78.7%	Low
HR					
Baseline	MD **0.14 Lower** (−3.41–3.14)	6 (495)	0.934	65.9%	Low
Induction	MD **1.41 Higher** (−0.36–3.17)	5 (466)	0.118	0%	High
Intubation	MD **2.44 Higher** (−1.08–5.96)	4 (360)	0.174	62%	Moderate
10 Minutes	MD **4.09 Higher** (−0.18–8.37)	6 (449)	0.061	87.4%	Low
MAP					
Baseline	MD **0.10 Higher** (−2.17–2.37)	7 (555)	0.933	49.6%	Moderate
Induction	MD **0.81 Lower** (−2.44–0.82)	4 (360)	0.332	0%	High
Intubation	MD **1.83 Higher** (−0.02–3.68)	5 (466)	0.052	40.4%	Moderate
10 Minutes	MD **0.69 Higher** (−1.80–3.18)	7 (555)	0.588	71.6%	Moderate
Bradycardia Incidence	RR **0.31** (0.11–0.87)	4 (363)	0.026	0%	High
Hypotension Incidence	RR **0.15** (0.03–0.79)	2 (293)	0.026	0%	High

IN, Intranasal Dexmedetomidine; HR, Heart Rate; MAP, Mean Arterial Pressure; SMD, Standardized Mean Difference; MD, Mean Difference; RR, Risk Ratio; CI, Confidence Interval; I^2, Heterogeneity statistic; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

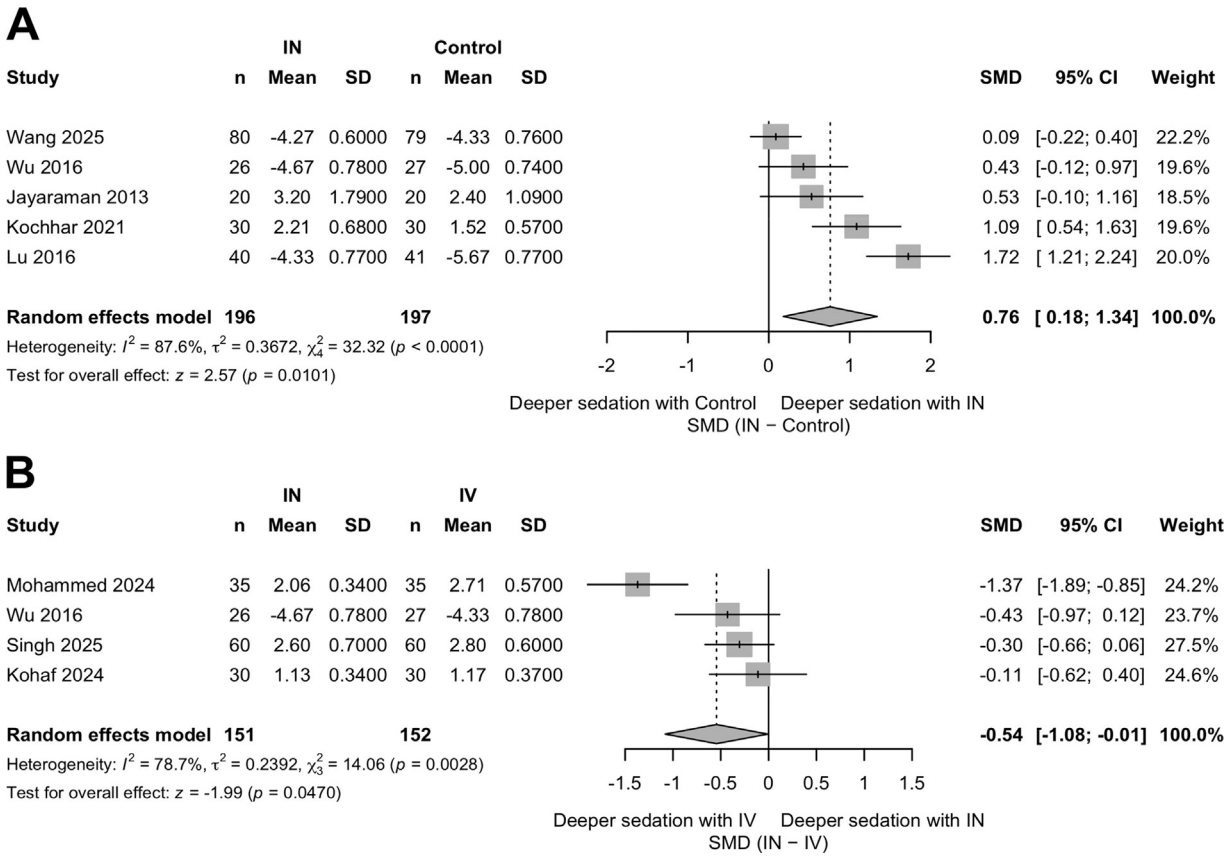

Figure 2 Forest plots for sedation score post-medication comparing Intranasal (IN) dexmedetomidine with (A) control and (B) Intravenous (IV) dexmedetomidine. The effect measure calculated was standardized mean difference. Positive values reflect deeper sedation with IN relative to the comparator.

decrease in the IV group,[30] whereas another reported no significant change in propofol requirements.[39]

24-hour postoperative opioid consumption

One study comparing IN dexmedetomidine with control found no significant difference in postoperative opioid consumption.[30] Conflicting findings were observed in studies that compared IN and IV dexmedetomidine. Namely, one study reported a significant increase (+12.9 μg sufentanil) in opioid consumption in the IN group,[30] while another study demonstrated no significant difference between the two routes of administration.[34]

PACU time

Among studies comparing IN dexmedetomidine with control, two reported no significant difference in PACU length of stay,[14,37] while one study demonstrated a significant reduction in PACU time (-6 minutes) in the IN group. [31] In comparisons between IN and IV dexmedetomidine, one study found no significant difference in PACU duration,[39] whereas another reported a significant decrease in PACU time with IN administration.[44]

Postoperative nausea and vomiting

Among studies comparing IN dexmedetomidine with control, two studies reported no significant differences in PONV incidence between groups.[14,31] In comparisons between IN and IV dexmedetomidine, two studies similarly demonstrated no significant differences in PONV outcomes.[36,44] Additionally, one study comparing IN, IV, and control groups found no significant differences in PONV incidence in any of the treatment arms.[42]

Sensitivity analyses

Leave-one-out sensitivity analyses showed that removing individual studies did not change the direction or significance for most outcomes. For outcomes that were borderline or non-significant, study removal produced minor shifts in effect size but did not alter the overall interpretation.

Heterogeneity across leave-one-out sensitivity analyses varied by outcome and comparison (Table S5). Exclusion of individual studies did not materially change the direction or statistical significance of pooled effects for most outcomes. However, the magnitude of between-study heterogeneity varied across outcomes and comparisons, as demonstrated in Table S5.

Cochrane risk of bias assessment

Two studies were rated as having a low risk of bias,[27,33] demonstrating robust methodological quality. The majority of studies

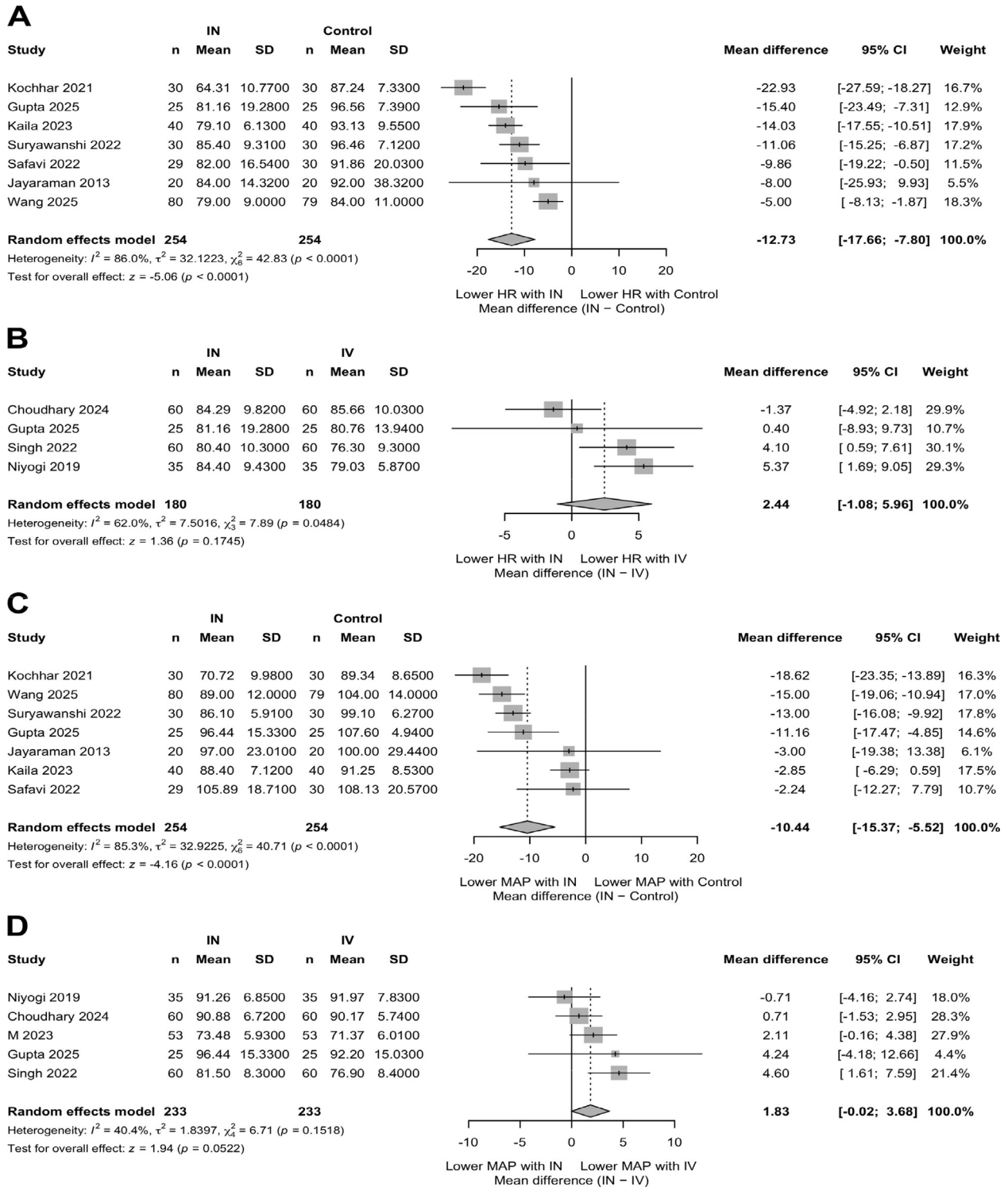

Figure 3 Forest plots for intraoperative hemodynamic outcomes comparing Intranasal dexmedetomidine (IN) to control or Intravenous dexmedetomidine (IV). (A) Heart rate at intubation: IN vs. control. (B) Heart rate at intubation: IN vs. IV. (C) Mean Arterial Pressure (MAP) at intubation: IN vs. control. (D) MAP at intubation: IN vs. IV. The effect measure calculated was mean difference. Negative values indicate lower HR or MAP with IN dexmedetomidine, whereas positive values indicate lower HR or MAP with the comparator.

were rated as having "some concerns",[14–16,26,29–32,34–36,39–45] except one with a "high" overall risk of bias (Figs. S6–S7).[37] Most concerns were related to selection of reported results due to measurement of outcomes at multiple time points. Other less common concerns were related to randomization and deviations from intended interventions.

GRADE certainty of evidence

The GRADE certainty of evidence across outcomes varied from very low to high. High-certainty evidence was observed for bradycardia and hypotension, while moderate-certainty evidence supported a subset of hemodynamic measures (Table S8). In contrast, sedation and several peri-intubation and post-induction hemodynamic outcomes were generally supported by low or very low certainty evidence. Downgrading most frequently resulted from inconsistency due to substantial between-study heterogeneity, with occasional downgrading for risk of bias.

Discussion

This systematic review and meta-analysis of 25 RCTs evaluated preoperative IN dexmedetomidine in adult patients having inpatient surgery under GA across two separate pairwise comparisons: IN dexmedetomidine vs. control and IN vs. IV dexmedetomidine. Preoperative IN dexmedetomidine was associated with sedative and hemodynamic effects that may be clinically relevant, although certainty varied across outcomes. Compared with control, IN dexmedetomidine was associated with significantly deeper preoperative sedation and consistent attenuation of hemodynamic responses at induction, intubation, and in the early intraoperative period. Compared with IV dexmedetomidine, IN administration resulted in lighter sedation and broadly similar hemodynamic control, with lower observed rates of bradycardia and hypotension. These findings suggest that IN dexmedetomidine may provide effective preoperative sedation and hemodynamic modulation, although the safety comparison with IV administration is based on a limited number of trials and events and should be interpreted with caution.

Although the evidence in adults should be interpreted cautiously given heterogeneity and low certainty for sedation, the observed direction of effect is consistent with pediatric literature, where IN dexmedetomidine has been associated with high sedation success and greater sedative efficacy than midazolam.[12,13,48] The sedative effects of dexmedetomidine are mediated primarily through selective activation of central α_2-adrenergic receptors, particularly within the locus coeruleus, leading to inhibition of norepinephrine release and reduced sympathetic outflow. This mechanism produces a state of cooperative sedation that resembles natural sleep, while preserving respiratory drive, a physiological profile that likely underlies its sedative effects across populations.[49]

Differences in route of administration and dosing kinetics provide a plausible explanation for the observed difference in sedative depth between IV and IN dexmedetomidine. Nevertheless, this difference may be clinically relevant, as deeper sedation has been associated with less favorable postoperative outcomes. One study reported longer time to awakening, delayed recovery, and prolonged PACU stays with IV administration compared with controls.[50] These findings suggest that higher peak plasma concentrations with IV dexmedetomidine may lead to residual sedation. In contrast, IN administration results in slower absorption and lower peak concentrations, producing a more gradual and moderate sedative effect. This likely explains the lighter sedation observed in our study, while maintaining adequate sympatholytic and hemodynamic stability. Clinically, lighter preoperative sedation may be preferable when the primary goals are anxiolysis and attenuation of sympathetic responses rather than deep sedation, facilitating quicker recovery.

The hemodynamic findings are biologically plausible given the sympatholytic effects of dexmedetomidine and are consistent with prior orthopedic studies reporting reduced perioperative sympathetic responses with IN administration.[51,52] Similar to sedative effects, this is likely explained by selective α_2-adrenergic receptor agonism in the locus coeruleus.[4] In addition, presynaptic α_2-receptor activation inhibits peripheral norepinephrine release, further contributing to reductions in HR and MAP.[53]

There is no consensus definition for the magnitude of HR or MAP attenuation that constitutes a clinically significant blunting of the intubation response. In anesthetic practice, the reductions observed with IN dexmedetomidine relative to control, approximately 13 bpm in HR and 8 to 11 mmHg in MAP, may represent a modest attenuation of the sympathetic response rather than a clearly established patient-important benefit. Importantly, these reductions were not accompanied by increased bradycardia or hypotension, supporting their overall clinical acceptability. Their clinical relevance may be greatest in patients for whom sympathetic surges during intubation are undesirable.[54]

The apparent similarity in peri-induction hemodynamic control between IN and IV administration may reflect convergence in central sympatholytic effects despite differences in route and sedative depth. The absence of hemodynamic differences between routes may reflect a ceiling effect of α_2-mediated autonomic modulation during GA, whereby additional drug exposure does not translate into further measurable cardiovascular suppression.

Dexmedetomidine has some known adverse cardiovascular side effects, with hypotension and bradycardia being the most commonly reported.[52] The apparent safety signal favoring IN administration is pharmacologically plausible given its slower systemic absorption and more gradual peak plasma concentrations. These safety estimates were derived from a small number of trials and few events, and should be regarded as preliminary rather than definitive evidence. Taken together with the lighter sedation observed with the IN route, these findings may suggest a possible efficacy-safety trade-off. A modest reduction in sedative depth may be an acceptable compromise when the priority is to avoid bradycardia and hypotension, particularly in patients in whom hemodynamic stability is critical. Confirmation in adequately powered safety trials is needed before this trade-off can be considered established.

Study strengths and limitations

This study has several strengths. This was a comprehensive systematic review and meta-analysis restricted to RCTs, enhancing internal validity and minimizing confounding. Rigorous quantitative synthesis was complemented by sensitivity analyses, allowing exploration of heterogeneity and assessment of the robustness of pooled estimates. Certainty of evidence was systematically evaluated using the GRADE framework, providing transparent appraisal of confidence

across outcomes. Finally, inclusion of a broad range of surgical populations enhances the generalizability of the findings to adult surgical patients, although this diversity may contribute to heterogeneity.

This study has several limitations. Although restricted to RCTs, some pooled outcomes were informed by a limited number of studies, reducing statistical power and precision. Substantial heterogeneity was observed for several outcomes, likely reflecting variability in IN dexmedetomidine dosing, timing of administration, surgical populations, and perioperative protocols, which contributed to low certainty of evidence for select endpoints. The predominance of single -country/single-region trials, variable quality of reporting, small sample sizes for several outcomes, differences in sedation scales, possible publication bias, and the limited ability to assess rare adverse events may limit the certainty and generalizability of these findings. Future research should focus on well-powered, multicenter RCTs to define optimal dosing, timing, and patient selection for IN dexmedetomidine, using standardized sedation and hemodynamic outcome measures to improve comparability across studies.

Clinical implications

IN dexmedetomidine may represent an option for noninvasive premedication that provides sedation and peri-induction hemodynamic stability without a clear increase in adverse effects, particularly when IV access is limited or lighter sedation is desired. Its alignment with enhanced recovery after surgery (ERAS) principles supports consideration in adult preoperative care.

Conclusion

Preoperative IN dexmedetomidine was associated with improved sedation and attenuation of peri-induction hemodynamic responses compared with controls. Compared with IV dexmedetomidine, IN administration showed broadly similar peri-induction hemodynamic effects and lower observed rates of bradycardia and hypotension, although these findings should be interpreted cautiously given heterogeneity and low or very low certainty for several outcomes. Overall, IN dexmedetomidine may represent a promising noninvasive premedication option in selected adult surgical patients, although confirmation in larger, standardized, adequately powered trials is still required.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. The extracted aggregate-level dataset, analytic files, and statistical code supporting the findings of this systematic review and meta-analysis have been deposited in Mendeley Data and are available at: https://doi.org/10.17632/jsdtydr35v.1. The dataset is currently under embargo and will be made publicly available after the embargo period on September 5, 2026. No individual participant data were used. All data were extracted from published studies cited in the manuscript.

Units

MAP was reported in mmHg and heart rate was reported in beats per minute (bpm).

Declaration of AI and AI-assisted technologies

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language editing and refinement. The authors reviewed and edited all AI-assisted content and take full responsibility for the final manuscript.

Author's contribution

Vitaliy Voznyy: Conceptualization; Methodology; Data extraction; Drafted manuscript; Manuscript reviewing and editing. Mouad Elganga: Conceptualization; Methodology; Full-text screening; Statistical analyses; Drafted manuscript; Manuscript reviewing and editing. Leya Tawfik: Methodology; Screening; Data extraction; Drafted manuscript; Manuscript reviewing and editing. Tony Tan: Screening; Data extraction; Manuscript reviewing and editing. Sammie Yu: Data extraction; Manuscript reviewing and editing. Ellene Yan: Conceptualization; Methodology; Manuscript reviewing and editing. Aparna Saripella: Methodology; Manuscript reviewing and editing. Marina F. Englesakis: Designed and executed the database search strategies; Manuscript reviewing and editing. Frances Chung: Conceptualization; Methodology; Manuscript reviewing and editing.

Funding

EY reports research support from the Canadian Institutes of Health Research (CIHR) Canada Graduate Scholarships Doctoral Award grant number: FBD-195197. AS reports research support from the University Health Network Foundation. FC reports research support from the Ontario Ministry of Health Innovation Grant, ResMed Foundation, University Health Network Foundation, and STOP-Bang Questionnaire proprietary to the University Health Network.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844820.

Associate Editor

Neuber Martins Fonseca

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Artificial intelligence in cardiopulmonary resuscitation: a systematic review

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Received 9 January 2026; accepted 5 July 2026
Available online 12 July 2026

KEYWORDS
Artificial intelligence;
Cardiopulmonary resuscitation;
Clinical decision support systems;
Emergency medical services;
Heart arrest;
Machine learning

Abstract Cardiac arrest remains a major cause of mortality and neurological disability, and its management depends on rapid recognition, effective resuscitation, and accurate post-arrest prognostication. Artificial intelligence (AI) has been increasingly investigated as a tool to support these stages of care. This narrative review summarizes recent evidence on AI applications in cardiac arrest, including prediction, recognition, intra-arrest support, prognostication, and cardiovascular risk stratification. Searches were conducted in PubMed/MEDLINE, Google Scholar, EMBASE, Scopus, IEEE Xplore, and ScienceDirect for studies published from January 2000 to June 2025. Studies addressing AI, machine learning, or deep learning in cardiac arrest-related contexts were descriptively synthesized according to clinical application, AI methodology, and care setting. Overall, 59 studies were included. Six application categories were identified: early prediction of cardiac arrest or clinical deterioration (n = 16), cardiac arrest recognition and emergency response activation (n = 3), intra-arrest CPR and defibrillation support (n = 6), post-cardiac arrest prognostication (n = 20), risk stratification for sudden cardiac death and malignant arrhythmias (n = 11), and related cardiovascular or perioperative prognostic models (n = 3). Deep learning and neural-network-based approaches were the most frequent methodologies (n = 35), followed by traditional machine learning (n = 18) and natural language processing (n = 6). AI showed particular promise for ECG-based prediction, temporal clinical trajectories, emergency call interpretation, waveform and defibrillation analyses, and neurological or mortality prognostication after cardiac arrest. However, the evidence remains heterogeneous, with many studies relying on retrospective datasets, selected populations, and limited external or prospective validation.

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https://doi.org/10.1016/j.bjane.2026.844795

Introduction

Cardiac Arrest (CA) constitutes a critical medical emergency characterized by an abrupt cessation of circulatory and respiratory function, resulting in interruption of oxygen supply to vital organs.[1] This condition represents one of the leading causes of mortality, with an estimated incidence of approximately 8.27 cases per 1,000 hospitalizations.[2] Despite significant advances in emergency medicine and resuscitation techniques over the past decades, survival rates remain challenging, with only 25% of patients surviving to hospital discharge and only 22% of survivors achieving a good neurological status.[3]

The management of cardiac arrest faces clinical challenges that directly impact patient outcomes, as there is a limited critical time window during which Cardiopulmonary Resuscitation (CPR) can be adequate, with the probability of success decreasing drastically with each minute of delay in recognition and initiation of resuscitation maneuvers.[4] Late recognition of cardiac arrest and delayed CPR initiation are factors frequently associated with unfavorable outcomes. Additionally, cardiac arrest survivors frequently develop significant neurological complications as part of an unpredictable long-term prognosis.[5] The complexity of cardiac arrest care is amplified by the need for rapid and precise decision-making in high-pressure environments, where healthcare professionals must integrate multiple clinical variables, interpret vital signs in real-time, and execute coordinated team interventions. Traditional prediction and risk assessment methods are based on clinical scores and guidelines that, although validated, do not exceed 50% accuracy in identifying high-risk patients.[6]

In this context, Artificial Intelligence (AI) offers opportunities to address limitations in cardiac arrest management. AI offers opportunities to address the limitations of conventional methods by processing large data volumes, identifying complex patterns that the human eye cannot detect, and providing real-time predictive analyses based on Electrocardiogram (ECG) data or multiple electronic health records.[7] Beyond prediction, AI can optimize resuscitation quality through real-time feedback systems for the team and assistance in coordinating actions.[8] Additionally, natural language processing systems can improve recognition of cardiac arrest in emergency calls, reducing the time between the event and the arrival of specialized assistance.[9]

The objective of this review was to provide an overview of recent advances, main methodological approaches, and potential clinical applications of AI in the prediction, detection, recognition, and management of cardiac arrest.

Methods

This study constitutes a narrative review of the contemporary scientific literature on the application of Artificial Intelligence (AI) in cardiac arrest, with searches conducted across databases including PubMed/MEDLINE, Google Scholar, EMBASE (Excerpta Medica Database), Scopus, IEEE Xplore, and ScienceDirect.

The literature search spanned the period from January 2000 to June 2025 and was conducted between January and June 2025, employing combinations of keywords related to artificial intelligence and cardiac arrest, such as “artificial intelligence cardiac arrest”, “machine learning cardiopulmonary resuscitation”, “AI emergency medicine cardiac arrest”, “deep learning ECG cardiac arrest prediction”, “artificial intelligence CPR quality”, and “machine learning emergency medical services”, along with variations, synonyms, and Boolean combinations incorporating terms like “prediction”, “detection”, “recognition”, “Electrocardiography” (ECG/EKG), “emergency medicine”, “resuscitation”, “sudden cardiac death”, and “sudden cardiac arrest” to capture relevant publications.

Titles and abstracts of retrieved publications were screened for relevance, focusing on studies addressing AI, machine learning, or deep learning applications in cardiac arrest contexts, including prediction, detection, recognition, or optimization of Cardiopulmonary Resuscitation (CPR); preference was given to original research articles in peer-reviewed journals written in English or Portuguese, with emphasis on publications on recent technological, while excluding editorials, commentaries, conference abstracts lacking full data, and unrelated studies.

When available in the studies, algorithm performance metrics such as sensitivity, specificity, Area Under the Receiver Operating Characteristic Curve (AUROC), and F1-score were extracted, with studies descriptively categorized by primary application (cardiac arrest prediction, recognition, CPR optimization, or post-arrest outcome prediction), AI methodology employed, and clinical setting (e.g., in-hospital or out-of-hospital cardiac arrest, emergency departments, or intensive care units).

Due to heterogeneity in study designs, datasets, and evaluation metrics, findings were synthesized qualitatively through narrative analysis rather than quantitative meta-analysis.

Before final manuscript submission, all included references were checked for retraction notices and formal expressions of concern using PubMed, Crossref/Crossmark, and the Retraction Watch Database. No retracted articles or articles subject to formal expressions of concern were identified among the references included in the final manuscript.

Results

The 59 included studies were grouped into six application categories according to their primary clinical purpose in cardiac arrest care: early prediction of cardiac arrest or clinical deterioration, cardiac arrest recognition and emergency response activation, intra-arrest support for CPR and defibrillation, post-cardiac arrest prognostication, risk stratification for sudden cardiac death and malignant arrhythmias, and related cardiovascular or perioperative prognostic models (Table 1).

Early prediction of cardiac arrest / clinical deterioration (16 studies)

Early prediction of cardiac arrest/clinical deterioration was the second largest category, comprising 16 studies.[10-25] These studies used AI models to anticipate cardiac arrest or clinical deterioration before the event, based on ECG data, vital signs, laboratory parameters, clinical history, or

Table 1 Application categories.

Application category	N	Articles	Description
Early prediction of cardiac arrest/clinical deterioration	16	Arnold et al.;[10] Cho et al.;[11] Fernandes et al.;[12] Hu et al.;[13] Jang et al.;[14] Javan et al.;[15] Kennedy et al.;[16] Kim et al.;[17] Kwon et al.;[18] Kwon et al.;[19] Lee et al.;[20] Lee et al.;[21] Lu et al.;[22] Matam et al.;[23] Ong et al.;[24] Shamout et al.[25]	AI models used to predict cardiac arrest or clinical deterioration before the event, based on ECG, vital signs, laboratory data, clinical history, or patient trajectories.
Cardiac arrest recognition and emergency response activation	3	Blomberg et al.;[26] Blomberg et al.;[27] Chen et al.[28]	AI tools for recognizing cardiac arrest in emergency calls or improving emergency response logistics, including dispatcher support and AED.
Intra-arrest, CPR, and defibrillation support	6	He et al.;[29] Howe et al.;[30] Islam et al.;[31] Liu et al.;[32] Rad et al.;[33] Yang et al.[34]	Studies applying AI during active resuscitation, including rhythm classification, waveform analysis, defibrillation outcome prediction, ROSC prediction, and biomedical signal processing during CPR.
Post-cardiac arrest prognostication	20	Al-Dury et al.;[35] Amorim et al.;[36] Andersson et al.;[37] Chung et al.;[38] Coult et al.;[39] Elmer et al.;[40] Ghassemi et al.;[41] Harford et al.;[42] Hirano et al.;[43] Johnsson et al.;[44] Jonas et al.;[45] Kwon et al.;[46] Le Duff et al.;[47] Nanayakkara et al.;[48] Park et al.;[49] Pugin et al.;[50] Seki et al.;[51] Tjepkema-Cloostermans et al.;[52] Tjepkema-Cloostermans et al.;[53] Wagner et al.[54]	AI models for predicting survival, neurological outcome, mortality, recovery, or post-anoxic brain injury phenotypes after cardiac arrest.
Risk stratification for sudden cardiac death and malignant arrhythmias	11	Alonso et al.;[55] Au-Yeung et al.;[56] Ebrahimzadeh et al.;[57] Lai et al.;[58] Liu et al.;[59] Liu et al.;[60] Martinez-Alanis et al.;[61] Moon et al.;[62] Tylman et al.;[63] Wu et al.;[64] Zoni-Berisso et al.[65]	Studies estimating the risk of sudden cardiac death, malignant ventricular arrhythmias, tachyarrhythmias, NSTEMI, or major adverse cardiovascular events before cardiac arrest occurs.
Related cardiovascular or perioperative prognostic models	3	Chong et al.;[66] Turton et al.;[67] Wise et al.[68]	Peripheral cardiovascular or perioperative prognostic models with indirect relevance to the review, but not directly focused on cardiac arrest or CPR.

AED, Automated External Defibrillator; AI, Artificial Intelligence; CPR, Cardiopulmonary Resuscitation; ECG, Electrocardiogram; NSTEMI, Non-ST-elevation Myocardial Infarction; ROSC, Return of Spontaneous Circulation.

patient trajectories. This group included both ECG-based models and structured-data approaches. Kwon et al.[18] developed a deep learning algorithm using 12-lead ECGs, achieving an AUROC of 0.913 in internal validation and 0.948 in external validation. More recently, Lu et al.[22] introduced EIANet (ECG-Image-Aware Network), an ECG-image-aware deep learning model for emergency department cardiac arrest prediction, with an internal AUROC of 0.896 and external AUROC of 0.803.

These findings suggest that AI models may identify subtle physiological or electrocardiographic patterns associated with deterioration before cardiac arrest becomes clinically evident.

Cardiac arrest recognition and emergency response activation (3 studies)

Cardiac arrest recognition and emergency response activation included three studies.[26-28] These studies focused mainly on recognizing cardiac arrest in emergency calls or improving emergency response logistics, including dispatcher support and AED. Natural language processing and related AI-based approaches were used to support earlier recognition of out-of-hospital cardiac arrest and reduce delays in emergency response activation.

Intra-arrest, CPR, and defibrillation support (6 studies)

Intra-arrest, CPR, and defibrillation support comprised six studies.[29-34] This category included AI applications during active resuscitation, such as rhythm classification, ECG waveform analysis, defibrillation outcome prediction, ROSC (Return of spontaneous circulation) prediction, and biomedical signal processing during CPR. These studies indicate that AI may support real-time decision-making during resuscitation by helping interpret complex physiological signals and potentially improving CPR and defibrillation strategies.

Post-cardiac arrest prognostication (20 studies)

Post-cardiac arrest prognostication was the largest category, comprising 20 studies.[35-54] These studies evaluated AI models designed to predict survival, neurological outcomes, mortality, recovery patterns, or post-anoxic brain injury phenotypes after cardiac arrest. The predominance of this category indicates a strong research focus on post-resuscitation risk assessment and prognostic support, particularly for neurological recovery and mortality prediction.

Risk stratification for sudden cardiac death and malignant arrhythmias (11 studies)

Risk stratification for sudden cardiac death and malignant arrhythmias included 11 studies.[55-65] These studies estimated the risk of sudden cardiac death, malignant ventricular arrhythmias, tachyarrhythmias, NSTEMI (Non-ST-elevation myocardial infarction), or major adverse cardiovascular events before cardiac arrest occurs. Lai et al.[58] developed the MAARS (Multimodal AI for Ventricular Arrhythmia Risk Stratification) model, which used cardiac magnetic resonance imaging to predict arrhythmic death in hypertrophic cardiomyopathy, achieving an overall accuracy of 89% and 93% accuracy among patients aged 40-60 years. This category broadens the scope of AI applications from immediate cardiac arrest prediction to preventive risk stratification in populations at increased cardiovascular risk.

Cardiovascular or perioperative prognostic models

Related cardiovascular or perioperative prognostic models represented the smallest category, with three studies.[66-68] These studies were not directly focused on cardiac arrest or CPR but were included because of their indirect relevance to cardiovascular or perioperative prognostication. Their inclusion highlights adjacent areas in which AI-based risk prediction may inform broader clinical decision-making related to acute cardiovascular deterioration.

Analysis by AI methodology

Deep Learning (35 studies)

Deep learning and neural-network-based approaches were the most frequent methodological strategies. These models included convolutional neural networks for ECG image analysis and biomedical signal processing, recurrent neural networks and long short-term memory networks for temporal trajectories, and artificial neural network models for clinical prediction or prognostic classification. They were mainly applied to early prediction of cardiac arrest or clinical deterioration, post-cardiac arrest prognostication, and risk stratification for sudden cardiac death or malignant arrhythmias.[13,14,17-22,25,29,33,34,36-38,41,45,46,52,53,57,58,60,65-67]

Traditional machine learning (18 studies)

Traditional machine learning methods, including support vector machines, random forests, Bayesian networks, supervised learning, data mining approaches, and machine learning scores, were identified across studies using structured clinical data, HRV-derived variables, waveform metrics, neuroimaging features, and cardiovascular risk predictors. These approaches were particularly frequent in intra-arrest defibrillation or ROSC prediction, post-arrest outcome prediction, and risk stratification for sudden cardiac death or major cardiovascular events.[10,11,15,16,23,24,30-32,35,39,40,42-44,47-51,54-56,59,61,63,64,68]

Natural language processing (6 studies)

Natural language processing was used in studies involving emergency call analysis, textual clinical data, or automated extraction of risk factors from medical records. These applications were mainly related to cardiac arrest recognition, emergency response activation, and integration of unstructured text with clinical prediction models.[12,26-28,62]

Overall, deep learning models appeared more frequently in ECG-based prediction, temporal physiological data, and complex signal or image interpretation, whereas traditional machine learning approaches were more common in structured clinical prediction, waveform-based defibrillation analyses, and cardiovascular risk stratification. Natural language processing represented a smaller but clinically relevant group, especially for emergency call interpretation and extraction of information from unstructured records.

Discussion

This narrative review summarizes current evidence on the use of artificial intelligence in cardiac arrest prediction, recognition, resuscitation support, and post-arrest prognostication. Overall, the included studies suggest that AI-based approaches have potential clinical relevance, particularly in ECG-based prediction and early detection of clinical deterioration.

Given the high-stakes nature of cardiac arrest care, AI applications in this field require particularly rigorous evaluation. Models intended to support prediction, recognition, resuscitation, or prognostication must demonstrate not only technical performance but also clinical validity, safety, interpretability, and reproducibility across different settings. The intersection between AI and emergency medicine also demands multidisciplinary expertise, as reliable development and implementation depend on both robust computational methods and a clear understanding of the clinical context in which these tools may be used.

The temporal analysis of studies reveals a clear progress in the technological sophistication of AI applications. The earliest studies (2018–2019) focused mainly on traditional machine learning algorithms applied to structured clinical data. Starting in 2020, a transition toward more complex deep learning models has been observed, particularly in ECG analysis and biomedical signal processing.

The development of the EIANet model by Lu et al.[22] represents a milestone in technological evolution, demonstrating

how deep learning architectures can be specifically adapted for the clinical context. The incorporation of spatial attention modules and a customized loss function (Binary Recall Loss) illustrates the field's growing methodological sophistication.

The advantage of AI-based ECG analysis deserves special emphasis. The fact that algorithms can identify patterns in the QRS complex and ST segment that are imperceptible to the human eye suggests that significant predictive information is being underutilized in current clinical practice. This discovery has potential clinical relevance for the development of continuous monitoring and early warning systems.

External validation was clearly reported in only a small subset of the included studies. Kwon et al.[19] externally validated an ECG-based deep learning algorithm in an independent hospital dataset, Lee et al.[20] performed a multicentre validation of the deep learning-based early warning score, Lu et al.[22] externally validated the EIANet model using an independent emergency department ECG-image dataset, and Tjepkema-Cloostermans et al.[53] externally validated a deep learning model for postanoxic coma using data from additional hospitals. Most remaining studies relied on internal validation, cross-validation, holdout test sets, or registry-based train-test splits, which may overestimate real-world generalizability.

The study by Kwon et al.[19] exemplifies both the potential and the challenges of external validation. Although the model demonstrated an AUROC of 0.948 in external validation, this performance was achieved in a hospital with characteristics similar to those of the development hospital. True generalization requires validation in more diverse populations and varied clinical contexts.

Studies with external validation have demonstrated greater robustness and generalization, though they often show slightly lower performance than internal validation, highlighting the importance of validation in independent populations. This is an implicit limitation of AI models, as they are trained on specific databases, and performance declines when applied to population data outside those databases.

The question of interpretability emerges as a critical challenge, particularly for deep learning models. Although these models demonstrate higher performance, their "black box" nature may limit clinical acceptance. The development of explainability techniques, such as attention maps and feature analysis, represents important progress but remains insufficient for many critical clinical applications.

Practical implementation of AI systems in real clinical environments faces significant challenges beyond technical performance. Issues of interoperability with hospital information systems, processing latency, and integration with existing clinical protocols are frequently underestimated in development studies.

Clinical confidence in AI systems requires not only high performance but also a thorough understanding of the decision-making mechanisms. The fact that the EIANet model identifies the ST segment as a region of interest provides important clinical validation, since ST segment alterations are known to be associated with adverse cardiac events.

The EIANet model, which uses ECG images obtained during screening, represents a pragmatic approach that recognizes the realities of clinical workflows. This strategy may facilitate the practical implementation compared to approaches that require significant modifications to existing processes. Results suggest AI applications may influence multiple aspects of cardiac arrest care. Early prediction capacity may enable preventive interventions that avoid cardiac arrest occurrence or improve medical team preparedness.

The MAARS model developed by Lai et al.[58] exemplifies the potential of AI for personalized care. These models may support future risk stratification strategies, but their role in routine care remains limited by the need for broader external validation, interpretability, workflow integration, and evaluation in prospective clinical settings.

The successful implementation of AI systems for cardiac arrest requires careful consideration of multiple factors. First, there is a need for adequate training of healthcare professionals to interpret and act based on AI predictions. Second, the development of clinical protocols that safely and effectively incorporate AI recommendations.

Experience with traditional early warning systems suggests that mere availability of predictive information does not guarantee improvement in clinical outcomes. Effectiveness depends on the healthcare system's capacity to appropriately respond to generated alerts.

Future perspectives

The future evolution of AI in cardiac arrest will likely follow several promising directions. The development of multimodal models that integrate ECG, vital signs, laboratory data, and medical images may offer promising performance in selected datasets compared to current unimodal models.

The application of federated learning techniques can address privacy and generalization issues, allowing the development of robust models without direct sharing of sensitive data between institutions. This approach is particularly relevant for cardiac arrest, where collaboration between multiple institutions is essential to obtain sufficiently large datasets.

This review identifies several important gaps that require future research, as there is an urgent need for randomized controlled trials to evaluate the real impact of AI implementation on clinical outcomes. Most current studies focus on the technical performance of algorithms, but evidence of real clinical benefits remains limited.

Furthermore, cost-effectiveness studies are necessary to inform implementation decisions in healthcare systems with limited resources. High technical performance must be balanced against the costs of implementation and maintenance.

Research on acceptance and usability by healthcare professionals is essential to ensure successful adoption. Resistance to change and concerns about the substitution of clinical judgment may limit the implementation of even technically superior systems.

Ethical and regulatory considerations

The application of AI in cardiac arrest raises important ethical questions that require careful consideration. Automation

of decisions that may impact the life or death of patients requires rigorous ethical standards and adequate human supervision.

The issue of responsibility in the event of system failures is particularly complex. When an AI algorithm fails to predict a cardiac arrest that subsequently occurs, or when it generates a false positive leading to unnecessary interventions, attribution of responsibility among developers, implementers, and clinical users remains undefined.

The regulation of AI systems in medicine is evolving rapidly, but it still faces significant challenges. The dynamic nature of machine learning algorithms, which may continue learning after implementation, challenges traditional regulatory frameworks based on static medical devices. The development of standards for validating, continuously monitoring, and updating AI systems in medicine is essential to ensure long-term safety and efficacy.

Limitations

This review has several limitations that should be acknowledged. First, the methodological heterogeneity of included studies allows only a narrative review. Second, the rapid evolution of the field means that important new studies may have been published during the conduct of this review, potentially altering the conclusions.

Finally, most included studies originate from developed countries with advanced technological infrastructures, which limits the generalizability of the findings to contexts with limited resources.

Conclusion

This narrative review indicates that AI has potential applications in cardiac arrest, including prediction, recognition of clinical deterioration, support for CPR quality, and post-arrest prognostication. Several studies reported promising algorithmic performance, particularly for ECG-based and structured-data models. However, the current evidence is heterogeneous, and most findings are based on retrospective datasets, selected populations, or limited validation settings.

Despite encouraging results, the clinical implementation of AI in cardiac arrest remains at an early stage. Limited external validation, scarce prospective evaluation, insufficient real-world implementation data, and uncertainty regarding workflow integration, interpretability, and clinical response to AI-generated alerts remain major barriers. Future research should prioritize multicenter external validation, prospective clinical studies, randomized or pragmatic implementation trials, cost-effectiveness analyses, and usability assessments involving healthcare professionals. Until such evidence is available, AI should be considered a promising adjunctive tool rather than a replacement for clinical judgment or established resuscitation protocols.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

AI assistance disclosure

AI-assisted tools were used to support language editing, textual organization, formatting, and refinement of the manuscript, including improvement of clarity, grammar, consistency, and reference presentation. These tools were not used to generate original data, perform independent study selection, conduct statistical analyses, or make clinical or scientific interpretations. All AI-assisted suggestions were critically reviewed, verified, and edited by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest for this review.

Funding

The authors declare no sources of funding for this review.

Associate Editor

Edmundo Pereira Souza Neto

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Sociedade Brasileira de Anestesiologia

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LETTER TO THE EDITOR

Point-of-care ultrasound for perioperative deep vein thrombosis assessment in anesthesiology: a narrative review

Dear Editor,

Deep vein thrombosis remains a major cause of preventable perioperative morbidity, and pulmonary embolism is one of the most feared complications in surgical patients.[1,2] Many episodes are clinically silent, which reinforces the importance of early recognition. Although duplex ultrasonography is the diagnostic reference standard, its availability may be limited during busy perioperative periods or in unstable patients who cannot be safely transported.[3] These challenges have driven growing interest in point-of-care ultrasound as a rapid bedside method for identifying lower limb thrombosis. Anesthesiologists, who routinely use ultrasound for vascular access, regional anesthesia, and hemodynamic assessment, are well positioned to incorporate venous compression protocols into perioperative evaluation. This narrative review summarizes available evidence on the diagnostic accuracy, applicability, and practical considerations of bedside ultrasound for deep vein thrombosis assessment in the perioperative setting.

The evidence included prospective and observational studies evaluating two-point, three-point, or extended compression approaches performed by clinicians from anesthesiology, emergency medicine, intensive care, and hospital medicine. These studies compared bedside ultrasound with duplex ultrasonography or contrast venography. To provide context for the diagnostic performance estimates presented, studies were identified through a structured literature search of MEDLINE and Embase using terms related to point-of-care ultrasound, compression ultrasound, deep vein thrombosis, and perioperative care, supplemented by reference list review. The reported sensitivity and specificity ranges cited in this review derive primarily from published systematic reviews and meta-analyses rather than from original synthesis. The 26 representative studies informing this narrative review are listed in Supplementary Table S1.

Across 26 representative studies identified through this search, reported sensitivity for proximal deep vein thrombosis ranged from 90% to 96%, and specificity from 95% to 97%.[4] These values suggest that trained clinicians may, under favorable conditions, produce diagnostic estimates in a range comparable to those reported in vascular laboratory settings; however, interpretation must remain cautious, as performance varies substantially with operator training, patient selection, disease prevalence, reference standard verification, and spectrum bias. The two-point protocol, which evaluates compressibility of the common femoral and popliteal veins, was the most frequently studied technique and proved efficient for rapid screening in low- to moderate-risk patients. The three-point method, adding the proximal femoral vein, and extended protocols that include more proximal or distal segments offered incremental diagnostic benefit in patients at higher risk or with suggestive clinical symptoms. No protocol reliably identified isolated distal calf thrombosis, and formal duplex scanning was recommended when distal disease was suspected.[5] The main differences between two-point and three-point compression protocols are summarized in Table 1.

The rapidity of point-of-care ultrasound is one of its most relevant advantages for anesthesiologists. Several studies have demonstrated that bedside evaluation shortens diagnostic delays compared with radiology-based imaging. Hospital-based cohorts reported average reductions of 5 to 6 hours in time to diagnosis, and emergency studies observed decreases exceeding one hour.[6] In perioperative care, these time savings may affect anticoagulation decisions, scheduling of surgical procedures, and the safety of neuraxial anesthesia. Incidental detection of deep vein thrombosis during routine preoperative scanning, vascular access attempts, or ultrasound-guided regional blocks has been documented and may significantly alter perioperative management.[7] Such findings highlight how venous evaluation can be seamlessly integrated into the ultrasound practices already common to anesthesiologists. It should be noted, however, that a positive proximal deep vein thrombosis finding may support clinical suspicion for pulmonary embolism, but a negative compression examination does not exclude pulmonary embolism; bedside ultrasound should be regarded as an adjunctive bedside tool rather than a surrogate for definitive vascular or pulmonary imaging.

The methodological limitations of the available evidence must be acknowledged. Many studies used convenience samples or included high-prevalence populations, which may overestimate accuracy. Blinding between

https://doi.org/10.1016/j.bjane.2026.844793

Table 1 Comparison between two-point and three-point compression ultrasound for deep vein thrombosis diagnosis.

Criteria	Two-point Compression Ultrasound (common femoral + popliteal veins)	Three-point Compression Ultrasound (adds femoral vein above the adductor canal)
Time and feasibility	Faster; ideal for bedside screening and emergency use.	Slightly longer exam; still feasible for perioperative assessment.
Overall diagnostic accuracy	High (sensitivity ≈ 90%–92%, specificity ≈ 95%–97%); may be considered for focused bedside assessment in selected perioperative patients with clinical suspicion of proximal DVT.	Similar overall accuracy; may detect additional cases of femoral thrombosis.
Detection of isolated femoral thrombosis	May miss up to 7% of isolated femoral thrombi.	Better sensitivity for isolated femoral segment thrombosis.
Distal DVT assessment	Does not evaluate calf veins.	Also does not assess calf veins; formal duplex ultrasonography required if suspicion remains high.
Learning curve	Shorter; easily standardized; ideal for training.	Slightly steeper; requires consistent identification of the femoral segment.
Best suited for	May be considered for focused bedside assessment in selected perioperative patients with clinical suspicion of proximal DVT; particularly useful for rapid pre-, intra-, and postoperative triage.	May provide a more extensive proximal venous assessment in high-risk or symptomatic patients; formal duplex ultrasonography remains indicated when available.
Impact on perioperative workflow	Maximizes agility and immediate decision-making (e.g., anticoagulation, regional block safety).	Maximizes completeness and safety in high-risk contexts.
Follow-up recommendation	Repeat ultrasound or full duplex ultrasonography at 5–7 days if clinical suspicion persists.	Same recommendation for high-risk patients with negative initial study.
Anesthesiology applicability	May support clinical assessment when proximal DVT is suspected before regional anesthesia or in intraoperative instability; findings should inform, not replace, clinical judgment and formal vascular imaging when available.	May provide a more extensive proximal venous assessment in high-risk or symptomatic perioperative patients; formal duplex ultrasonography remains indicated when available.

CUS, Compression Ultrasound; DUS, Duplex Ultrasonography; DVT, Deep Vein Thrombosis; POCUS, Point-of-Care Ultrasound.

bedside examiners and reference imaging results was not consistently reported. In some studies, negative bedside scans were not systematically verified by duplex ultrasonography, which introduces verification bias. Nonetheless, the consistency of diagnostic performance across heterogeneous study designs and operator backgrounds suggests that compression ultrasound is a useful bedside tool for proximal deep vein thrombosis identification in selected clinical scenarios.

For anesthesiologists, the implications extend across the perioperative continuum. In the preoperative setting, rapid bedside scanning can identify unrecognized venous thrombosis in patients undergoing orthopedic, oncologic, trauma, or other high-risk procedures. Detecting a proximal thrombosis may influence the selection and timing of neuraxial techniques and prompt adjustment of thromboprophylaxis. During intraoperative care, episodes of hypoxemia, hypotension, or acute right ventricular dysfunction may raise suspicion for pulmonary embolism. A focused femoral-popliteal compression ultrasound can assist in determining whether a deep vein thrombosis is likely, thereby supporting timely clinical decisions when diagnostic resources are limited.[8] Although bedside ultrasound does not replace definitive imaging in unstable patients, it can guide early management while arrangements for confirmatory testing are underway.

In the postoperative period, targeted bedside evaluation may aid in the early detection of new or progressive thrombotic events in immobilized or oncologic patients. While routine screening is not supported by current evidence, selective examination in symptomatic or deteriorating patients is practical and may reduce diagnostic uncertainty. Postoperative compression ultrasound can be particularly useful in clinical contexts where transport to radiology carries risk or delay.[4]

Integration of point-of-care venous ultrasound into anesthesiology practice requires structured training and standardization. Most studies evaluating learning curves demonstrate that clinicians with existing ultrasound experience require relatively few supervised examinations to become proficient.[9]

The technique relies primarily on recognition of venous compressibility, a concept familiar to practitioners performing ultrasound-guided procedures. Incorporating venous scanning into perioperative ultrasound curricula and credentialing pathways can help ensure consistent performance. Standardizing scanning sequences, documentation, and image storage also facilitates quality assurance and interdisciplinary communication. Additional implementation considerations include the establishment of credentialing thresholds, protocols for image documentation and archiving, quality assurance processes, interdepartmental communication workflows, medicolegal accountability frameworks, and clearly defined thresholds for referral to confirmatory duplex ultrasonography.

Although the current body of evidence supports point-of-care ultrasound as a useful bedside technique, further investigation is needed to better define its role in perioperative outcomes. Few studies have focused specifically on anesthesiologists as primary operators, and the impact of bedside venous ultrasound on surgical timelines, regional anesthesia safety, or thromboembolism-related complications has not been formally quantified. Establishing competency benchmarks, validating risk-adapted scanning strategies, and exploring outcome-based applications are important next steps. Future research could also examine whether perioperative integration of compression ultrasound affects the timing of anticoagulation, length of hospital stay, or postoperative complication rates.

In summary, point-of-care venous ultrasound is an adjunctive bedside tool for selected perioperative scenarios, particularly when formal vascular imaging is delayed or unavailable. When performed by appropriately trained clinicians, compression ultrasound may provide useful bedside diagnostic support for proximal deep vein thrombosis assessment in these selected contexts. Applying a risk-adapted strategy – using two-point compression ultrasound for general perioperative screening and reserving three-point or extended evaluations for high-risk or symptomatic patients – balances efficiency with diagnostic precision. As ultrasound becomes increasingly embedded in perioperative care, venous compression protocols represent a natural extension of anesthesiologists' skill sets and a valuable addition to patient safety practices.

Data availability statement

Data not applicable. This study is a narrative review and did not generate or analyze original datasets.

Declaration of AI and AI-assisted technologies

During the preparation of this manuscript, the authors used Claude (Anthropic, claude.ai) and Paperpal solely for language editing and grammar checking. The authors reviewed and edited the output as needed and take full responsibility for the scientific content and final version of the manuscript.

Note

A completed SANRA checklist is provided as Supplementary Material 1. The 26 representative studies informing this narrative review are listed in Supplementary Table S1.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

Luis Alberto Rodriguez Linares: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Writing — review & editing. **Rodrigo Souza da Silva:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing — original draft. **Marco Antonio Duarte Carneiro:** Data curation, Formal analysis, Methodology, Writing — review & editing.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844793.

Editor

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Received 7 May 2026; accepted 23 June 2026
Available online 9 July 2026

Brazilian Journal of Anesthesiology 2026;76(5): 844791

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Intranasal dexmedetomidine: does the delivery device matter?☆

Dear Editor,

We read with great interest the systematic review and meta-analysis by Rocha et al. on intranasal dexmedetomidine (IN-DEX) for procedural sedation in children.[1] This rigorous synthesis, encompassing 28 randomized controlled trials and more than 1,600 participants, provides a comprehensive quantitative framework for the clinical planning of IN-DEX monotherapy. The finding that doses of 2–3 $\mu g.kg^{-1}$ yield an 84% success rate with high-quality evidence represents a meaningful advance for pediatric sedation practice.

Beyond these contributions, we wish to highlight an important variable not addressed in the analysis, namely the device used for intranasal delivery. In clinical practice, there is a widespread assumption that effective IN-DEX administration requires a mucosal atomization device, which disperses the drug as a fine mist (particle size 30–100 μm) to maximize mucosal contact and absorption.[2] Simple instillation via a standard 1 mL syringe (the "drops" technique) is often regarded as an inferior alternative, despite being universally available and requiring no additional equipment or cost. Notably, among the trials that specified the delivery device (15 of 28), drops were the most frequently reported method, applied in 10 studies.

Two trials directly compared both delivery methods.[2,3] Li et al. (2016), included in the meta-analysis, represents the largest prospective RCT to date directly comparing atomizer with drops (n = 279, children aged 2–36 months undergoing echocardiography, 3 $\mu g.kg^{-1}$).[2] The study found no statistically significant differences in sedation success or onset time between the two delivery methods in this specific population and clinical context; however, it was not designed or analyzed as a non-inferiority trial.[2] Xie et al., not included in this meta-analysis, possibly due to differences in outcome definitions, similarly found that onset time and patient acceptance of intranasal administration were comparable between devices (23 vs. 25 min, p = 0.281; p = 0.242, respectively).[3]

These clinical observations align with pharmacokinetic data. The transmucosal bioavailability of dexmedetomidine has been estimated at 40.6% (95% CI 34.7%–54.4%) with atomization and 40.7% (95% CI 36.5%–53.2%) with drops (virtually identical values), reflecting the drug's high lipophilicity and the nasal mucosa's rich vascularity.[4] Atomization may offer marginally faster onset than drops, yet this advantage does not consistently translate into a clinically meaningful difference in sedation outcomes, particularly when the drug is administered in the small volumes permitted by dexmedetomidine's commercial concentration of 100 $\mu g.mL^{-1}$.

Beyond pharmacology, this question carries direct implications for healthcare access. Drop administration requires no specialized equipment beyond a standard 1 mL syringe, which is universally available in any clinical setting. As reported by Li et al.,[2] the institutional cost of atomizer use has been estimated at approximately USD 13 per patient, while simple drops carry no additional cost. The recurring expenditure may discourage adoption even in well-resourced centers and may represent a meaningful barrier in low- and middle-income countries and in resource-limited emergency and primary care settings, where non-invasive, needle-free sedation would offer the greatest benefit.

Nevertheless, device choice may still matter in specific clinical contexts. In uncooperative or crying children, drops may be less reliable, as swallowing during administration reduces mucosal bioavailability, a limitation that the atomization device may partially mitigate.[3] Similarly, when larger volumes are required, drops carry a greater risk of oropharyngeal runoff and partial oral absorption, which is particularly relevant given dexmedetomidine's poor oral bioavailability.[4,5] This concern is especially applicable in older or heavier children, for whom dividing the dose equally between both nostrils is advisable to minimize runoff and maximize mucosal surface area.[5] Nasal obstruction and excessive secretions, frequently observed in children selected for upper airway surgeries, should also be considered, as they may impair absorption regardless of delivery method.[5] Finally, operator familiarity with the chosen device, whether a standard syringe or a atomization device, may also influence clinical outcomes in practice, independently of pharmacological considerations.[4]

We acknowledge that, although drop-based administration was reported in 10 of the included studies, the available direct comparative evidence between drops and atomization devices remains limited to two clinical trials with different designs, populations, and outcome measures,[2,3] only one

☆ In reference to the paper Rocha KO, Santos ERFA, Pombeiro MM, et al. Intranasal dexmedetomidine for procedural sedation in children: a systematic review and meta-analysis. Braz J Anesthesiol. 2026;76(1):844717.

https://doi.org/10.1016/j.bjane.2026.844791

of which was included in the Rocha et al. meta-analysis.[1] Nevertheless, our group has accumulated considerable clinical experience with nasal drop-based administration as a routine alternative to pre-anesthetic sedation for the last 5 years, and we respectfully wish to draw attention to this evidence, as many institutions still do not consider IN-DEX a viable option due to the perceived need for a mucosal atomization device.

We congratulate Rocha et al. on their rigorous and clinically relevant contribution and hope this perspective will stimulate further research to optimize intranasal sedation strategies.

Sincerely,

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Authors' contributions

Eliane C.S. Soares: Conception and design of the study; acquisition, analysis and interpretation of data; drafting the article.

Paulo C.P. Figueiredo: Conception and design of the study; revising the article critically for important intellectual content.

Fabiano Soares Carneiro: Conception and design of the study; revising the article critically for important intellectual content.

Eduardo M.O. Melo e Silva: Acquisition and analysis of data; revising the article critically for important intellectual content.

Patrícia B. Amaral: Acquisition and analysis of data; revising the article critically for important intellectual content.

Generative AI and AI-assisted technologies

During the preparation of this work, the authors used Claude (Anthropic version 3.5 Sonnet) and Grammarly (Grammarly Inc. version 1.2) to improve the English writing structure. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding

This study did not receive any funding.

Conflicts of interest

The authors declare no conflicts of interest.

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Received 6 May 2026; accepted 21 June 2026
Available online 8 July 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Social support and partner presence in chronic pain recovery: clarifying the mechanism behind an observed association

Dear Editor,

We read with interest the prospective longitudinal study by Castro et al.[1] examining the clinical and psychological evolution of patients with chronic pain undergoing standard multidisciplinary treatment. By integrating pain intensity with quality of life, anxiety, depression, and sleep outcomes, the authors provide valuable real-world insight into the multidimensional nature of chronic pain recovery.

A notable finding was the association between partner presence and clinically meaningful pain reduction (≥ 30%; p = 0.022). In the adjusted analysis, partner presence was associated with clinically meaningful pain reduction.[1] However, this observational finding should be interpreted cautiously, as the study cannot establish causality or determine the pathway underlying the observed association.

The binary categorization of participants as living with or without a partner cannot capture the quality, nature, or consistency of interpersonal support. Previous literature suggests that social interactions in the context of chronic pain may have heterogeneous associations with pain-related behaviours and adjustment.[2-4] These studies provide possible explanatory frameworks, but they do not establish the mechanisms responsible for the association reported by Castro et al.

We also noted that patients who improved showed a significant increase in SF-36 social functioning scores over the six-month follow-up.[1] It would be informative to know whether this gain was specifically associated with partner presence or whether it reflected broader social integration. Such an analysis could help clarify whether the observed association was more specifically related to partner presence or reflected wider social support.

In addition, the authors acknowledge the lack of control over medication adherence as a limitation[1]. One untested hypothesis is that partner presence could be associated with practical support in managing complex treatment regimens. However, because treatment adherence was not measured, the available data cannot determine whether adherence contributed to the observed association. Future prospective studies could assess medication adherence, the quality of social support, and partner responses to pain to explore these possible pathways.

Castro et al.[1] should be commended for drawing attention to a factor that extends beyond conventional biomedical predictors. Future studies incorporating more detailed measures of partner-related and broader social support may help determine whether family-oriented or caregiver-oriented strategies warrant evaluation within multidisciplinary chronic pain programmes, including those delivered in public health settings such as the Brazilian Unified Health System.

Data availability statement

No new data were created or analyzed in this article. Data sharing is not applicable to this article.

Conflicts of interest

The authors declare no conflicts of interest.

Institutional Review Board approval

Not applicable.

Study registration

Not applicable.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT, an AI-assisted language model developed by OpenAI, solely for language editing and improving the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the submitted manuscript.

Authors' contributions

Betul Kozanhan: Conceptualization; Supervision; Critical revision of the manuscript.

https://doi.org/10.1016/j.bjane.2026.844815

Mahmut Sami Tutar: Literature review; Drafting of the manuscript; Revision of the manuscript.
Munise Yildiz: Conceptualization; Supervision; Critical revision of the manuscript; Correspondence.

Funding

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Editor

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Received 14 May 2026; accepted 18 July 2026
Available online 14 August 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Partner presence, social support and chronic pain recovery: reply to a Letter to the Editor

Dear Editor,

We sincerely thank the authors for their thoughtful comments on our study and for the opportunity to further discuss the influence of interpersonal relationships on the clinical course of patients with chronic pain.[1] The letter raises important considerations regarding the interpretation of the association between partner presence and clinically meaningful pain improvement observed in our cohort.[2]

Partner presence should not be interpreted as a direct measure of social support. In our study, marital status was collected as a sociodemographic variable and included in the multivariable model because of its potential association with clinical outcomes. However, this study did not assess relationship quality, emotional or financial support, or the broader social support network of participants. Therefore, our findings do not allow us to infer that the observed association reflects a specific partner effect, nor do they permit the identification of the mechanisms through which partner presence may influence recovery.

Indeed, the literature demonstrates that the influence of interpersonal relationships on chronic pain is more complex than the simple presence or absence of a partner. A recent systematic review showed that the type of support provided by a partner may help explain differences in pain-related outcomes.[3] Overly protective or pain-reinforcing responses may contribute to disability and symptom maintenance, whereas behaviors that encourage autonomy, adaptive coping strategies, and continued engagement in daily activities are associated with better functional outcomes.

Building on this line of research, we are currently conducting a prospective cohort study at the same center, where perceived social support and family climate are being assessed using validated instruments, as well as standard clinical outcomes. Although the results of this study are currently not available, we expect it to shed light on how different aspects of interpersonal relationships influence response to chronic pain treatment and whether the association identified in our previous study is driven by particular characteristics of social support and the family environment and not by the simple presence of a partner.

In our sample, no statistically significant difference was observed in SF-36 Social Functioning scores between patients with and without a partner (median [IQR], 37.25 [15.25—50.00] vs. 42.50 [25.00—63.00]; p = 0.397). This finding may reflect the broad scope of the SF-36 Social Functioning domain, which assesses the extent to which health interferes with social activities in a broad sense, encompassing family, occupational, and community interactions rather than exclusively intimate relationships. Thus, the observed improvement may reflect social reintegration resulting from pain reduction and overall improvement in physical and psychological functioning, rather than a specific effect of living with a partner.

We also appreciate the comment regarding medication adherence. As discussed in the original manuscript, adherence was not systematically assessed and therefore could not be included in our analyses. It is plausible that the presence of a partner or caregiver facilitates the management of complex therapeutic regimens, attendance at medical appointments, and adherence to non-pharmacological interventions. However, since these variables were not measured, any hypothesis that treatment adherence mediates this association remains speculative. We consider this an important issue for future prospective research.

Thus, we believe that our findings should be interpreted not as evidence of a causal effect of partner presence, but rather as an indication that interpersonal context may represent a factor associated with the clinical course of chronic pain. It is widely recognized as a condition influenced by biological, psychological, and social determinants that interact dynamically over time. In this context, identifying marital status as an independent predictor of clinical improvement does not imply that the relationship itself is the causal mechanism; rather, it suggests that this variable may serve as a proxy for broader interpersonal and social dimensions that warrant further investigation through more comprehensive psychosocial assessments.

We thank the authors once again for their valuable observations, which enrich the interpretation of our findings and reinforce the importance of further investigation into the interpersonal and social determinants of recovery in patients with chronic pain.

Data availability statement

No new dataset was generated for this Letter. The additional aggregate analysis reported here was derived from the dataset of the original study and is available from the corresponding

https://doi.org/10.1016/j.bjane.2026.844819

author upon reasonable request, subject to the same ethical restrictions described in the original article.

AI assistance disclosure

During the preparation of this work, the authors used OpenAI exclusively for language editing and to improve the clarity of the manuscript. After using this tool, the authors reviewed and edited the content as necessary and assume full responsibility for its content.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This work did not receive specific funding from any public, commercial, or not-for-profit funding agency.

Editor

Liana Azi

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Received 14 July 2026; accepted 7 August 2026
Available online 14 August 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Optic nerve sheath ultrasonography in the setting of laparoscopic surgery

Dear Editor,

The recent research on variations in Optic Nerve Sheath Diameter (ONSD) assessed non-invasively by Ultrasonography (USG) amongst patients undergoing laparoscopic prostatectomy merits the attention of readers.[1] Application of non-invasively assessed ONSD variations in neurologic and non-neurologic scenarios is a rapidly evolving domain of knowledge.[2] Given that intraoperative infusion of intravenous mannitol for patients with non-pathologic transient variations in intracranial pressure adds novelty to the research by Barreto et al, a few caveats in this research need further elaboration.[1]

To begin with, intra- or inter-observer variability and the imaging experience of the anesthesiologist can present an important limiting factor when sub-millimetric variations in USG-assessed ONSD are extrapolated to significant study outcomes. Herein, we note that the index authors assigned senior anesthesiologists with more than five years USG hands-on experience for intraoperative measurements and therefore, suggest a more tenable alternative.[1] The GE HealthCare Logiq® USG systems are equipped with software to capture screenshots of 'frozen' images and store it for future analysis. Offline 'blinded' ONSD measurements can be randomly performed on such stored images outside the operating room by observers not directly involved in the patient management. We believe that this minor technical change in approach can render the ONSD measurements more methodologically robust with reduced observer-related variability.[3]

Further, a predominantly elder group of patients undergoing prostatic surgery in the index research attracts close attention.[1] Ageing-related cerebral cortical atrophy can result in physiologically widened Cerebrospinal Fluid (CSF) spaces among this subgroup. These changes are compounded by astrocytic degeneration and septations in the CSF space that surround the optic nerve. Altogether this contributes to a physiologically wide CSF space on USG image which warrants special consideration while ONSD measurements are undertaken herein.[3] Therefore, we assume that factors that affect plasticity of ONS need careful narration while results of ONSD measurements are elaborated in elderly.[1,3]

For explicit understanding and to substantiate this research context; we conducted a literature search on the point-of-care clinical utility of USG for ONSD estimation, to capture transient fluctuations in ICP in an elective setting as in the Barreto et al. study i.e., capnoperitoneum due to laparoscopy.[1] Using MeSH search terms "Optic nerve sheath diameter" [AND] "Laparoscopy" in PubMed, we found 63 results which were downloaded as a Microsoft Excel spreadsheet. Citations metrics of the top 10 articles in this dataset were retrieved using iCite® tool of the National Institute of Health and is depicted in Table 1. The majority of top cited articles focused on ONSD measurements during laparoscopic/robotic prostatic surgery with consistent research interest in gynecologic and pelvic surgery. It is evident here that the application of ONSD as a noninvasive technique to estimate intraoperative variations in ICP, in completely non-neurologic scenarios, is attaining widespread readership attention and applause.[1,2]

At the same time, there exists another pertinent technical intricacy with point-of-care ONSD measurements, that needs to be elucidated. B-scan ultrasound technique for ONSD measurements are prone to "Blooming effect" artifacts due to a lack of standard sensitivity setting in the ultrasound machine.[4] Such effects are general technical limitations of bedside ONSD assessment that future research needs to address.[1,2,4] The A-scan ultrasound features as an alternative imaging method wherein high reflective spikes can be visualized at the interface between the arachnoid membrane and the CSF; yet the logistic nuance of having a much larger module of ultrasonography inside a laparoscopic operating room cannot be forgotten.[4,5]

The research by Barreto et al is praiseworthy considering the novelty in methodology wherein they attempt pharmacologic ICP reduction with IV Mannitol among patients undergoing laparoscopy; with standardized peak inspiratory airway pressures and end-tidal carbon-dioxide levels throughout all four timeframes of their measurements.[1] Nevertheless, the extent to which imaging technicalities can affect the ONSD measurements among a predominant geriatric cohort of patients, needs simultaneous emphasis. We suggest adherence to expert consensus on the bedside-imaging of ONSD as a ready reckoner to future research in the subject.[5]

https://doi.org/10.1016/j.bjane.2026.844789

Table 1 Citation counts of the top 10 articles in the field of optic nerve sheath diameter assessment during a Laparoscopic surgery setting.

Sl No	Year of publication	Title of the article	Journal Name	Total Citations[a]
1	2014	Increase in intracranial pressure during carbon dioxide pneumoperitoneum with steep trendelenburg positioning proven by ultrasonographic measurement of optic nerve sheath diameter	Journal of Endourology	72
2	2017	Changes in intraocular pressure and optic nerve sheath diameter in patients undergoing robotic-assisted laparoscopic prostatectomy in steep 45° Trendelenburg position	BMC Anesthesiology	46
3	2015	Detection of elevated intracranial pressure in robot-assisted laparoscopic radical prostatectomy using ultrasonography of optic nerve sheath diameter	Journal of Neurosurgical Anesthesiology	45
4	2019	Ultrasound optic nerve sheath diameter evaluation in patients undergoing robot-assisted laparoscopic pelvic surgery	Journal of Robotic Surgery	34
5	2014	Optic nerve sheath diameter remains constant during robot assisted laparoscopic radical prostatectomy	PLoS One	32
6	2019	Effects of pneumoperitoneum and steep Trendelenburg position on cerebral hemodynamics during robotic-assisted laparoscopic radical prostatectomy: A randomized controlled study	Medicine (Baltimore)	29
7	2018	Ultrasonographic optic nerve sheath diameter for predicting elevated intracranial pressure during laparoscopic surgery: a systematic review and meta-analysis	Surgical Endoscopy	23
8	2018	Effect of Pneumoperitoneum and Patient Positioning on Intracranial Pressures during Laparoscopy: A Prospective Comparative Study	Journal of Minimally Invasive Gynecology	23
9	2021	Comparison of different end-tidal carbon dioxide levels in preventing postoperative nausea and vomiting in gynaecological patients undergoing laparoscopic surgery	Journal of Obstetrics and Gynaecology	20
10	2018	Propofol attenuates the increase of sonographic optic nerve sheath diameter during robot-assisted laparoscopic prostatectomy: a randomized clinical trial	BMC Anesthesiology	19[b]

[a] Total citation here are inclusive only to PubMed data analyzed on 04 February 2026 (Google scholar citation counts may vary).
[b] Article titled "Elevation in optic nerve sheath diameter due to the pneumoperitoneum and Trendelenburg is associated to postoperative nausea, vomiting and headache in patients undergoing laparoscopic hysterectomy" published in Minerva Anestesiologica (2020) also received 19 citations, till date (as on 04 February 2026).

Data availability statement

No new data were generated or analysed in this article. Data sharing is not applicable to this article.

IEC approval

IEC approval is NOT required.

AI assistance disclosure

The authors declare that no generative artificial intelligence or AI-assisted technologies were used in the preparation of this manuscript.

Funding

Not applicable.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

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Received 16 March 2026; accepted 19 June 2026
Available online 1 July 2026

Brazilian Journal of Anesthesiology 2026;76(5): 844794

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Reply to the Letter to the Editor: "Impact of mannitol on intracranial pressure assessed by optic nerve sheath ultrasonography during video-laparoscopic prostatectomy: a randomized clinical trial"

Dear Editor,

We would like to thank Dr. Suresh and colleagues[1] for their thoughtful comments regarding our recently published randomized clinical trial evaluating the impact of mannitol on intracranial pressure assessed by Optic Nerve Sheath Diameter (ONSD) ultrasonography during video-laparoscopic prostatectomy.[2] We appreciate the opportunity to further discuss important methodological aspects related to bedside ONSD assessment.

We fully acknowledge that optic nerve sheath ultrasonography is an operator-dependent technique, and that observer-related variability is a well-recognized and widely discussed limitation of the method, particularly when interpreting submillimetric ONSD variations. Nevertheless, recent meta-analyses have demonstrated an adequate correlation between ONSD measurements and intracranial pressure, reinforcing the clinical applicability of this non-invasive bedside method.[3]

In our study, several methodological strategies were implemented to minimize measurement variability. All examinations were performed by anesthesiologists with more than five years of practical experience and specific training in optic nerve ultrasonography. In addition, ONSD measurements were obtained bilaterally at each predefined intraoperative time point, and the mean binocular value was used for statistical analysis. According to the study protocol, measurements would be repeated if the inter-eye difference exceeded 0.5 mm; however, this threshold was never reached, and no repeated measurements were required. Although formal intraobserver variability analysis was not performed, the standardized acquisition protocol and the absence of clinically significant inter-eye discrepancies suggest consistent image acquisition throughout the study. However, these measures do not replace formal assessment of intraobserver and interobserver reliability.

Regarding ultrasound mode limitations, we acknowledge that B-mode ultrasonography is susceptible to blooming-related artifacts and that ultrasound system settings may influence ONSD measurements. Although standardized A-mode ultrasonography has been proposed as a more accurate technique for delineating optic nerve sheath interfaces, it requires dedicated ophthalmic equipment and specific operator expertise, limiting its availability and applicability in most perioperative point-of-care settings, particularly in the operating room. Consequently, B-mode ultrasonography remains the technique most commonly used in perioperative and critical care research. Notably, the recent international consensus statement on ONSD point-of-care ultrasonography focused on standardizing B-mode image acquisition and measurement criteria and did not recommend the routine use of A-mode ultrasonography.[4] We agree that future studies should report ultrasound acquisition settings in greater detail and continue efforts toward standardized imaging protocols to improve reproducibility.

The authors' suggestion about storing frozen ultrasound images for subsequent blinded offline analysis is interesting and potentially valuable from a methodological perspective. However, this approach was not incorporated into our original study protocol. As ours is a teaching hospital with continuous development of perioperative ultrasonography protocols, we believe this may represent an important methodological refinement for future studies in this field.

Concerning the comments about age-related cerebral atrophy and possible anatomical changes in cerebrospinal fluid spaces in elderly patients, we agree that these factors should be considered when interpreting ONSD measurements. Previous studies have demonstrated that ONSD increases with age, particularly in individuals older than 65 years.[5] However, in our study, the mean age was similar between groups (approximately 64 years in both groups), making it unlikely that age-related anatomical variations represented a major confounding factor in our analysis.

Another relevant aspect is the variation in ONSD according to ethnicity and population characteristics. Previous studies conducted worldwide have demonstrated substantial differences in normal ONSD values across populations, ranging from a mean of 3.68 mm (95% CI 2.85–4.40 mm) in a Canadian population[6] to 5.1 mm (95% CI 4.7–5.4 mm) in a healthy Chinese population.[7] These findings highlight the importance of establishing normative population-specific databases for more accurate interpretation of ONSD measurements in both screening and diagnostic settings.

Despite these recognized limitations and population-related variations in ONSD measurements, we would like to emphasize

https://doi.org/10.1016/j.bjane.2026.844794

that the primary objective of our study was not to validate the ultrasonographic method itself, nor to compare imaging modalities for intracranial pressure assessment. Rather, our aim was to investigate whether mannitol administration could attenuate the increase in a surrogate marker of intracranial pressure during prolonged laparoscopic surgery in the Trendelenburg position.

Once again, we sincerely thank the authors for their constructive comments and for contributing to the ongoing scientific discussion regarding perioperative ONSD assessment.

Data availability statement

No new data were created or analyzed in this article. Data sharing is not applicable to this article.

AI assistance disclosure

The authors declare that no generative artificial intelligence or AI-assisted technologies were used in the preparation of this manuscript.

Authors' contributions

George Pereira Barreto contributed to the study conception, conducted the study execution, and participated in manuscript drafting. Wallace Andrino da Silva led the study, developed the original idea, coordinated all phases of the project, and was responsible for writing and revising the manuscript.

Funding

The authors received no financial support for this Letter.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

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Received 24 May 2026; accepted 5 July 2026
Available online 16 July 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Erector spinae plane block versus paravertebral block for pediatric percutaneous nephrolithotomy: interpreting procedural time and statistical non-significance

Dear Editor,

We read with great interest the recent randomized trial by Nabil et al.[1] comparing Erector Spinae Plane Block (ESPB) with thoracic Paravertebral Block (PVB) for pediatric Percutaneous Nephrolithotomy (PCNL). The authors suggest that ESPB "could be considered as an easy alternative to thoracic PVB". The conclusion appears to place considerable emphasis on the shorter procedural time (4.37 ± 1.08 vs. 5.05 ± 1.17 minutes, p = 0.028). While we commend the authors for addressing a vital evidence gap with the first prospective trial of its kind in this population, we would like to offer a nuanced perspective on the clinical contextualization of these findings.

In a study designed as a superiority trial that found no significant difference in the primary outcome – time to first rescue analgesia (15.98 ± 10.17 vs.18.18 ± 9.18 hours, p = 0.464) – emphasizing procedural speed as a decisive factor may inadvertently oversimplify the complex priorities of pediatric regional anesthesia. Reliability of analgesia and established safety profiles typically carry greater clinical weight than marginal efficiency gains.

The methodology employed by Nabil et al. is robust, utilizing assessor-blinding, standardized anesthetic protocols, and the validated FLACC scale assessment.[2] The finding that no statistically significant difference was observed in analgesic efficacy – supported by overlapping 95% Confidence Intervals and similar intraoperative hemodynamics – suggests that a clinical advantage of one technique over the other was not demonstrated in this study. However, the 40-second time difference, while statistically significant, represents less than 1% of the total operative time (approximately 85 minutes), which likely limits its practical relevance for operating room throughput. Furthermore, as the study was powered to detect differences in analgesia rather than procedural duration, the p = 0.028 finding should be interpreted with caution in the absence of a dedicated sample size calculation for this secondary outcome.

Beyond statistics, certain mechanistic distinctions warrant consideration. PVB involves the direct deposition of local anesthetic into the paravertebral space, providing reliable blockade of spinal nerves and sympathetic fibers at T10–L1, which is critical for managing the visceral pain associated with renal surgery. In contrast, ESPB relies on indirect diffusion through the costotransverse foramina. Anatomical studies suggest this pathway may yield more variable dermatomal coverage, particularly in pediatric patients whose fascial anatomy differs from that of adults.[3]

Regarding safety, a cohort of 55 patients lacks the statistical power to detect rare but serious complications such as pneumothorax or neuraxial spread. While ESPB is often favored for its theoretical safety due to its superficial nature, the pediatric evidence base for PVB is currently more robust. For instance, an observational study of 871 thoracic PVB cases demonstrated reassuringly low complication rates, whereas the pediatric safety database for ESPB remains relatively limited.[4]

Finally, we note that the blocks were performed by a single, highly experienced practitioner. The exceptionally low block failure rate (one per group) suggests that both techniques are highly reliable when performed with expertise, perhaps diminishing the perceived advantage of "ease of use" in settings where technical proficiency is already established.

In conclusion, these data demonstrate a lack of clear analgesic superiority for ESPB, suggesting it should be viewed as a comparable alternative. Optimal block selection should likely remain a tailored decision based on institutional expertise, patient anatomy, and specific surgical requirements. We endorse the authors' call for larger trials, which might ideally be powered to evaluate complication rates and cost-effectiveness.

Sincerely.

Data availability statement

No new data were generated or analyzed in this article. Data sharing is not applicable to this article.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the authors used Gemini for language editing and grammatical clarity only.

https://doi.org/10.1016/j.bjane.2026.844788

The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Authors' contributions

Yirui Peng: Conceptualization; data curation; formal analysis; investigation, methodology; writing-original draft preparation.

Yuebing Li: Critical revision for important intellectual content, and final approval.

Funding

None.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 11 April 2026; accepted 17 June 2026
Available online 1 July 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ERRATUM

Erratum to "Noninvasive intracranial pressure real-time waveform analysis monitor during prostatectomy robotic surgery and Trendelenburg position: case report" [Brazilian Journal of Anesthesiology. Volume 71, Issue 6, November–December 2021, Pages 656–659]

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The publisher regrets that the Conflict of Interest statement was incomplete in the original publication. The correct statement is: "Gustavo Frigieri declares that he is the co-founder and Scientific Director of Brain4care. The other authors declare no conflicts of interest."

DOI of original article: http://dx.doi.org/10.1016/j.bjane.2021.09.003
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https://doi.org/10.1016/j.bjane.2026.844823

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