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Vol. 76, N. 2 | Mar-Apr 2026 | ISSN 0104-0014

bjan-sba.org

BJAN
Brazilian Journal of Anesthesiology

Brazilian Journal of ANESTHESIOLOGY

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Brazilian Journal of Anesthesiology | Vol. 76 N. 2 | March/April 2026

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Brazilian Journal of ANESTHESIOLOGY

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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 2 • March—April 2026

The Brazilian Journal of Anesthesiology is indexed by **Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)** since 1989, **Excerpta Médica Database (EMBASE)** since 1994, **Scientific Electronic Library Online (SciELO - Brasil)** since 2002, **MEDLINE** since 2008, **Scopus since** 2010 and **Web of Science (SCIE - Science Citation Index Expanded)** since 2011.

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Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Patient Blood Management in Brazil: between evidence, reality and transformation

Nearly two decades after the formal consolidation of the Patient Blood Management (PBM) concept,[1] the global healthcare community now benefits from a substantial and consistent body of evidence demonstrating its association with improved clinical outcomes, rational utilization of blood components, and enhanced sustainability of healthcare systems.[2] PBM has evolved beyond a set of procedural steps into a comprehensive strategy that prioritizes patient-centered, physiology-based care, seeking to minimize unnecessary allogeneic transfusion, optimize the management of anemia and bleeding, and foster evidence-based clinical decision-making.[3] This evolution reflects not only advances in clinical science but also a growing recognition that blood is a finite and precious healthcare resource with significant implications for patient safety, system costs, and quality of care.

Despite this robust evidence and clear clinical rationale, the practical implementation of PBM remains heterogeneous across healthcare settings worldwide — particularly in environments marked by structural complexity, inequity, and operational constraints.[4] These conditions are exemplified by the Brazilian healthcare context, where disparities in infrastructure, workforce distribution, and data systems intersect with broader socioeconomic challenges. In Brazil's large and diverse health system — one of the world's most expansive public healthcare systems — translating PBM from concept into practice has revealed not only clinical barriers but also systemic ones that reflect broader health system strengths and limitations.[5]

PBM was initially conceived as a technical framework structured around three foundational pillars: optimization of erythropoiesis through the identification and treatment of anemia, minimization of blood loss through evidence-based surgical and anesthetic practices, and enhancement of physiologic tolerance to anemia when appropriate.[1,6] However, its evolution has revealed a broader scope. PBM is now understood as a model of care reorganization that requires cultural transformation, coordinated clinical governance, multidisciplinary integration, and institutional alignment. This inherently transformative character explains, in part, the persistent gap between scientific evidence and routine clinical practice.[7]

Even with compelling evidence supporting improved patient outcomes and reduced inappropriate blood use, adoption of PBM remains uneven. International experience indicates that successful PBM adoption is contingent upon factors extending beyond dissemination of clinical protocols.[8] Jurisdictions that have demonstrated sustained progress have combined strong clinical leadership — often in the form of PBM "champions" — with institutional engagement, structured data governance, and alignment with national health policy frameworks. These factors create an enabling environment in which PBM practices can be standardized, monitored, and continuously refined.[9]

The Brazilian healthcare landscape illustrates these tensions with notable clarity. Brazil operates one of the world's largest public health systems, the Sistema Único de Saúde (SUS), which serves more than 200 million individuals and coexists with a technologically sophisticated private sector. At the same time, the system is marked by pronounced regional disparities, fragmentation of care delivery, and variability in infrastructure capacity. These disparities influence not only access to care but also capacity for consistent implementation of complex care models like PBM.[10]

Brazil's blood donation and transfusion ecosystem provides an instructive example. Recent official data indicate that approximately 1.9% of the Brazilian population donated blood in 2024, accounting for roughly 3.3 million units collected nationally. This rate is within the World Health Organization's recommended range of 1–3% blood donors per population, but it remains low compared with many high-income countries and reflects persistent challenges in building a stable donor base. Despite this modest donor rate, blood usage in Brazil remains high. In 2024, over 3.1 million blood component units were transfused in SUS facilities, reflecting both the scale of demand and the complexity of clinical care delivered.[11] This discrepancy between collection and utilization highlights a critical challenge: managing

https://doi.org/10.1016/j.bjane.2026.844738

scarce blood resources efficiently while meeting the needs of patients requiring transfusions for trauma, surgery, cancer care, hematologic conditions, and obstetric emergencies. In many cases, such demand occurs within systems that lack advanced preoperative anemia management programs or standardized PBM pathways, amplifying reliance on transfusion rather than evidence-based alternatives.

Recent Brazilian data underscore the magnitude of this challenge. A retrospective cohort study conducted in a university hospital in northeastern Brazil evaluated 508 patients undergoing major elective surgeries and found that preoperative anemia was present in 59.6% of patients, with mean hemoglobin levels of 11.66 g/dL in women and 11.13 g/dL in men. More strikingly, postoperative anemia increased to 94.6%. Patients with preoperative anemia were 4.6 times more likely to require intraoperative transfusion compared to non-anemic patients (OR = 4.58; 95% CI: 2.78−7.52; $p < 0.001$). These findings highlight the critical importance of preoperative anemia detection and management as a cornerstone of PBM implementation in Brazilian surgical practice.[12]

The association between preoperative anemia and adverse perioperative outcomes has been further analyzed by a large retrospective cohort study involving 23,579 adults undergoing elective noncardiac surgery. This study demonstrated that preoperative anemia, even when mild (hemoglobin 11.1 to 12.9 g/dL), was independently associated with higher in-hospital mortality, a greater ICU admission rate, and a prolonged hospitalization. Severe anemia (hemoglobin < 8.0 g/dL) emerged as the strongest predictor of in-hospital mortality (adjusted RR 24.7; 95% CI 13.3-46.0; $p < 0.001$). Notably, these adverse associations persisted even in patients that were ASA I and II, undergoing low-risk procedures, challenging a therapeutic inertia that often leads clinicians to overlook anemia in seemingly "simple" surgical scenarios.[13]

Regional variations further complicate the picture. In the state of São Paulo alone, government data reported 789,000 units of blood collected in 2024, up from 721,000 the previous year — a 9.5% increase — reflecting localized improvements in donation campaigns and infrastructure.[11,14] Meanwhile, states such as Ceará recorded 110,784 units collected in 2024, the highest in decades, indicating areas of excellence that nevertheless remain isolated.[15] These localized increases are encouraging, yet they underscore the heterogeneity of blood donation systems across Brazil's regions and the need for national coordination to scale effective practices.

The interplay between blood collection rates and broader health system indicators also reveals deeper structural considerations. Brazil's health system must respond to a broad spectrum of healthcare needs, from infectious and chronic diseases to emergency care and advanced surgical interventions. In 2024, the SUS coordinated over 30,000 organ transplants, an 18% increase compared with 2022, demonstrating the complexity of care delivered in the public system. Such high complexity care often relies on safe, timely transfusion support but also highlights the importance of integrated care pathways that can reduce unnecessary interventions and optimize resource use.[16]

The persistent reliance on transfusions reflects, in part, entrenched clinical paradigms. Transfusion medicine has historically been viewed as an immediate and inherently benign intervention, and this perception persists among many clinicians.[17] Contemporary evidence, however, underscores both the clinical risks associated with allogeneic blood transfusion — including immunomodulation, infection risk, and increased length of stay — and the potential for PBM to improve outcomes by reducing unnecessary exposure to blood products.[18] This shift in evidence has spurred international calls for PBM adoption as a standard of care, yet changing deeply rooted clinical norms requires sustained educational efforts, interprofessional collaboration, and institutional reinforcement.

Beyond the traditional transfusion management, PBM implementation in surgical scenarios requires perioperative monitoring of coagulation and hemostasis. A recent randomized clinical trial conducted in Brazil evaluated the accuracy of point-of-care CoaguChek XS testing versus standard laboratory coagulation monitoring in 50 patients undergoing cardiac surgery with cardiopulmonary bypass. The study demonstrated that CoaguChek XS provided results comparable to standard laboratory methods both pre- and post-cardiopulmonary bypass, with Lin's concordance correlation coefficients of 0.72 (95% CI: 0.60−0.82) pre-CPB and 0.66 (95% CI: 0.50−0.77) post-CPB, both indicating good agreement. Although statistically significant differences were observed, they fell within the predefined clinically irrelevant tolerance range of $\pm$ 0.5 INR units. This validation of point-of-care testing in the Brazilian context is particularly important, as it provides evidence for the adoption of rapid coagulation monitoring strategies that can facilitate real-time clinical decision-making in perioperative settings, especially in resource-constrained environments where laboratory turnaround times may be prolonged.[19]

Cultural resistance remains a primary barrier in many Brazilian institutions. Variability in professional training, unequal access to advanced diagnostics (such as accurate anemia work-up tools), and high care demand environments contribute to hesitation in adopting PBM practices. Clinicians often lack familiarity with structured anemia pathways or may feel constrained by time pressures and established workflows that do not prioritize preoperative optimization. These human and organizational factors are as significant as technical ones and underscore the need for comprehensive educational strategies integrated into medical, nursing, and allied health curricula.[18]

Structural limitations constitute another critical challenge. Effective PBM implementation requires organized pathways for anemia screening and management, systematic clinical risk assessment, availability of alternatives such as intravenous iron and erythropoiesis — stimulating agents, coordinated perioperative planning, and interdisciplinary care teams. In many healthcare settings across Brazil, deficiencies in health information systems impede the generation of actionable data required to identify quality gaps, monitor performance, and support continuous improvement. In the absence of reliable metrics, PBM risks being perceived as an optional or aspirational initiative rather than a core institutional strategy.[4]

Health information infrastructure is central to overcoming this barrier. Robust systems such as DATASUS — Brazil's primary national health data repository — exist to collect and process health indicators across epidemiologic, clinical,

and administrative domains.[16] However, the utility of such systems for PBM implementation remains underleveraged. Integration of transfusion data, preoperative anemia prevalence, and patient outcomes into interoperable dashboards could facilitate performance tracking and stimulate continuous improvement at local and national levels.

The broader contextual environment also influences implementation. Healthcare systems under financial constraints frequently prioritize immediate therapeutic interventions over preventive strategies, particularly in environments where acute care demand is high. Paradoxically, although PBM has been consistently associated with cost containment and efficiency gains — including reduced blood unit expenditure, shorter hospital lengths of stay, and decreased transfusion-related complications — it requires upfront investments in infrastructure, training, and process reorganization.[2,20,21] This temporal disconnect between investment and measurable return represents a tangible barrier to administrative adoption, especially when short-term budget pressures dominate decision-making.

Despite these challenges, meaningful progress is evident within Brazilian clinical and professional communities. Leading medical associations, including the Brazilian Society of Anesthesiology (SBA) and the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy (ABHH), have increasingly incorporated PBM principles into clinical guidelines, educational activities, and consensus documents.[18] These efforts signal recognition of PBM as not only a clinical innovation but also a strategy aligned with quality improvement and long-term sustainability objectives.

At the institutional level, both public and private hospitals have initiated structured PBM programs with promising clinical and operational outcomes. These include preoperative anemia screening protocols, enhanced hemostasis strategies, and blood utilization review committees that provide real-time feedback to clinicians. Early data from these initiatives suggest improved perioperative management and reduced transfusion rates, mirroring international PBM experience.[22,23]

Clinical champions continue to play a pivotal role in catalyzing PBM adoption. National and international experience demonstrates that many successful programs originate from professionals capable of integrating scientific evidence, educational initiatives, and management strategies.[9,10] However, enduring sustainability requires institutionalization. PBM must transcend individual advocacy and be embedded within formal governance structures supported by measurable objectives, performance indicators, and executive endorsement. Institutional leadership involvement — including hospital directors and clinical chiefs — is essential to formalizing PBM within organizational priorities and resource allocation frameworks.

Data governance represents another essential dimension. PBM is intrinsically metrics-driven. Monitoring indicators such as preoperative anemia prevalence, transfusion rates, complication profiles, and cost parameters enables continuous evaluation and refinement of clinical strategies. In a country of continental scale, collaborative networks that facilitate shared learning and benchmarking across institutions could significantly accelerate performance improvement and reduce regional disparities. Standardized data collection and transparent reporting are essential to creating this learning environment.[20]

Within the global context, Brazil shares characteristics with other middle-income healthcare systems — including Mexico, Colombia, India, and parts of Africa — where PBM implementation encounters comparable infrastructure and governance challenges. Yet Brazil also possesses distinctive strengths: demographic scale, a universal public health framework, expanding technological capacity, and a growing community of PBM advocates within clinical sciences.[18] These attributes create a unique opportunity to develop hybrid implementation models that integrate clinical innovation, health policy alignment, and organizational governance.

Advancing PBM implementation requires a structured strategic roadmap. Priority actions should include: embedding multidisciplinary PBM education within professional training programs; formal institutional recognition of PBM as a quality-of-care initiative; strengthening of health information systems to enable real-time performance tracking; alignment with national and regional health policies that recognize PBM as a sustainability strategy; and development of collaborative networks to facilitate knowledge exchange, benchmarking, and progressive standardization.[3]

Establishing robust performance indicators is vital for translating PBM principles into measurable outcomes and to ensure accountability at institutional and system levels. Key performance indicators (KPIs) for PBM implementation should encompass both the process measures and the outcome measures, enabling continuous monitoring and quality improvement.[24] In Brazil's context, where health information systems such as DATASUS exist, but remain underutilized for PBM monitoring, establishing standardized KPI dashboards could really facilitate real-time performance tracking across SUS facilities and private hospitals. A systematic approach to KPI selection and measurement has been demonstrated to improve program effectiveness and sustainability.[25]

Beyond a collection of clinical protocols, PBM embodies a paradigm of patient-centered, physiology-based, and evidence-informed care. Its implementation serves as a marker of a healthcare system's capacity to translate scientific knowledge into operational practice. In Brazil, this transformation is ongoing — complex, uneven, but directionally irreversible. Successful PBM implementation requires establishing systematic monitoring mechanisms and feedback loops that can engage clinical teams in continuous improvement cycles. Data collection should be conducted prospectively using standardized definitions and electronic health record systems to ensure consistency and reduce measurement bias.[26] In resource-constrained Brazilian settings, establishing collaborative networks among institutions can facilitate shared learning and benchmarking, allowing the hospitals to compare their performance against regional and national standards. The ultimate impact of PBM extends beyond traditional transfusion metrics. It reflects the institutional maturity required to integrate culture, governance, and clinical management in pursuit of safer, more efficient care delivery. In healthcare systems of substantial complexity, such transformation is challenging but indispensable.[3]

The Iberoamerican Society of Patient Blood Management (SIAPBM) was established with the mission of advancing PBM

as a standard of quality, safety, and sustainability across Ibero-American healthcare systems. Its vision aligns with global recommendations from the World Health Organization and the International Foundation of Patient Blood Management (IFPBM), while recognizing the structural and socioeconomic particularities of low and middle-income countries. SIAPBM conceptualizes PBM not merely as a clinical innovation, but as a regional health policy movement designed to standardize PBM principles across Ibero-American healthcare systems, strengthen governance and institutionalization of PBM, develop certified PBM implementers and multidisciplinary leadership, promote data-driven implementation models, foster collaborative regional research networks and align PBM with sustainability and economic efficiency frameworks.[27]

Within Brazil's complex health ecosystem, characterized by the coexistence of the Sistema Único de Saúde (SUS) and a technologically advanced private sector, SIAPBM's strategic roadmap provides a structured pathway to bridge the persistent gap between scientific evidence and operational practice. The Society's regional perspective positions Brazil not only as a beneficiary of PBM implementation, but as a continental leader capable of developing scalable hybrid models that integrate: Clinical excellence, data governance modernization, policy alignment and multidisciplinary cultural transformation. In this framework, PBM becomes a measurable quality indicator of institutional maturity. The integration of SIAPBM objectives into Brazil's implementation strategy reinforces the idea that PBM is not a discretionary innovation, but a structural reform aligned with patient safety, economic sustainability, and ethical stewardship of blood as a finite public resource.[28] This vision recognizes that sustainable PBM adoption requires, institutional embedding within hospital governance, formal KPI monitoring linked to executive accountability, continuous professional education integrated into residency and specialist training, regional benchmarking networks to reduce inequities and policy level recognition of PBM as a national health priority that represents more than clinical optimization, it reflects the healthcare system's capacity to operationalize science, integrate governance, and transform professional culture toward safer, physiology based, patient-centered care. In this evolving landscape, SIAPBM functions as a regional accelerator of structured implementation, ensuring that PBM progresses from isolated institutional initiatives to a coordinated, measurable, and policy-aligned continental strategy.[27]

PBM should therefore be understood not merely as a clinical strategy but as a test of a system's ability to harmonize scientific evidence, organizational governance, and professional culture in service of sustainable, high-quality patient care.

Data availability statement

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

Declaration of competing interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Available online 28 February 2026

Brazilian Journal of Anesthesiology 2026;76(2): 844736

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

Working together for perioperative excellence in pediatric perioperative research

KEYWORDS
Clinical excellence;
Collaboration;
Consumer;
Multi-disciplinary;
Outcomes;
Perioperative Team

Pediatric perioperative care can be described as a journey, starting when surgery is first contemplated, all the way through to a patient's full recovery. For the child and their family, this journey spans from the time at home pre-operatively through a hospital stay and finishes with at-home recovery. The continuum of care, ideally seamless, is extremely important to our patients and their families and requires close collaboration among all relevant clinical disciplines.

Pediatric perioperative research should follow the same path, bringing together experts from various disciplines to ensure that all medical, psychological, social, and functional considerations are taken into account as we work toward the common goal of improving outcomes and the perioperative experience for our young patients. Perioperative research collaborations can be thought of as a jigsaw puzzle, where the pieces must be assembled correctly so that we have the necessary skills to assess the problem from all angles, find solutions to our clinical questions, and guide innovation in the perioperative space. In some cases, this may involve partners from various institutions, locally, nationally and internationally.[1,2]

This jigsaw will be incomplete without the inclusion of consumers/patient/parent/community representatives/stakeholders (referred to as consumers hereafter for simplicity) to ensure that our research is truly patient- and family-centered. A diverse group of consumers should be involved in all stages of the research project, from conceptualization through to implementation and translation. Ensuring a diversity in any consumer involvement is critical. For example, the lived experience of children and young people will differ from adults who have lived perioperative experience as a child, coupled with their additional adult perspective, as well as from the experience of parents.[3] Efforts must be made to engage with consumers from different walks of life, representing the breadth of our community, including minority groups and those from Culturally and Linguistically Diverse (CaLD) backgrounds, including First Nation representatives. Consumers can guide us not just on individual projects, but also on their research priorities, ensuring that the research we conduct is not only acceptable and useful to clinicians and researchers but also to our young patients and their families.[3–7] Our research group has been purposefully involving consumers with lived experience in all of our research from bench to bedside and endeavors to involve consumers and community in the four stages outlined in the Guidelines from the Australian National Health and Medical Research Council:[6] 1) Research prioritization; 2) Developing research concepts/hypotheses/questions and designing research projects; 3) Research conduct including participant recruitment, consent and responsibility (ethics, governance) and oversight or governance of the conduct of the research and 4) Reporting, communications and publication/dissemination and translation. In line with institutional and state practice, our consumers are reimbursed for their time. To date, we have not acknowledged consumers in all our research publications, but the decision has been taken to do this more systematically in the future.

While this seems like the obvious standard for patient/family-centred care and research, we wonder whether meaningful consumer involvement is as widespread as some believe. Additionally, meaningful consumer involvement is distinct from consumer consultation or participation in studies.[8]

We have received pushback from some interstate and international collaborators and manuscript reviewers who

https://doi.org/10.1016/j.bjane.2026.844736

questioned the appropriateness of consumer involvement due to the consumers' perceived lack of medical and subject-specific expertise. We have been asked how the consumer could know the details of the research? How and why should they know about something that happens when they are asleep? Patients and families have the right to participate in shared clinical decision-making and receive full information about their treatment, the same holds true for research. It is also reductive to consider the perioperative experience as only concerning the time under anesthesia. Additionally, a significant number of trials are funded by government agencies around the world. There is not only the need for full transparency on how the public funding is spent, but the public should also have their voice heard on which projects should be prioritized.

In addition to consumers, a multidisciplinary research team should not just reflect the multidisciplinary perioperative clinical team but also include, from the beginning, biostatisticians and data scientists. These are vital to ensure that research is designed in the appropriate way to test our hypotheses, that our sample size is sufficient and to build a solid data analysis plan at to ensure as early biostatistics/data-science involvement strengthens methodology and rigor. While this is standard practice in large centers, access to statistical support can be much harder outside large academic centers and in less resourced settings. This is critical to ensure that research is not only approved by an ethics committee but also performed in an ethical manner and will ensure that the study design can actually answer the research question.

We also need to ensure that any research outcomes are economically beneficial and implementable. This is an increasingly important imperative, given that the pockets of our healthcare systems are not bottomless, and society is increasingly confronting aging populations and rising healthcare needs. Mindful of the resources available to us as a community, we should assess the cost-effectiveness of proposed research interventions. Health economists and implementation scientists should be included, not as an afterthought, but from the conceptualization stage, to improve the translation and implementation of any findings.

Last but not at all least, research teams require the operational backbone, the clinical research coordinator or clinical program manager, the person who is responsible for the day-to-day running of the study. While this practice may be standard in large, well-funded academic institutions and, in fact, may form part of the requirements in some Ethical/IRB processes, it is not universally followed, mostly due to resource constraints. This role can span a range of functions, depending on the individual research team's set-up, investigator skills and time, and institutional/country norms. One function can be consenting participants for research, which avoids the potential for subtle coercion of patients into research participation, thereby reducing the perception that enrolment into the research is a requirement and also reducing the risk of therapeutic misconceptions.[9]

A major benefit of the research coordinator/research manager role is to take on administrative/managerial tasks that would otherwise fall to the clinical principal investigator, who is commonly the clinician team lead behind the project. In reality, the medical principal investigator is often busy, often wearing many hats, e.g., clinical care, research, and teaching. The research coordinator, on the other hand, can focus fully on protocol adherence and team communications, as well as managing timelines, reporting, and budgets, ensuring that all necessary information is collected and maintained to the highest standards. The research coordinator often leads the hub for a multidisciplinary team, ensuring seamless communication between all parties involved, including close communication with all participants and their families.

Beyond simple teamwork

Collaboration within a perioperative, multidisciplinary research team is not as easy as assembling a group of experts. Such a group needs to learn how to work together as a cohesive team. Different craft groups may have different viewpoints; they attempt to set a different focus. This may set the scene for conflicting priorities within the research team. A clinician, for example, is likely to prioritize patient care and comfort, while a statistician pushes for a double-blinded study — potentially leading to discussions. If these differences are discussed constructively, it can be highly beneficial, leading to better mutual understanding, more innovative research protocols, improved study designs, and ultimately, better patient outcomes. However, if not led constructively and respectfully, these task conflicts have the potential to evolve into relationship conflicts, which are detrimental to any team. It is therefore vital for all team members to separate the content of the discussion or disagreement from a personal level. Different viewpoints should not be seen as a personal attack, but rather as an opportunity to benefit from a diverse team dynamic and work together as equals to forge a better path through the complex perioperative jungle.

If all parties work together collaboratively and respectfully, putting their egos aside, then the work will not only be more enjoyable but also more constructive. It may be a challenge for some clinicians, trained and experienced in the traditional medical hierarchical structure, to accept non-clinical staff as equals and adapt to a multidisciplinary dynamic, but this improved culture and collaboration will make any team thrive. Adding differing perspectives ensures that researchers are not in an echo chamber. It will further aid the successful implementation of the research findings, with all individual specialists working together, both clinically and in research, driving the clinical and research agendas in parallel, thereby impacting innovation and clinical change with a shared vision to improve patient outcomes.

For this to be possible, we need to learn each other's language and develop a common language and understanding based on mutual respect for each and every partner in the team, recognizing their strengths and weaknesses. In larger projects, building a formal collaborative framework may be helpful, to define roles, objectives, a clear roadmap, expectations and contributions.[1] From personal experience, our large multidisciplinary team, involving many clinical and non-clinical specialties as well as consumers of all ages, with a wide range of experience and skills, is what drives us, what motivates us; we keep learning from and with each other. It lets us grow individually and makes us stronger as a team. It allows us to design better projects and to drive our vision together to improve the safety, care, and outcomes

for all children requiring perioperative care. Only together, we have the jigsaw pieces required to see the full picture. Only together, we can find solutions which improve care for all our patients around the globe.

Actions to establish and sustain multidisciplinary pediatric perioperative research teams

- Ensure an appropriate team composition including clinical and non-clinical multidisciplinary expertise (e.g., medical, nursing, allied health, statisticians, data scientists, research coordinators, psychologists, pharmacists, health economists, and implementation scientists).
- Establish clear expectations around contributions as well as authorship and communication principles, and for larger projects consider a formal collaborative framework.
- Involve a diverse range of consumers (all ages with representation from minority groups and culturally and linguistically diverse backgrounds) in all stages from prioritization and research conceptualization through the research project and into implementation and translation.
- Incorporate early statistical expertise.
- Don't neglect relationship factors such as fostering a respectful and psychologically safe environment with open communication to ensure a true research partnership.

In summary, a successful perioperative research team needs to incorporate not only clinicians, but also non-clinical multidisciplinary expertise, including a diverse range of consumers of all ages, to ensure the community truly has a voice. We all need to walk alongside one another, as equal partners, following the same vision, being respectful and willing to actively listen and learn from everyone. Such a team, comprising consumers, clinicians, non-clinical specialties, statisticians, data scientists, research coordinators/managers, health economists, and implementation scientists, will have a large talent pool with a range of expertise, skills and experience to drive the project successfully. The main challenge lies in creating a single, cohesive team that overcomes communication barriers, fosters a culture of open and safe communication, and thrives on the natural friction of different ideas and approaches. This will collectively shape our research into the best possible project, as all angles will be covered, and will help the rapid translation and implementation of findings into practice, reducing the amount of research waste.

Data availability statement

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

Declaration of competing interest

The authors declare no conflicts of interest.

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Liana Azi

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Received 9 January 2026; Accepted 1 February 2026
Available online 5 February 2026

Brazilian Journal of Anesthesiology 2026;76(2): 844742

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

EDITORIAL

A physiology-driven approach to postoperative sedation after urgent liver transplantation for acute liver failure

KEYWORDS
Acute liver failure;
Bispectral index;
Cerebral autoregulation;
Conscious sedation;
Liver transplantation

There are no formal recommendations regarding postoperative sedation in patients with Acute Liver Failure (ALF) undergoing urgent Liver Transplantation (LT). Owing to the risk of intracranial hypertension in the perioperative period, many centers have adopted the practice of continuing propofol-based sedation for 48—72 hours after transplantation.[1] In clinical practice, however, postoperative sedation strategies are heterogeneous and may pursue different objectives, ranging from deep sedation aimed at metabolic suppression and neuroprotection (e.g., RASS -4/-5) to lighter levels intended to facilitate airway protection, mechanical ventilation, and overall intensive care unit management. This editorial seeks to dwell into the physiological rationale that should guide the postoperative sedation in this complex clinical scenario.

A growing body of evidence indicates that many patients with ALF already exhibit profound suppression of cerebral electrical activity at the time of transplantation, with Bispectral Index (BIS) values frequently below 40 and, in some cases, approaching zero.[2] The use of BIS has been shown to reliably track recovery of consciousness before and after LT in patients with fulminant hepatic failure,[3] including reports of extreme cortical suppression during transplantation.[4] Post-transplant BIS monitoring has further been explored as a tool to assess neurological recovery in acute-on-chronic liver failure patients.[5]

These observations raise an important physiological question: when cortical activity is already markedly suppressed as a consequence of severe metabolic encephalopathy, is further pharmacological suppression necessary, and does it confer additional neuroprotective benefit? This is particularly relevant because additional pharmacological suppression of cortical activity in patients with altered neurotransmission and heightened cerebral sensitivity may amplify pharmacodynamic effects, thereby increasing the risk of anesthetic overdose even at modest doses.[6]

Acute liver failure is characterized by rapid hepatic dysfunction, high-grade encephalopathy, and coagulopathy.[7] Cerebral edema with increased Intracranial Pressure (ICP) remains the most feared neurological complication and a major contributor to mortality in this population.[8] The pathogenesis of cerebral edema in ALF is multifactorial, involving ammonia-induced astrocytic swelling, systemic inflammation, oxidative stress, disruption of the blood-brain barrier, and impaired cerebral autoregulation.[8] Therapeutic strategies therefore focus on minimizing cerebral edema while maintaining adequate neuroprotection. Unlike traumatic brain injury, invasive ICP monitoring is rarely employed in ALF because of severe coagulopathy and the associated risk of intracranial hemorrhage.[9] Consequently, clinicians often rely on non-invasive surrogates, such as transcranial Doppler ultrasonography or optic nerve sheath diameter, in conjunction with clinical and physiological parameters.[10,11]

Neuroprotective measures in ALF include aggressive control of hyperammonemia, head elevation to facilitate cerebral venous drainage, avoidance of hyponatremia, maintenance of normocapnia, and the selective use of hypothermia.[1] Early airway protection is recommended in patients with advanced encephalopathy, typically using short-acting sedative agents. However, the optimal depth and duration of postoperative sedation after LT remain poorly defined.

Propofol has traditionally been favored in this context because of its ability to reduce the Cerebral Metabolic Rate of Oxygen ($CMRO_2$), with secondary reductions in cerebral blood flow leading to potential beneficial effects on ICP.[6,12] Consequently, elective postoperative ventilation with continuous propofol sedation has become a widespread practice

https://doi.org/10.1016/j.bjane.2026.844742

in patients with ALF undergoing LT. Importantly, cerebral autoregulation is frequently impaired in ALF, and reductions in $CMRO_2$ do not necessarily translate into proportional decreases in cerebral blood flow or ICP. Experimental and clinical data from neurocritical care settings further suggest that neurovascular coupling may be disrupted in critically ill brains, thereby limiting the effectiveness of metabolism-based strategies for ICP control. Moreover, variability in cerebrovascular response to sedative agents has been demonstrated in neurocritical care populations, highlighting the heterogeneity of propofol's physiological effects.[13]

The direct cerebral vasoconstrictive effect of propofol, often cited as an independent mechanism for ICP reduction, remains controversial and appears to play a secondary role relative to metabolic suppression.[6,13] Moreover, the magnitude and direction of propofol's effects on cerebral physiology may vary according to baseline disease severity, mean arterial and cerebral perfusion pressure targets, autoregulatory status, and ventilation strategy, particularly $PaCO_2$. Such physiological heterogeneity further challenges the assumption that continued deep sedation confers uniform benefit in terms of decreasing the ICP across all patients.[6]

In unconscious patients with ALF, clinical assessment of encephalopathy severity is inherently limited. Conventional electroencephalography remains the reference standard for evaluating cerebral electrical activity but is impractical for routine perioperative use.[14] Processed EEG monitoring, such as the BIS, derived from frontal electroencephalographic signals, has therefore been adopted as a surrogate of cortical activity. It should be emphasized, however, that BIS was primarily developed to assess the depth of anesthesia and may be influenced by encephalopathy-related EEG patterns, electromyographic activity, and artifacts. Accordingly, BIS and other processed EEG indices should be interpreted as adjunctive tools rather than stand-alone indicators of cerebral protection or neurological prognosis. Importantly, low BIS values do not directly reflect intracranial pressure status and do not exclude the presence of intracranial hypertension.

Notably, intracranial hypertension may still occur despite profound cortical electrical suppression, reinforcing the need for a multimodal approach to clinical interpretation. Hemodynamic variables, ventilation parameters, temperature, metabolic control, and available neuromonitoring surrogates should all be integrated when guiding postoperative management in this vulnerable population.

From a practical perspective, postoperative sedation after urgent LT for ALF may be approached using a physiology-guided framework aligned with established clinical recommendations. The primary goal of sedation should first be clearly defined – whether airway protection and ventilatory synchrony, control of agitation, temperature management, or treatment of suspected seizures. Alongside sedation decisions, priority should be given to established multimodal neuroprotective strategies, as outlined above. When available, modern frontal EEG monitoring may assist in titrating sedative exposure and avoiding unnecessary escalation when cortical activity is already profoundly suppressed.[15]

This physiology-guided perspective should not be interpreted as an argument against postoperative sedation per se. Sedation may remain clearly indicated in several clinical scenarios after LT for ALF, including agitation compromising airway safety or causing significant ventilator dyssynchrony; suspected or evolving intracranial hypertension based on clinical course or non-invasive surrogates; suspected seizures or status epilepticus, particularly when EEG monitoring is available; and during targeted temperature management protocols.

In the absence of definitive guidelines, this editorial reasons that postoperative sedation after urgent LT for ALF should be individualized and guided by physiological principles rather than applied routinely. Based on the foregoing discussion, the authors advocate routine monitoring of BIS in all patients undergoing LT for ALF. The BIS value should be incorporated into decision-making regarding postoperative sedation, with the clear understanding that sedation should not be administered in patients who already have very low BIS values solely with the objective of lowering $CMRO_2$ in an attempt to lower the ICP. In this context, processed EEG monitoring may serve as a valuable adjunct within a multimodal management framework, assisting clinicians in balancing the potential benefits and risks of continued sedative exposure.[15] Future prospective studies integrating processed EEG, non-invasive ICP surrogates, and neurological outcomes are needed to define optimal sedation strategies in this complex and high-risk population.

Data availability statement

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

Authors' contributions

Both authors contributed to the conception and critical discussion of the editorial. Deepak K. Tempe drafted the manuscript. Luiz Guilherme V. da Costa critically revised the manuscript for important intellectual content. Both authors approved the final version of the manuscript.

Funding

None.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 6 February 2026; Accepted 23 February 2026
Available online 7 March 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Preoperative anemia as a marker of postoperative outcomes: a retrospective cohort study

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Received 27 October 2025; accepted 19 March 2026
Available online 28 March 2026

KEYWORDS
Anemia;
Anesthesiology;
Elective surgical procedures;
Preoperative care;
Postoperative complications

Abstract

Background: Preoperative anemia is common and associated with adverse postoperative outcomes.

Objective: To evaluate the association between preoperative anemia severity and clinical outcomes in patients undergoing elective noncardiac surgery.

Methods: This retrospective cohort included 23,579 adults assessed preoperatively between January 2015 and August 2025, all with documented hemoglobin (Hb) and hospitalized for noncardiac surgery. Patients were stratified as no anemia ($\geq$ 13 g.dL^{-1}), mild (11.1–12.9 g.dL^{-1}), moderate (8.1–11.0 g.dL^{-1}), or severe anemia ($\leq$ 8.0 g.dL^{-1}). Outcomes were in-hospital mortality, Intensive Care Unit (ICU) admission, and Length of Stay (LOS). Analyses used Poisson regression with robust variance adjusted for confounders.

Results: Among the participants, 15,909 (67.5%) had no anemia, 6,396 (27.1%) mild, 1,174 (5.0%) moderate, and 100 (0.4%) severe anemia. Overall, 62.6% were female, and the mean age was 60.7 years (SD $\pm$15.4). Compared with no anemia, all anemia categories were independently associated with higher in-hospital mortality, increased ICU admission, and longer LOS. Severe anemia was the strongest predictor of in-hospital mortality (adjusted RR = 24.7; 95% CI 13.3–46.0; $p < 0.001$). Intermediate or major surgeries (RR = 4.7; 95% CI 3.4–6.6), age > 54 years (RR = 4.4; 95% CI 2.6–7.6), and male sex (RR = 2.1; 95% CI 1.6–2.9) were also independent predictors of in-hospital mortality.

Conclusions: Preoperative anemia, even when mild, was independently associated with higher in-hospital mortality, greater ICU admission, and prolonged hospitalization. These results

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https://doi.org/10.1016/j.bjane.2026.844747

support systematic screening and targeted management, including Patient Blood Management (PBM) strategies, to improve perioperative outcomes.

Introduction

Preoperative anemia is highly prevalent worldwide, affecting nearly 30% of patients scheduled for elective surgery, and is recognized as a public health concern by the World Health Organization (WHO).[1] In the surgical setting, anemia is commonly defined as Hemoglobin (Hb) levels < 13 lt; 13 g.dL^{-1}, regardless of sex, due to the expected blood loss and the reduced physiological reserve of surgical patients.[2-4]

Previous studies have demonstrated that preoperative anemia increases the risk of transfusion, prolongs the hospital stay, and elevates mortality.[5] Despite its clinical relevance, most anemic patients do not receive treatment before surgery, representing a missed opportunity for anemia correction and perioperative risk reduction.[6,7]

In this context, Patient Blood Management (PBM) programs are strongly recommended by international consensus and national guidelines as strategies to optimize anemia management and reduce transfusion exposure.[8]

In Brazil and Latin America, there is still a significant evidence gap regarding the impact of preoperative anemia on surgical outcomes, characterized by data scarcity and high heterogeneity in the implementation of Patient Blood Management (PBM) programs.[9]

Therefore, the objective of this study was to evaluate the association between the presence and severity of preoperative anemia and clinical outcomes in adult patients undergoing elective noncardiac surgery. The primary outcome was in-hospital mortality, and the secondary outcomes were Intensive Care Unit (ICU) admission and hospital Length of Stay (LOS).

Materials and methods

Study design and ethical aspects

This was a retrospective cohort study conducted in accordance with the STROBE guidelines for observational research. The study was carried out at a tertiary university hospital. The protocol was approved by the Research Ethics Committee of Santa Casa de Porto Alegre (CAAE 83879224.0.0000.5335), with a waiver of informed consent due to its retrospective nature.

Population and inclusion criteria

Adult patients (≥ 18 years) evaluated at the Preoperative Assessment Service between January 2015 and August 2025 were eligible if they had a recorded Hemoglobin (Hb) level and underwent elective noncardiac surgery requiring hospitalization.

To ensure the independence of observations and minimize potential bias, only the first consultation and its corresponding primary surgical procedure were analyzed for each patient; reconsultations and repeat assessments were excluded. The database was queried for patients with a complete triad of initial preoperative assessment, baseline hemoglobin measurement, and confirmed subsequent surgery. Patients with missing laboratory values at the first visit or those whose surgeries were canceled were ineligible and excluded during the screening phase. This selection process is detailed in the STROBE-style flow diagram (Fig. 1). For the overall cohort, the median Hemoglobin-to-Surgery (Hb-S) interval was 26.7-days (IQR 7.9–90.9). This timeframe supports the clinical relevance and stability of the laboratory findings, as it is consistent with the standard preoperative window for elective procedures and ensures that the reported levels reflect patients' clinical status prior to surgery.

Exclusion criteria

Patients undergoing urgent or emergency procedures, those already hospitalized at the time of evaluation, cases with incomplete laboratory data, and patients whose surgeries were canceled after evaluation were excluded.

Data sources and variables

Data were retrieved from the institutional electronic health record system (Tasy®) and included demographics, comorbidities, American Society of Anesthesiologists Physical Status (ASA-PS), Body Mass Index (BMI), estimated functional capacity in Metabolic Equivalents (METs), laboratory tests (hemoglobin, creatinine, and glucose), in-hospital mortality, Intensive Care Unit (ICU) admission, and hospital LOS.

Anemia was defined as Hemoglobin (Hb) concentration < 13 lt; 13 g.dL^{-1} for both sexes, following the International Consensus Statement on the peri-operative management of anemia, which recommends this threshold to ensure adequate physiological reserve for surgical stress in all adult patients.[3] Patients were stratified into four groups based on Hb levels: no anemia (≥ 13.0 g.dL^{-1}), mild anemia (11.1–12.9 g.dL^{-1}), moderate anemia (8.1–11.0 g.dL^{-1}), and severe anemia (≤ 8.0 g.dL^{-1}). The age threshold of 54 years was selected based on the demographic profile of our surgical population and clinical relevance. This threshold aligns with physiological considerations, as it often marks the post-menopausal period in women – a factor that influences the interpretation of hemoglobin levels and supports the movement toward a unified preoperative hemoglobin target to optimize surgical management. This approach is further supported by the World Health Organization guidance on Patient Blood Management, which emphasizes the need to optimize 'blood health' to improve surgical safety and outcomes.[10] Creatinine was classified as < 1.5 mg.dL^{-1} or ≥ 1.5 mg.dL^{-1}, and glucose was categorized as normal

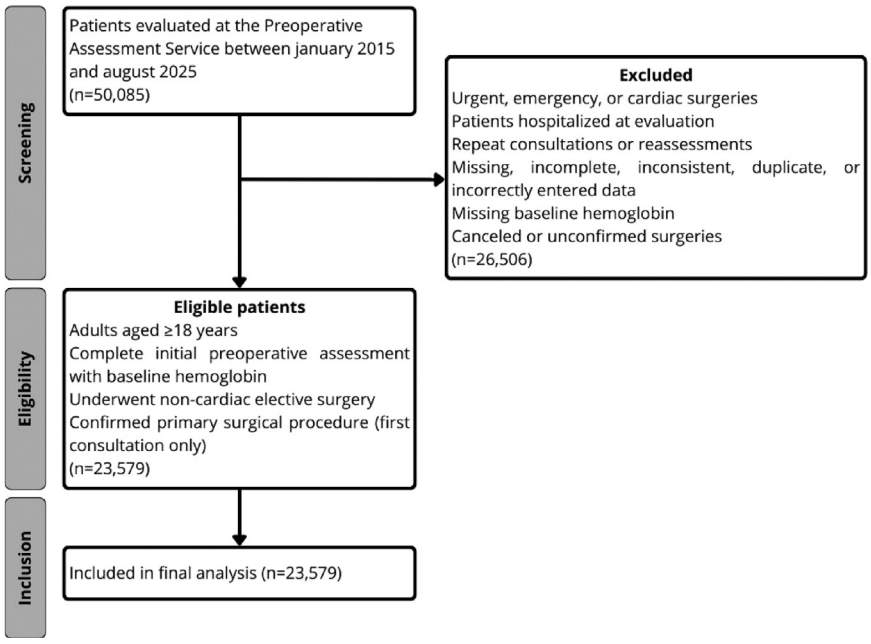

Figure 1 STROBE flowchart of study population identification and enrollment.

(< 100 mg.dL^{-1}), prediabetes (100–125 mg.dL^{-1}), or diabetes (≥ 126 mg.dL^{-1}). BMI was classified as underweight (< 18.5), normal weight (18.5–24.9), overweight (25.0–29.9), obesity class I (30.0–34.9), obesity class II (35.0–39.9), and obesity class III (≥ 40.0). Surgical complexity was categorized as minor, intermediate, or major, based on a previous classification.[11] Functional capacity was categorized as low (≤ 4 METs) or moderate-to-high (≥ 5 METs), in accordance with clinical standards for preoperative risk assessment.[11]

Outcomes

The primary outcome was in-hospital mortality, while secondary outcomes included Intensive Care Unit (ICU) admission and hospital Length of Stay (LOS).

Statistical analysis

Data were initially entered into Microsoft Excel and subsequently exported to SPSS version 20.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Continuous variables were described as mean $\pm$ standard deviation or median and interquartile range, depending on distribution assessed by the Shapiro-Wilk test. Categorical variables were expressed as absolute and relative frequencies and compared using the Chi-Square test with Yates' correction when appropriate. Continuous variables without normal distribution were analyzed using the Mann-Whitney test for two groups and the Kruskal-Wallis test with Dunn-Bonferroni post hoc analysis for three or more groups.

The selection of covariates for the multivariable analysis was based on the principle of parsimony and clinical relevance. Variables were included in the final model if they demonstrated a significant association in the univariate analysis or if they were clinically established predictors of postoperative outcomes, such as age, sex, ASA-PS, and surgical complexity. This approach was specifically chosen considering the low-risk profile of the cohort, which is predominantly composed of relatively healthy individuals (ASA-PS I–II) undergoing minor procedures. In such a population, the potential influence of other clinical confounders or complex comorbidities is expected to be minimal, and a focused model ensures greater stability and avoids overfitting.

Analyses were performed on the entire cohort and repeated on the subgroup of patients undergoing intermediate or major procedures. To adjust for potential confounders, variables selected according to the aforementioned criteria were included in Poisson regression models with robust variance. Relative Risks (RR) with 95% Confidence Intervals (95% CI) were estimated for in-hospital mortality, ICU admission, and hospital LOS. The latter was defined as hospitalization exceeding 4 days, corresponding to the 75th Percentile (P75) of the study population. This threshold was specifically chosen due to the right-skewed distribution of LOS data, ensuring that the P75 accurately represents the clinical boundary of prolonged stay while minimizing the impact of extreme outliers. This approach aligns with established benchmarking methodologies in surgical literature, which utilize the 75th percentile to define reference standards for postoperative outcomes.[12] A two-tailed p-value < 0.05 was considered statistically significant.

Results

A total of 23,579 patients with available hemoglobin values and requiring hospitalization were included. The median interval between the preoperative assessment (Hb measurement) and the surgical procedure was 26.7 days (IQR 7.9–90.9). Of these, 15,909 (67.5%) had no anemia, 6,396 (27.1%) had mild anemia, 1,174 (5.0%) had moderate anemia, and 100 (0.4%) had severe anemia. The cohort comprised 14,768 women (62.6%), with a mean age of 60.7 years (SD $\pm$15.4) (Table 1).

Patients with anemia had higher in-hospital mortality, increased ICU admission, and longer LOS compared with those without anemia (Table 2).

Among all patients, 7,647 underwent intermediate and 417 underwent major surgeries, totaling 8,064 individuals. In this subgroup, 5,327 (66.1%) had no anemia, 2,217 (27.5%) had mild anemia, 475 (5.9%) had moderate anemia, and 45 (0.6%) had severe anemia. Of these, 5,015 (62.2%) were women, with a mean age of 63.4-years (SD ±14.6). Again, in-hospital mortality, ICU admission, and hospital LOS were higher in patients with anemia than in those without anemia. These data are presented in Table 3.

In the overall sample, in-hospital mortality and ICU admission were progressively more frequent with increasing anemia severity, with statistically significant differences across all groups. LOS was longer among patients with moderate and severe anemia. In patients undergoing intermediate or major surgeries, in-hospital mortality was higher among those with moderate or severe anemia compared with patients without anemia or with mild anemia. ICU admission was lower in patients without anemia than in those with mild anemia, while patients with moderate or severe anemia had the highest rates. Regarding LOS, patients with moderate anemia had longer stays than those with mild anemia, and those with mild anemia stayed longer than patients without anemia. No significant differences were observed for severe anemia, likely due to small sample size. These results are detailed in Table 3 and illustrated in Figure 2.

Poisson regression models with robust variance were applied to assess factors associated with in-hospital mortality, ICU admission, and prolonged LOS (> 4 days, 75th percentile) in the overall sample and in the subgroup of patients undergoing intermediate or major surgeries. The models were adjusted for potential confounders, including BMI, ASA-PS, hypertension, diabetes, chronic kidney disease, METs, creatinine, sex, age, and surgical complexity.

Primary outcome

Severe anemia had the greatest impact on in-hospital mortality, with a Relative Risk (RR) of 24.7 (95% CI 13.3–46.0), indicating that severe anemia was associated with a nearly 25-fold increase in the risk of in-hospital death compared to non-anemic patients (adjusted RR = 24.7; 95% CI 13.3–46.0). Moderate anemia was also significantly associated (RR = 4.6; 95% CI 3.0–7.1), as was mild anemia (RR = 2.5; 95% CI 1.8–3.5). Male sex and age > 54 years were also risk factors, as was undergoing intermediate or major surgery compared with minor procedures. When restricted to patients undergoing intermediate or major surgeries, the analysis confirmed anemia severity as a major risk factor. Severe anemia remained the strongest predictor associated with in-hospital mortality (RR = 10.9; 95% CI 4.4–27.4), followed by moderate (RR = 3.6; 95% CI 2.2–5.9) and mild anemia (RR = 1.7; 95% CI 1.1–2.5). Male sex, age > 54 years, and major surgery were also significantly associated with in-hospital mortality. Final model results are shown in Table 4.

Secondary outcome

In the overall sample, anemia, ASA-PS, sex, surgical complexity, and age were independently associated with ICU admission. Risk increased with anemia severity, as well as with ASA-PS III–V, male sex, intermediate or major surgeries, and age > 54 years. When restricted to patients undergoing

Table 1 Baseline patient characteristics by anemia group.

Total sample	Overall cohort (n = 23,579)	No anemia (n = 15,909)	Mild (n = 6,396)	Moderate (n = 1,174)	Severe (n = 100)	p-value
Age (years)	60.7 ± 15.4[a]	60.2 ± 15.1[a]	61.2 ± 15.8[a]	64.0 ±1 6.0[b]	58.8 ± 18.2[a]	< 0.001*
Sex						< 0.001**
Female	14,768 (62,6%)[a]	8,619 (54.2%)[a]	5,270 (82.4%)[b]	814 (69.3%)[c]	65 (65.0%)[a,c]	
Male	8,811 (37.4%)[a]	7,290 (45.8%)[a]	1,126 (17.6%)[b]	360 (30.7%)[c]	35 (35.0%)[a,c]	
ASA-PS						< 0.001**
I – II	20,353 (87.8%)	14,200 (90.7)[a]	5,370 (85.3%)[b]	740 (64,5%)[c]	43 (44.8%)[d]	
III – V	2,840 (12.2%)[a]	1,453 (9.3%)[a]	926 (14.7%)[b]	408 (35.5%)[c]	53 (55.2%)[d]	
Procedure complexity						< 0.001**
Minor	15,515 (65.8%)[a]	10,582 (66.5%)[a]	4,179 (65.3%)[a]	699 (59.5%)[b]	55 (55.0%)[a,b]	
Intermediate	7,647 (32.4%)[a]	5,065 (31.8%)[a]	2,106 (32.9%)[a]	435 (37.1%)[b]	41 (41.0%)[a,b]	
Major	417 (1.8%)[a]	262 (1.6%)[a]	111 (1.7%)[a]	40 (3.4%)[b]	4 (4.0%)[a,b]	
Comorbidities						
Hypertension	10,502 (46.4%)[a]	6,699 (43.8%)[a]	3,038 (49.7%)[b]	705 (62.6%)[c]	60 (64.5%)[c]	< 0.001**
DM	3,507 (14.9%)[a]	2,134 (13.4%)[a]	1,072 (16.8%)[b]	273 (23.3%)[c]	28 (28.0%)[c]	< 0.001**
PMI	880 (3.7%)[a]	558 (3.5%)[a]	247 (3.9%)[a]	67 (5.7%)[b]	8 (8.0%)[a,b]	< 0.001**
Hypothyroidism	1,746 (7.4%)[a]	1,052 (6.6%)[a]	581 (9.1%)[b]	105 (8.9%)[b]	8 (8.0%)[a,b]	< 0.001**
Hyperthyroidism	100 (0.4%)	64 (0.4%)	32 (0.5%)	4 (0.3%)	–	< 0.642
CKD	945 (4.5%)	305 (2.1%)[a]	345 (6.1%)[b]	261 (25.3%)[c]	34 (38.6%)[d]	< 0.001**
Hb-S (days)	26.7 (7.9–90.9)	27 (8–92)	24 (8–87)	28 (10–89)	31 (11–77)	< 0.086***

*Independent *t*-test; **Chi-Square; ***Kruskal-Wallis test.
[a,b] Different letters indicate statistically significant differences.
DM, Diabetes Mellitus; PMI, Previous Myocardial Infarction; CKD, Chronic Kidney Disease; Hb-S, Hemoglobin-to-surgery interval: median and Interquartile Range (IQR).

Table 2 Comparisons between patients with and without anemia regarding in-hospital mortality, ICU admission, and LOS in the overall sample and in those undergoing intermediate or major surgery.

Overall sample	No anemia (n = 15,909)	Anemia (n = 7,670)	p-value
In-hospital mortality, n (%)	78 (0.5%)	102 (1.3%)	< 0.001[a]
ICU admission, n (%)	514 (3.2%)	453 (5.9%)	< 0.001[a]
LOS, median (IQR)	1.0 (0.3 – 2.1)	1.0 (0.3 – 2.3)	< 0.001[b]

Intermediate or major surgeries	No anemia (n = 5,327)	Anemia (n = 2,737)	p-value
In-hospital mortality, n (%)	65 (1.2%)	69 (2.5%)	< 0.001[a]
ICU admission, n (%)	452 (8.5%)	368 (13.4%)	< 0.001[a]
LOS, median (IQR)	2.1 (1.0 – 4.1)	2.2 (1.0 – 5.2)	< 0.001[b]

ICU, Intensive Care Unit; LOS, Length of Stay; IQR, Interquartile Range.
[a] Chi-Square test with Yates' correction.
[b] Mann-Whitney *U* test.

Table 3 Comparisons of outcomes (in-hospital mortality, ICU admission, and LOS) between patients without anemia and those with anemia (overall and according to severity), in the total sample and among those undergoing intermediate or major surgery.

Total sample	No anemia (n = 15,909)	Mild (n = 6,396)	Moderate (n = 1,174)	Severe (n = 100)	p-value
In-hospital mortality, n (%)	78 (0.5%)[a]	64 (1.0%)[b]	27 (2.3%)[c]	11 (11.0%)[d]	< 0.001*
ICU admission, n (%)	514 (3.2%)[a]	304 (4.8%)[b]	128 (10.9%)[c]	21 (21.0%)[d]	< 0.001*
LOS, median (IQR)	1.0 (0.3 – 2.1)[a]	1.0 (0.3 – 2.2)[b]	1.2 (0.4 – 5.0)[c]	1.3 (0.3 – 8.0)[c]	< 0.001**

Intermediate or major surgeries	No anemia (n = 5,327)	Mild (n = 2,217)	Moderate (n = 475)	Severe (n = 45)	p-value
In-hospital mortality, n (%)	65 (1.2%)[a]	42 (1.9%)[a]	22 (4.6%)[b]	05 (11.1%)[b]	< 0.001*
ICU admission, n (%)	452 (8.5%)[a]	245 (11.1%)[b]	110 (23.2%)[c]	13 (28.9%)[c]	< 0.001*
LOS, median (IQR)	2.1 (1.0 – 4.1)[a]	2.1 (1.0 – 4.4)[b]	3.9 (1.2 – 9.0)[c]	5.1 (0.6 – 14.4)[a,b,c]	< 0.001**

ICU, Intensive Care Unit; LOS, Length of Stay; IQR, Interquartile Range.
*Chi-square; **Kruskal-Wallis test.
[a,b] Different letters indicate statistically significant differences.

intermediate or major surgery, patients with severe anemia had a three-fold higher risk of ICU admission (RR = 3.0; 95% CI 1.8–4.9), those with moderate anemia had a two-fold higher risk (RR = 1.8; 95% CI 1.2–2.8), and those with mild anemia had a 1.4-fold higher risk (RR = 1.4; 95% CI 1.2–1.6), compared with patients without anemia. Patients classified as ASA-PS III–V, male sex, undergoing major procedures, and older than 54 years were also at higher risk of ICU admission. The results of the final model are presented in Table 5.

Prolonged hospital stay (> 4 days) was also evaluated. In the overall sample, severe, moderate, and mild anemia were significantly associated with longer hospitalization. Male sex, intermediate or major surgery, and age > 54 years increased the risk of prolonged stay, while higher functional capacity (moderate-to-high functional capacity category) was protective. In the subgroup of patients undergoing intermediate or major surgery, anemia severity remained significantly associated with prolonged stay. Male sex, major surgery, and age > 54 years increased the risk, while the moderate-to-high functional capacity category reduced it. Results are presented in Table 6.

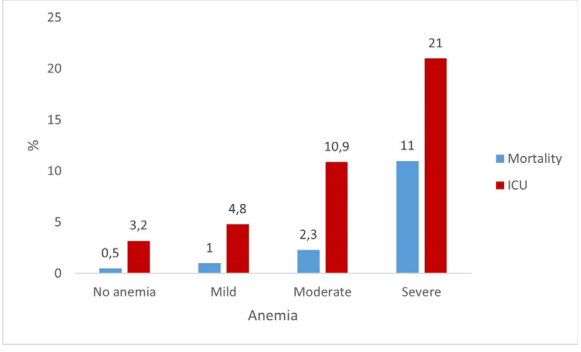

Figure 2 Mortality and ICU admission rates in the overall sample.

Discussion

In this study, the presence of preoperative anemia was associated with worse clinical outcomes, including higher in-hospital mortality, increased ICU admission, and prolonged LOS. A severity-dependent association was also observed, characterized by a progressive increase in risk with worsening

Table 4 Poisson regression model with robust variance for factors associated with in-hospital mortality in the overall sample and in patients undergoing intermediate or major surgery.

	Overall sample		Intermediate or major surgery subgroup	
Factors	RR (95% CI)	p-value	RR (95% CI)	p-value
Anemia				
Severe	24.7 (13.3 – 46.0)	< 0.001	10.9 (4.4 – 27.4)	< 0.001
Moderate	4.6 (3.0 – 7.1)	< 0.001	3.6 (2.2 – 5.9)	< 0.001
Mild	2.5 (1.8 – 3.5)	< 0.001	1.7 (1.1 – 2.5)	< 0.011
No anemia	1		1	
Sex				
Male	2.1 (1.6 – 2.9)	< 0.001	1.5 (1.0 – 2.1)	< 0.036
Female	1		1	
Procedure complexity				
Major	4.7 (3.4 – 6.6)[a]	< 0.001[a]	4.8 (3.2 – 7.1)	< 0.001
Intermediate			1	
Minor	1		–	–
Age				
> 54 years	4.4 (2.6 – 7.6)	< 0.001	3.8 (2.0 – 7.1)	< 0.001
≤ 54 years	1		1	

RR, Relative Risk; 95% CI 95% Confidence Interval.
[a] Intermediate or major subgroup.

anemia severity, with severe anemia emerging as the strongest independent predictor of mortality in the adjusted model.

A fundamental and distinct characteristic of our study is the demonstration that preoperative anemia remains a robust marker of adverse outcomes even in a population predominantly composed of patients with low clinical complexity (ASA-PS I–II) undergoing low-risk surgeries.

While much of the existing literature focuses on high-complexity cohorts — such as cardiac, major oncological, and large-scale orthopedic surgeries – where anemia is a well-recognized complication, evidence shows that the overwhelming majority of these patients still undergo surgery without adequate anemia optimization. Our findings reveal that this systemic failure extends even to routine elective procedures, where anemia remains a clinically significant and frequently neglected risk factor. By investigating a population often underrepresented or diluted in massive datasets, this study provides the clinical specificity necessary to audit current institutional practices. Such

Table 5 Poisson regression model with robust variance for factors associated with Intensive care unit admission in the overall sample and in patients undergoing intermediate or major surgery.

	Overall sample		Intermediate or major surgery subgroup	
Factors	RR (95% CI)	p-value	RR (95% CI)	p-value
Anemia				
Severe	4.2 (2.9 – 6.3)	< 0.001	3.0 (1.8 – 4.9)	< 0.001
Moderate	2.4 (2.0 – 2.9)	< 0.001	2.3 (1.8 – 2.8)	< 0.001
Mild	1.5 (1.3 – 1.8)	< 0.001	1.4 (1.2 – 1.6)	< 0.001
No anemia	1		1	
ASA-PS				
III – V	2.7 (2.4 – 3.1)	< 0.001	2.0 (1.7 – 2.3)	< 0.001
I – II	1		1	
Sex				
Male	1.8 (1.6 – 2.1)	< 0.001	1.7 (1.5 – 1.9)	< 0.001
Female	1		1	
Procedure complexity				
Major	9.0 (7.6 – 10.8)[a]	<0.001[a]	3.8 (3.2 – 4.4)	< 0.001
Intermediate			1	
Minor	1		–	–
Age				
> 54 years	1.7 (1.5 – 2.1)	< 0.001	1.7 (1.4 – 2.1)	< 0.001
≤ 54 years	1		1	

RR, Relative Risk; 95% CI, 95% Confidence Interval.
[a] Major or intermediate subgroup.

Table 6 Poisson regression model with robust variance for factors associated with LOS (> 4 days, 75th percentile) in the overall sample and in patients undergoing intermediate or major surgery.

	Overall population		Intermediate or major surgery subgroup	
Factors	RR (95% CI)	p-value	RR (95% CI)	p-value
Anemia				
Severe	3.0 (2.3 – 3.8)	< 0.001	2.1 (1.6 – 2.8)	< 0.001
Moderate	2.3 (2.1 – 2.5)	< 0.001	1.9 (1.7 – 2.1)	< 0.001
Mild	1.4 (1.3 – 1.6)	< 0.001	1.3 (1.2 – 1.4)	< 0.001
No anemia	1		1	
METs				
Moderate-to-high	0.6 (0.6 – 0.7)	< 0.001	0.8 (0.7 – 0.8)	< 0.001
Low	1		1	
Sex				
Male	1.8 (1.7 – 1.9)	< 0.001	1.7 (1.5 – 1.8)	< 0.001
Female	1		1	
Procedure				
Major	4.5 (4.2 – 4.9)[a]	< 0.001[a]	1.6 (1.4 – 1.8)	< 0.001
Intermediate			1	
Minor	1		–	–
Age				
> 54 years	1.7 (1.5 – 1.9)	< 0.001	1.9 (1.7 – 2.1)	< 0.001
≤ 54 years	1		1	

RR, Relative Risk; 95% CI, 95% Confidence Interval.
[a] Intermediate or major subgroup.

contemporary real-world evidence is essential to address the persistent discrepancy between clinical evidence and surgical practice, thereby mitigating the 'therapeutic inertia' that contributes to avoidable postoperative morbidity and mortality. As emphasized in the 2024 World Health Organization Guidance, anemia remains a major global public health challenge, and new data from diverse surgical populations are vital to drive the implementation of Patient Blood Management standards.[10]

Furthermore, it is essential to consider that preoperative anemia may serve as a surrogate marker for broader clinical vulnerability, including advanced comorbidities, chronic inflammation, and frailty syndromes, rather than acting solely as a direct causal driver of mortality. The interplay between low hemoglobin and decreased physiological reserve – often exacerbated by chronic inflammatory states – creates a high-risk surgical phenotype. Although our multivariable models were adjusted for key confounders such as age, ASA-PS, and comorbidities, the retrospective nature of this study limits our ability to fully decouple anemia from these complexes, overlapping syndromes.

Our study distinguishes itself from most of the existing literature by adopting a single hemoglobin threshold of 13 g.dL^{-1} to define anemia for both sexes, rather than the traditional gender-based WHO criteria. This deliberate choice is supported by growing evidence within the Patient Blood Management framework, specifically the International Consensus Statement, which establishes that a Hb concentration ≥13 g.dL^{-1} is necessary to provide sufficient physiological reserve for surgical stress in all adult patients.[3] The age threshold of 54 years used in our analysis also aligns with these physiological considerations, as it often marks the post-menopausal period in women – a factor that influences the interpretation of hemoglobin levels and supports the movement towards a unified preoperative hemoglobin target to optimize 'blood health', a core concept of the 2024 WHO PBM framework.[10] By applying this stricter criterion, we identified a significant proportion of women who would otherwise be classified as non-anemic by traditional standards, yet who remain at increased risk for adverse postoperative outcomes.

These findings are consistent with international literature. In a UK cohort including more than 39,000 patients, preoperative anemia was identified as an independent predictor of complications and mortality, regardless of other clinical factors.[2] Similarly, a meta-analysis involving more than 200,000 patients demonstrated that even mild anemia significantly increases the risk of postoperative death.[1] In orthopedic surgery, a systematic review confirmed that preoperative anemia is associated with higher transfusion risk, prolonged hospitalization, and increased mortality.[5] More recently, a systematic review with meta-analysis in cardiac surgery reinforced these findings, linking preoperative anemia not only to higher mortality but also to greater morbidity and longer LOS.[13]

Another relevant aspect was the prolongation of hospitalization among patients with anemia, especially in moderate and severe forms. This finding is consistent with prospective studies in colorectal surgery, which demonstrated the feasibility of early preoperative anemia detection and correction, with favorable impacts on recovery.[14] Regarding ICU admission, since our cohort is predominantly composed of low-to-intermediate risk surgeries where routine ICU use is not standard, admission serves as a proxy for surgical complexity or clinical instability. Importantly, even mild anemia was associated with worse outcomes, underscoring the need for intervention across all severity levels. In our study, higher functional capacity (moderate-to-high functional capacity category) acted as a significant protective factor

against prolonged hospital stay, reinforcing the importance of preoperative physical reserve.[11]

The higher rate of ICU admissions among anemic patients identified in this study may be related to reduced physiological reserve, increased vulnerability to infectious complications, and a higher risk of hemodynamic instability. These findings are consistent with international series reporting a higher incidence of infectious and cardiovascular complications in surgical patients with anemia.[1,2,5]

In this context, Patient Blood Management (PBM) strategies have gained significant relevance. Current international and national guidelines emphasize the importance of preoperative laboratory screening, etiological investigation, and the specific treatment of anemia before elective surgery.[3,4,8] Intravenous iron supplementation and, in selected cases, the use of erythropoiesis-stimulating agents are effective measures to reduce transfusion requirements and improve outcomes.[6,7] Recent evidence from a randomized controlled trial in elderly patients undergoing hip fracture surgery demonstrated that preoperative intravenous iron administration significantly reduced mortality at 6 and 12 months and decreased transfusion needs.[15] However, it is important to note that hip fracture populations involve urgent orthopedic scenarios, which may differ significantly from the elective noncardiac procedures examined in our study. Differences in surgical urgency, baseline physiological reserve, and the available window for Patient Blood Management (PBM) interventions must be considered when extrapolating these results to elective settings.

In Brazil, a multicenter study reported a high prevalence of preoperative anemia across different regions, regardless of sex and age, characterizing the condition as a public health issue.[9] Accordingly, the consensus of the Brazilian Association of Hematology, Hemotherapy, and Cellular Therapy recommends postponing elective procedures whenever possible until anemia is diagnosed and corrected, with a minimum of four weeks for treatment.[16]

Our study has limitations that warrant consideration. First, its retrospective, single-center design may limit the generalizability of the findings to centers with different discharge practices or ICU protocols. Second, for the entire study cohort, the overall median interval between Hb measurement and surgery was 26.7 days (IQR 7.9–90.9). While this interval is clinically acceptable and remained consistent across all anemia severity levels ($p < 0.006$), changes in Hb levels between the assessment and the procedure were not captured. Additionally, the lack of intraoperative data, such as blood loss and hypotension, precludes a more granular analysis of the surgical insult. Furthermore, the subgroup of patients with severe anemia was relatively small (n = 100); although the association with mortality was profound and clinically significant, the precision of this specific estimate is limited, as reflected by the wider confidence intervals. Finally, while we adjusted for major confounders, the potential for residual confounding from unmeasured frailty or inflammatory markers remains.

Conclusion

In summary, this study supports the evidence that preoperative anemia is strongly associated with increased surgical mortality, ICU admission, and prolonged LOS. These results reinforce the importance of implementing institutional protocols for screening and treating anemia before elective procedures, in alignment with national and international PBM guidelines, aiming to reduce complications, optimize hospital resources, and improve surgical patient safety. As an observational study, these findings highlight a significant clinical association but do not establish a direct causal link between hemoglobin levels and postoperative outcomes.

Data availability statement

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

Declaration of generative AI in the writing process

During the preparation of this work, the authors used Gemini (Google) to refine the English language and improve the structural flow of the discussion. The authors reviewed the final content and accepted full responsibility for the manuscript.

Declaration of competing interest

The authors declare no conflicts of interest.

Funding

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

Associate Editor

Luís Vicente Garcia

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Preoperative and postoperative anemia in major elective surgery: insights from a retrospective cohort in a Brazilian University Hospital

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Received 14 April 2025; accepted 16 November 2025
Available online 22 November 2025

KEYWORDS
Anemia;
Blood transfusion;
Intraoperative period

ABSTRACT

Background: Anemia is a common and critical condition in the perioperative management of patients undergoing major elective surgeries, posing significant risks to postoperative recovery. This study aimed to evaluate the prevalence of preoperative and postoperative anemia in surgical patients from a university hospital in northeastern Brazil.

Methods: This retrospective study included 508 patients aged 18 years or older who underwent major elective surgeries between October 2021 and October 2022. Anemia was defined according to World Health Organization criteria (hemoglobin < 13 g.dL^{-1} for men and < 12 g.dL^{-1} for women). Data were extracted from medical records and included preoperative and postoperative hemoglobin levels, surgical types, and transfusion requirements.

Results: Preoperative anemia was observed in 59.6% of 508 patients analyzed, with a mean Hb level of 11.66 ($\pm$ 2.75) g.dL^{-1} and 11.13 ($\pm$ 2.08) g.dL^{-1} for women and men, respectively. In the postoperative period, the anemia rate increased to 94.6%, with a mean Hb level of 9.36 ($\pm$ 1.55) g.dL^{-1} and 9.49 ($\pm$ 1.36) g.dL^{-1} for women and men, respectively. The transfusion rate was 27% in the total sample. Patients with preoperative anemia were 4.6 times more likely to require intraoperative transfusion compared to non-anemic patients (OR = 4.58; 95% CI: 2.78–7.52; $p < 0.001$). Higher preoperative hemoglobin levels were identified as protective against transfusion (OR = 0.65; 95% CI: 0.59–0.72; $p < 0.001$).

Conclusions: Preoperative anemia is a highly prevalent and modifiable risk factor associated with increased transfusion requirements and adverse perioperative outcomes. The study highlights the importance of implementing patient blood management protocols in surgical practice.

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https://doi.org/10.1016/j.bjane.2025.844715

Introduction

Anemia is a critical condition in the perioperative management of patients undergoing elective surgeries. Defined by the World Health Organization (WHO) as Hemoglobin (Hb) levels < 13 $g.dL^{-1}$ in men and < 12 $g.dL^{-1}$ in women, preoperative anemia is a prevalent comorbidity affecting up to 40% of surgical candidates and poses significant risks to postoperative recovery.[1] The etiology is often multifactorial, including chronic disease, iron deficiency, and inflammatory states. Notably, preoperative anemia serves as an independent predictor of adverse outcomes, including increased mortality, prolonged hospitalization, and higher rates of postoperative complication.[2,3]

Postoperative anemia is even more prevalent than its preoperative counterpart, with rates reaching 80%—90% after major surgeries. The condition arises from perioperative blood loss, hemodilution, and inflammation-induced suppression of erythropoiesis. Elevated levels of hepcidin, a regulatory protein of iron metabolism, further impair iron availability, delaying Hb recovery.[2,3]

The recognition of anemia as a modifiable risk factor has prompted the adoption of Patient Blood Management protocols, which encompass three pillars: 1) Detection and treatment of preoperative anemia, 2) Minimization of intraoperative blood loss, and 3) Optimization of patient-specific anemia tolerance.[4]

This study aimed to conduct an epidemiological assessment of preoperative and postoperative anemia cases in elective major surgeries performed at a university hospital in northeastern Brazil.

Methods

This was a retrospective study conducted between October 2021 and October 2022. The project was submitted to and approved by the Research Ethics Committee under protocol number CAAE 67056522.7.0000.5292.

Study population and data collection

All patients aged 18 years or older who underwent elective surgery and had blood component reservations between October 2021 and October 2022 were included in the study. According to international and institutional protocol, blood components are reserved for major surgeries and/or procedures with an estimated blood loss of 500 mL or greater.[5]

Data were collected from both electronic and physical medical records archived at the University Hospital Onofre Lopes. The following variables were extracted: sex, age, type of surgical procedure, and preoperative and postoperative Hb levels ($g.dL^{-1}$). Preoperative Hb levels were defined if collected 24—48 hours prior to surgery, while postoperative levels were defined if collected on the first postoperative day. The occurrence of intraoperative red blood cell concentrate transfusion was confirmed through data from the hospital's Blood Bank.

Anemia was defined according to the WHO criteria: Hb levels < 13 $g.dL^{-1}$ in males and < 12 $g.dL^{-1}$ in females.[6] There were no pregnant women enrolled in this study.

The surgical procedures analyzed included cardiovascular, oncological, neurological, and urological surgeries, as well as a subgroup categorized as "other". This subgroup encompassed gastrointestinal, orthopedic, thoracic, and other surgical procedures.

Statistical analysis

The analyses were conducted using STATA software, version 14 (StataCorp LP, College Station, USA) for Windows. Measures of central tendency and dispersion were presented as means and standard deviations. Frequency distributions were employed for variables measured on a nominal scale.

Data distribution and completeness were assessed prior to analysis. Missing data were handled using listwise deletion (complete case analysis), wherein entire records were excluded if any variable had missing values.

Comparisons between means were performed using Student's *t*-test, while associations between qualitative variables were analyzed using the Chi-Square test. A p-value < 0.05 was considered statistically significant for all two-tailed tests.

Multivariate analysis was performed using "need for blood transfusion" as the primary outcome variable. Covariates were selected based on two criteria: a) Variables with a p-value < 0.05 in the bivariate analysis; b) Variables reported in the literature as key covariates (e.g., age and sex). Binary logistic regression was used to evaluate the association between preoperative Hb levels or anemia and the occurrence of transfusion. The logistic regression model was adjusted for sex and age. Odds Ratios (ORs) with 95% Confidence Intervals (95% CIs) were calculated, and statistical significance was determined at a p-value < 0.05.

Results

A total of 508 patients undergoing major elective surgeries were analyzed. Among them, 397 had only preoperative hemoglobin data, 111 had only postoperative data, and 110 had both preoperative and postoperative hemoglobin measurements, as shown in Figure 1.

Of the total sample analyzed, the mean age was 57.1 (± 14.4) years, of whom 51% were male. The overall rate of intraoperative transfusion was 27%. Preoperative anemia was more prevalent in urological surgeries (73%). In the preoperative evaluation, anemia was observed in 59.6% of 508 patients analyzed, with a mean Hb level of 11.66 (±/ 2.75) $g.dL^{-1}$ and 11.13 (± 2.08) $g.dL^{-1}$ for women and men, respectively. In the postoperative period, among 110 patients evaluated, the anemia rate increased to 94.6%, with a mean Hb

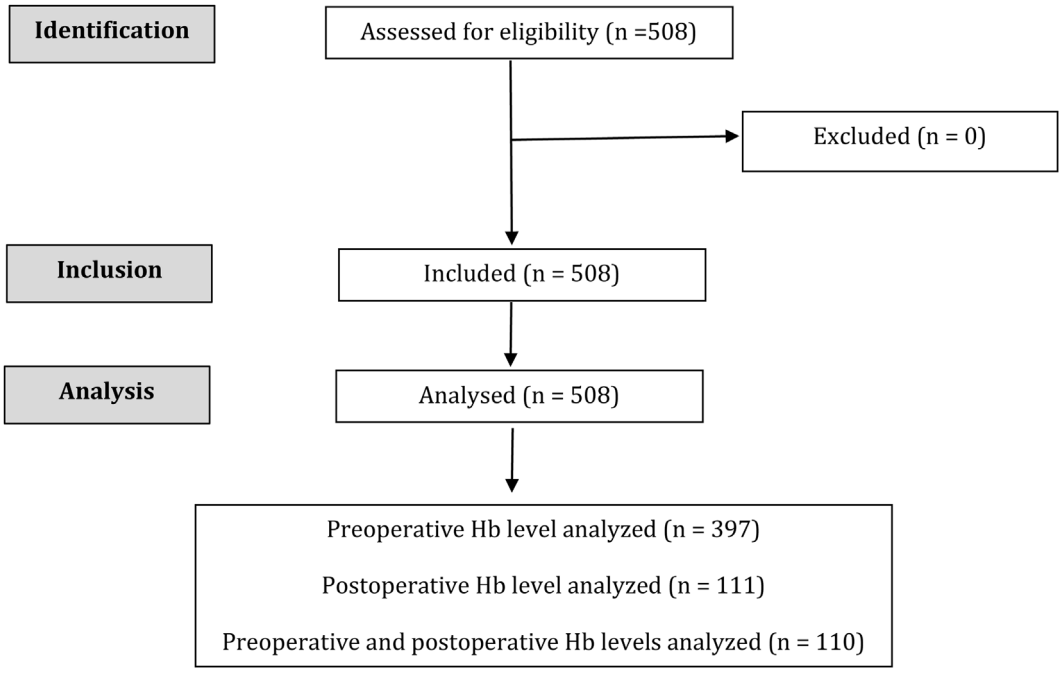

Figure 1 STROBE diagram showing the flow of patients in the study.

level of 9.36 (± 1.55) g.dL^{-1} and 9.49 (± 1.36) g.dL^{-1} for women and men, respectively.

When analyzing preoperative anemia, patients with anemia were older (58.0 ± 14.0 years). Among those with preoperative anemia, the highest prevalence was observed in patients who underwent urological surgery (73%), and most of these patients required blood transfusions (83%). There was no significant difference between male and female patients. Regarding postoperative anemia, no association was found with any of the studied variables (Table 1).

Among the 110 patients with Hb levels monitored both preoperatively and postoperatively, 92 (83.6%) had preoperative anemia. Of these, 97.8% (90 patients) remained anemic postoperatively, while only 2.2% (2 patients) no longer exhibited anemia postoperatively. Among the 18 (16.4%) patients without preoperative anemia, 22.2% (4 patients) remained non-anemic postoperatively, whereas 77.8% (14 patients) developed anemia in the postoperative period (Fig. 2).

Multivariate analysis revealed that patients with preoperative anemia were approximately 4.6 times (95% CI: 2.78 −7.52) more likely to require red blood cell transfusions compared to those without preoperative anemia. In a second regression model, higher preoperative Hb levels were identified as a protective factor against the need for blood transfusion (OR = 0.65; 95% CI: 0.59−0.72) (Table 2).

Table 1 Characteristics and prevalence of the patients with preoperative and postoperative anemia.

Variables	Total (n = 508)	Preoperative anemia			Postoperative anemia		
		No (n = 205)	Yes (n = 302)	p-value	No (n = 6)	Yes (n = 105)	p-value
Sex, n (%)							
Female	250 (49)	100 (40)	150 (60)	0.844	3 (6)	50 (94)	0.910
Male	258 (51)	105 (41)	152 (59)		3 (5)	55 (95)	
Age (years), mean ± SD	57.1 ± 14.4	54.4 ± 14.8	58.0 ± 14.0	**< 0.001**	61.8 ± 12.3	58.0 ± 12.8	0.483
Surgery, n (%)							
Cardiovascular	131 (26)	60 (46)	71 (54)	**< 0.001**	3 (10)	28 (90)	0.210
Neurological	24 (5)	14 (61)	9 (39)		0 (0)	5 (100)	
Oncological	134 (26)	67 (50)	67 (50)		0 (0)	14 (100)	
Urological	136 (27)	37 (27)	99 (73)		0 (0)	34 (100)	
Others	83 (16)	27 (33)	56 (67)		3 (11)	24 (89)	
Intraoperative transfusion[a], n (%)							
No	371 (73)	181 (49)	190 (51)	**< 0.001**	0 (0)	0 (0)	–
Yes	135 (27)	23 (17)	111 (83)		6 (5)	105 (95)	

[a] One or more red blood cell unit.

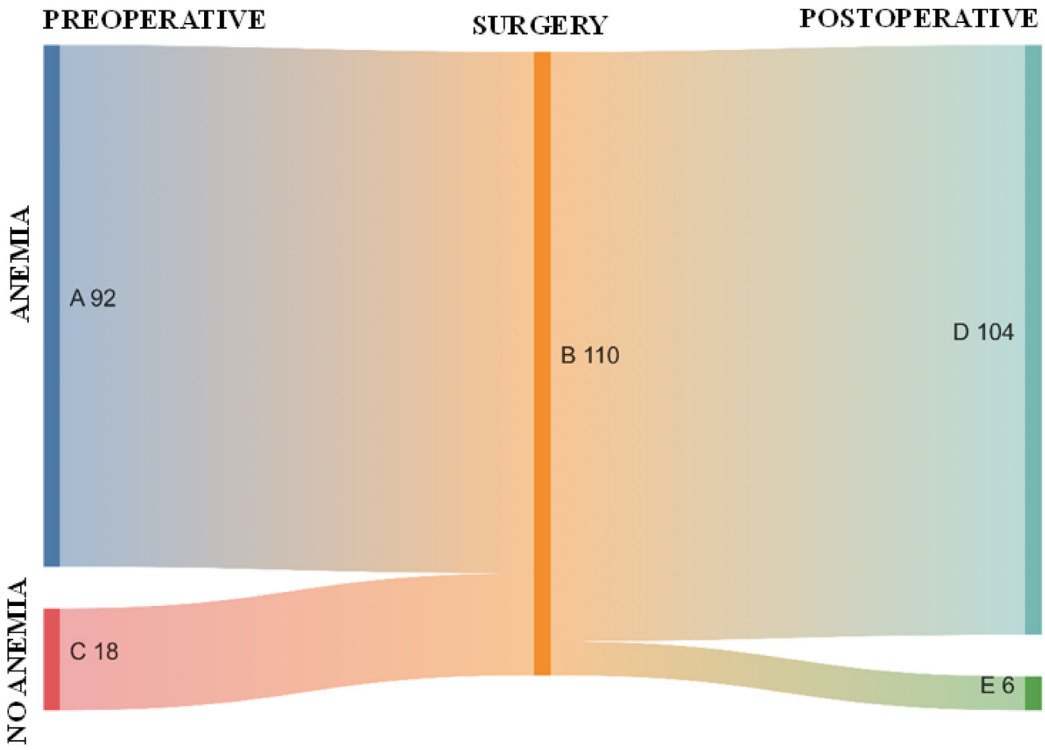

Figure 2 Sankey diagram illustrating the perioperative development of anemia status in the 110 patients analyzed in the study. (A) 92 patients with preoperative anemia; (B) 110 patients who underwent surgery; (C) 18 patients without preoperative anemia; (D) 104 patients with postoperative anemia (90 from preoperative anemia group and 14 from preoperative no anemia group); (E) 6 patients without postoperative anemia (4 from preoperative no anemia group and 2 from preoperative anemia group).

Discussion

Our study revealed that over 50% of patients presented with preoperative anemia, and more than 90% experienced anemia in the postoperative period following major elective surgery. These findings align with global literature, where the average prevalence of preoperative anemia is approximately 40%, and postoperative anemia is reported in around 90% of cases.[1,2,7-9]

A retrospective cohort study conducted in a public hospital in Brazil examined the prevalence of preoperative anemia and its impact on postoperative outcomes among 15,166 surgical patients. The study found that preoperative anemia was prevalent (42.1% of the population studied) and was associated with increased postoperative complications, including higher morbidity and mortality rates. These results underscore the importance of early detection and management of anemia in surgical patients to improve postoperative outcomes.[10]

Another Brazilian study, conducted across 16 blood centers, analyzed data from over 20,000 surgical patients to assess the burden of perioperative anemia and its implications for surgical care. This study reported a prevalence of preoperative anemia of 60.9% within the cohort. Key findings included gender disparities (66.9% of women had anemia), age-related trends (68.2% of patients over 65 years exhibited the highest anemia prevalence), and regional variability (64% in the Northeast, 66.3% in the South, and 63.9% in the

Table 2 Adjusted logistic regression between preoperative hemoglobin and anemia with intraoperative red blood cell transfusion.

	Model I[b] OR (95% CI)	p-value	Model II[b] OR (95% CI)	p-value
Anemia[a]				
No	1	**< 0.001**	–	-
Yes	4.58 (2.78:7.52)		–	
Preoperative Hb (g.dL-1)	–	–	0.65 (0.59:0.72)	**< 0.001**

[a] Hb < 13 g.dL^{-1} in males and < 12 g.dL^{-1} in females.
[b] Adjusted for sex and age.

Southeast). Notably, there was no significant correlation between anemia prevalence and the Human Development Index of the regions, suggesting that anemia affects diverse socioeconomic strata.[11]

Preoperative anemia is an independent predictor of adverse outcomes, including increased mortality, prolonged hospitalization, and higher rates of postoperative complications.[2,3] A meta-analysis of over 900,000 patients demonstrated that preoperative anemia is associated with nearly a threefold increase in 30-day mortality (Odds Ratio [OR = 2.90]), as well as elevated risks of acute kidney injury (OR = 3.75) and postoperative infections (OR = 1.93).[3] Additionally, patients with anemia are more likely to require perioperative blood transfusions, which are linked to poorer outcomes. These findings highlight the critical need for routine preoperative anemia screening and management as part of Patient Blood Management (PBM) strategies.[2,3] However, significant gaps remain, as nearly 25% of patients undergoing elective surgeries are not evaluated for anemia.[12] Standardized protocols for anemia management are essential to improve surgical outcomes.

Postoperative anemia is a common complication after major surgery due to the inflammatory response triggered by surgical trauma.[2] The consequences of postoperative anemia are significant, with studies linking it to increased morbidity, delayed functional recovery, and higher rehospitalization rates.[1] In cardiac and orthopedic surgeries, postoperative anemia has been associated with myocardial infarction, prolonged rehabilitation, and higher mortality rates.[12] Management strategies include judicious use of blood transfusions, which, while effective in rapidly increasing hemoglobin levels, carry risks such as immunosuppression and infection.[1]

Oral iron therapy has traditionally been the first-line treatment for perioperative anemia, but its effectiveness is limited by poor absorption in inflammatory states, gastrointestinal side effects, and delayed onset of action. Consequently, intravenous iron has emerged as a more effective alternative, allowing rapid replenishment of iron stores and hemoglobin synthesis. Modern intravenous iron preparations are associated with low risks of adverse reactions and are considered safe in the perioperative setting.[1,13]

The PREVENTT trial demonstrated that preoperative intravenous iron increased perioperative hemoglobin levels and reduced hospital readmissions, although it did not significantly reduce perioperative blood transfusion rates or mortality.[14]

Considering these findings, the implementation of structured PBM programs becomes particularly relevant in our local context. The high prevalence of preoperative anemia, coupled with the very high rates of postoperative anemia and the observed association between preoperative anemia and intraoperative transfusion, underscores the need for systematic strategies to optimize patients' hematologic status before surgery. Practical measures include routine preoperative screening for anemia, timely initiation of iron supplementation (preferably intravenous in patients with limited surgical timelines or inflammatory states), and standardized perioperative transfusion protocols tailored to minimize unnecessary exposure to allogeneic blood products. Integrating these measures into surgical pathways could not only reduce transfusion requirements but also improve functional recovery, shorten hospital stays, and mitigate postoperative complications. In resource-constrained settings such as ours, strengthening PBM initiatives offers a cost-effective and evidence-based approach to enhance surgical safety and outcomes.[15]

Recommendations from the International Consensus Conference on Anemia Management in Surgical Patients emphasize the importance of preoperative anemia screening, the evaluation of postoperative anemia, and the strategic use of intravenous iron during the perioperative period to optimize patient outcomes.[16]

This study is subject to several potential sources of bias inherent to its retrospective design. Selection bias may have occurred given that only patients with reserved blood components for major elective surgeries were included, potentially excluding cases of comparable surgical magnitude without preoperative reservations. Information bias is also a concern, particularly due to reliance on medical records, which may contain inconsistencies or omissions in hemoglobin measurements and transfusion data. Additionally, missing data – especially regarding postoperative hemoglobin levels, which were unavailable for a substantial portion of the cohort – may have introduced bias and limited the ability to comprehensively assess perioperative hemoglobin dynamics. Furthermore, our logistic regression model was adjusted only for age and sex because data on other potential confounders, such as comorbidities and surgical complexity, were not consistently available due to the retrospective design of the study. Furthermore, the sample size limited the inclusion of additional variables without risking model overfitting.

Conclusions

This study revealed a high prevalence of both preoperative and postoperative anemia among patients undergoing major elective surgeries in northeastern Brazil. The association between preoperative anemia and increased intraoperative transfusion rates underscores anemia as a modifiable and clinically relevant risk factor. These findings reinforce the urgent need for systematic preoperative anemia screening and proactive treatment strategies, particularly intravenous iron therapy, as integral components of patient blood management PBM programs. Implementing these measures can optimize preoperative hemoglobin levels, reduce transfusion requirements, and ultimately improve surgical outcomes. Future studies should prioritize prospective designs and long-term follow-up to assess the sustained impact of anemia correction within PBM frameworks.

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

No Artificial Intelligence (AI) tools were used in the preparation, writing, editing, or analysis of this manuscript. All

content was produced entirely by the authors, who take full responsibility for the accuracy and integrity of the work.

Ethics approval and consent to participate

Ethical approval was granted by the Onofre Lopes University Hospital Research Ethics Committee, under the Ethical Appreciation Presentation Certificate number CAAE 67056522.7.0000.5292, approved on April 7, 2023.

Declaration of competing interest

The authors declare no conflicts of interest.

Funding

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

Editor

Luís Vicente Garcia

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Brazilian Journal of Anesthesiology 2026;76(2): 844746

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Bleeding management in adolescent idiopathic scoliosis: the role of low-dose tranexamic acid

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Received 17 September 2025; accepted 3 March 2026
Available online 7 March 2026

KEYWORDS
Adolescent;
Blood transfusion;
Hemorrhage;
Scoliosis;
Spinal fusion;
Tranexamic acid

Abstract
Background: Despite advances in surgical and blood management techniques, it continues to carry risks of excessive blood loss and transfusion. Tranexamic Acid (TXA), an antifibrinolytic agent, has shown efficacy in reducing these risks across various surgeries. This retrospective cohort study evaluated factors influencing intraoperative blood loss in Adolescent Idiopathic Scoliosis (AIS) surgery, focusing on low-dose TXA administration.
Methods: This retrospective cohort study included 187 AIS patients undergoing posterior spinal fusion with or without intraoperative TXA. Patients were grouped into non-TXA (116 patients) and TXA (71 patients) cohorts. The TXA group received a 10 $mg.kg^{-1}$ intravenous loading dose over 15 minutes, followed by a continuous infusion of 1 $mg.kg^{-1}.h^{-1}$ until skin closure. Outcomes included estimated blood loss, transfusion needs, length of stay, and thromboembolic or neurologic complications. Multivariate regression adjusted intraoperative blood volume loss for potential covariates.
Results: Baseline demographic characteristics were similar between groups. However, differences in surgical complexity cannot be excluded and are acknowledged. TXA use was associated with a 39% reduction in estimated intraoperative blood volume loss compared with the non-TXA group. Blood loss correlated significantly with TXA use, sex, ASA status, number of fused levels, curve type, and surgery duration.

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https://doi.org/10.1016/j.bjane.2026.844746

Conclusion: Low-dose TXA significantly reduced intraoperative blood loss and transfusion requirements during AIS surgery. Greater blood loss was linked to longer procedures and more fused levels, whereas lumbar curve type appeared protective. This study provides insights into AIS outcomes and their associations with predictive factors and TXA use.
Level of evidence: Level III — retrospective cohort study.

Introduction

Scoliosis is a three-dimensional deformity of the spine, including a lateral deviation of the normal vertical line equal to or greater than 10 degrees, rotation of the vertebral body, and a paravertebral hump. Primary curves are the earliest to appear and occur most frequently in the thoracic and lumbar regions.[1] The magnitude of scoliosis severity is mainly measured using the Cobb method. Adolescent Idiopathic Scoliosis (AIS) is the most common form of scoliosis, affecting 1%–4% of adolescents.[1] Surgical treatment involves extensive soft tissue dissection and significant bone bleeding during instrumentation and decortications, there for transfusions of blood may possible necessary. Meantime, there is strong evidence that transfusion-related side effects are associated with increased morbidity and mortality, such as transfusion-related infections, transfusion-related acute lung injury, transfusion-related acute circulatory overload, and transfusion-related immunomodulation.[2] Therefore, decreasing blood loss and transfusion requirements should improve patients' safety, their post-operative recovery, and their long-term outcome.[2,3] Factors related to the individual patient that influence blood loss during surgery include gender, height, weight, severity and type of spinal deformity, as well as surgical factors like operative time, the procedure performed, surgical approach, number of vertebrae fused, number of anchors (pedicle screws, hooks, and wires) placed, average mean arterial pressure during the procedure, blood salvage techniques and the use of antifibrinolytic medications.[4] Therefore, the etiology of blood loss is multifactorial. However, activation of fibrinolysis plays a central role in bleeding during scoliosis surgery. Therefore, antifibrinolytic drugs can serve as a valuable resource in this context.

The concepts of a ceiling effect and dose-dependent side effects for Tranexamic Acid (TXA) are well documented, particularly neurological complications such as seizures, which increase with higher doses of tranexamic acid. High-dose regimens have also been associated with a higher incidence of thromboembolic events and other adverse effects without additional efficacy. Nevertheless, TXA has been used in this population due to the growing evidence supporting its safety profile.[5] TXA is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules, reducing fibrin degradation.[5] Chen et al., in a meta-analysis, found that TXA treatment significantly reduces blood transfusion demand and blood loss, but the results should be interpreted with caution due to high heterogeneity and limited data.[6] Our retrospective observational cohort study uses a homogenized patient population, and all surgeries are performed by the same team of surgeons and anesthesiologists, which can substantially reduce clinical and methodological variability. This approach directly addresses key sources of heterogeneity identified in meta-analyses and systematic reviews, such as differences in patient baseline characteristics, surgical technique, and perioperative management, which have been shown to influence outcomes like blood loss, transfusion rates, and adverse events with tranexamic acid.[7-9] By minimizing these variables, our study can provide more precise estimates of the effectiveness and safety of tranexamic acid and help clarify whether observed heterogeneity in pooled analyses is due to true differences in intervention effect or confounding factors.

This study aimed to evaluate the association between low-dose TXA use and percentage of intraoperative estimated blood volume loss in patients undergoing surgery for adolescent idiopathic scoliosis, adjusted for known confounders, to better characterize TXA use in this population.

Methods

A retrospective cohort study was performed in a university hospital in Portugal, approved by Ethical Research Committee on June 5, 2015, with the registration number 2015.083 (077-DEFI/072-CES). We reviewed medical records and operative reports of surgically treated patients during five consecutive years.

During the study period, this retrospective cohort comprised two distinct stages: a pre—September 2012 stage, during which TXA was not administered, and a post-implementation stage following the introduction of TXA, during which was administered to all patients unless. unless contraindicated.

Participants and procedures

We included patients under 18 years who underwent PSF with pedicle screw or hybrid hook-screw constructs and had complete medical records. Patients with scoliosis of other etiologies, revision surgery, or combined posterior-anterior fusion were excluded. Patients' data collected included age, gender, body weight, ASA status, curve angle, anchors used, levels fused, surgery duration, and hospital stay. Intraoperative blood loss and transfusion data were obtained from operative reports and chart reviews.

Anesthetic management was standardized using intravenous total anesthesia with Target Controlled Infusion of sufentanil (PK model Gepts et al.)[10] and propofol (PK model Schnider et al.).[11] Rocuronium was given for intubation. Anesthesiologists maintained mean arterial pressure (MAP) of 60 mmHg during exposure/anchor placement and 70—90 mmHg during correction. Monitoring included pulse oximetry, ECG, invasive pressure, neuromuscular blockade (TOF), and core temperature. Normothermia was maintained with forced-air warming and fluid warmer.

Intraoperative somatosensory and motor evoked potential monitoring was performed in all patients. Fluid therapy, blood loss, and transfusion were guided by arterial pressure, hematocrit, and blood gas measurements. No predefined hemoglobin trigger for transfusion existed; decisions relied on clinical judgment. When indicated, advanced hemodynamic monitoring with PulsionFlex® (ProAQT) was added. Surgical technique was consistent across cases and performed by senior orthopedic surgeons.

TXA treatment group

TXA group: an intravenous infusion of 10 $mg.kg^{-1}$ of TXA was administered over 15 minutes, 15 minutes before surgical incision, followed by perfusion of 1 $mg.kg^{-1}.h^{-1}$ since incision up to surgical wound closure after surgery.

Outcome parameters

The primary outcome was the percentage of intraoperative estimated blood volume loss. Blood loss was quantified by weighing all surgical swabs using a calibrated analytical scale and measuring the volume of blood in the suction canister after subtracting irrigation fluids. Total blood loss was then expressed as a percentage of each patient's estimated blood volume, thereby standardizing blood loss relative to patient size.

This was done using the formula: Estimated Blood Loss (EBL) / Estimated Blood Volume (EBV) $\times$ 100. The EBV was determined to be 70 $mL.kg^{-1}$ of body weight.[12] This approach offers a more physiological indication of the extent of blood loss for each patient. The number of units of Packed Red Blood Cells (PRBCs) transfused intraoperatively and during the postoperative course was recorded and analyzed primarily as a binary outcome (i.e., whether a patient received a transfusion or not), rather than by the total volume of blood transfused.

During hospitalization post-surgery, all patients were monitored for clinical signs of complications, including venous thromboembolic events and seizures. Surgeons assessed these patients in outpatient clinics at intervals of two weeks, three months, and one-year post-surgery. The length of stay was assessed for each patient. Fused levels were calculated by counting all levels from the proximal level to the distal level.

Statistical analysis

Categorical variables were described using absolute and relative frequencies (%). Numeric variables were summarized as means with Standard Deviations (SD) for normally distributed data, and as medians with interquartile ranges for non-normal distributed data. Normality was verified using the Shapiro-Wilks test and histograms. Group differences were analyzed with Student's *t*-test or Mann-Whitney *U*-test, and proportions with Chi-square or Fisher's exact test. Associations between variables were explored with Pearson's or Spearman's coefficients. Missing data were assessed for all variables and handled using a complete-case analysis. Patients with missing information on the outcome (percentage of intraoperative estimated blood volume loss), exposure (TXA), or key covariates were excluded, resulting in 9.7% of patients being excluded from the primary analysis. This approach ensured a consistent analytical sample across all variables, and the characteristics of excluded patients were reported to assess potential selection bias.[13]

Univariable and multivariable linear regression models were used to estimate the association between TXA use and blood loss expressed as a percentage of estimated blood volume, adjusting for prespecified clinically relevant covariates (age, sex, weight, ASA status, Cobb angle, number of levels, number of pedicle screws, and duration of surgery). Because TXA exposure was determined by study period, calendar year and era were not included in the primary adjusted model, as they were inherent to the exposure definition. For the multivariable regression models, covariates were selected a priori based on clinical relevance and not only on univariable statistical significance. The multivariable regression model included prespecified clinically relevant covariates and was evaluated for linearity, homoscedasticity, and normality of residuals (Fig. S7 in the Supplementary Material). Linearity and variance patterns were examined using residual-versus-fitted plots, normality was assessed with quantile-quantile and cumulative distribution plots, and heteroscedasticity was tested using the Breusch-Pagan/Cook-Weisberg test. Because heteroscedasticity was present, models were fitted using heteroscedasticity-consistent (robust) standard errors. Regression coefficients with 95% Confidence Intervals were reported. Several sensitivity analyses were performed to evaluate the robustness of model specification and potential confounding. First, for specification sensitivity models examined the alternative inclusion of surgical variables (number of fused levels and number of pedicle screws) given observed baseline imbalances. Three models were fitted, excluding (i) Screws only, (ii) Fused levels only, and (iii) Both screws and fused levels, while retaining all other covariates.

Second, a propensity score sensitivity analysis was conducted to address potential confounding by indication. A propensity score for receiving TXA was estimated using logistic regression, including age, weight, gender, ASA status, Cobb angle, number of fused levels, number of screws, duration of surgery, and scoliosis type. Baseline covariate balance before weighting was assessed using Standardized Mean Differences (SMDs), with values < 0.10 indicating adequate balance. Stabilized Inverse Probability of Treatment Weights (IPTW) were then calculated to create a weighted pseudo-population balanced on measured covariates. Two weighted linear regression models were fitted: (i) A marginal IPTW model including TXA only and (ii) A doubly robust IPTW model additionally adjusting for the covariates included in the multivariable model. Propensity-score overlap, and weight distributions were examined graphically. Data were analyzed using Stata 17.0. We used the STROBE reporting guideline to draft this manuscript, included in Table S1 in the Supplementary Material.[14]

Results

Participants and procedures

In total, 207 patients' perioperative records were evaluated from January 2009 to December 2014; 187 met the inclusion

Table 1 Demographic and preoperative data of adolescents who underwent surgery for idiopathic scoliosis with or without Tranexamic acid (TXA).

		Non TXA (n = 116)		TXA (n = 71)		*p*-value
Age (years)[a]		14.6	(1.8)	14.7	(1.8)	0.659[1]
Sex, n (%)	Female	106	(91%)	62	(87%)	0.373[2]
	Male	10	(9%)	9	(13%)	
Weight (kg)[b]		53	(46–59)	53	(49–58)	0.806[3]
ASA class, n (%)	I	62	(53%)	37	(52%)	0.201[4]
	II	49	(42%)	34	(48%)	
	III	5	(4%)	0	(0%)	
Type of curve, n (%)	Dorsal	83	(72%)	52	(73%)	0.834[4]
	Lumbar	15	(13%)	7	(10%)	
	Dorsolumbar	18	(15%)	12	(17%)	
Cobb angle ([b]**)**		58.6	(48.7–67.9)	54.2	(46–68)	0.304[3]

Values are presented as the [a] mean (SD), [b] median (Q1–Q3), or number (%).
[1] t-test; [2] χ2 test; [3] Mann-Whitney test; [4] Fisher test.
ASA, American Society of Anesthesiologists.

Table 2 Intraoperative and postoperative data of adolescents who underwent surgery for idiopathic scoliosis with or without Tranexamic acid (TXA).

	Non TXA (n = 116)		TXA (n = 71)		*p*-value
N° of anchors[b]	16	(14–18)	18	(16–20)	< 0.001[2]
N° of levels fused[a]	11.5	(1.6)	11.3	(1.6)	0.521[1]
Duration of surgery (min)[b]	202	(179–219)	190	(167–210)	0.008[2]
Length of stay (days)[b]	6	(5–7)	6	(5–7)	0.539[2]

Values are presented as the [a] mean (SD), [b] median (Q1–Q3), or number (%).
[1] t-test; [2] Mann-Whitney test.

criteria Fig. S1 in the Supplementary Material (information about blood loss was missing in 16 patients, data regarding TXA administration were not available in 2 patients, and the Cobb angle was not registered in 1 patient, one was a kyphosis correction). Patients' demographics are presented for both the TXA and non-TXA groups in Table 1. One hundred sixteen (106 female and 10 males; mean age 14.6 years) did not receive TXA, while 71 did (62 females and 9 males; mean age 14.7 years). The frequency of female patients was higher in both groups (comparably so), which is an epidemiological characteristic of this population that has been well described in the literature.[15]

Intraoperative and postoperative variables are shown in Table 2. There were significant differences between the two groups for the number of anchors ($p < 0.001$) and duration of surgery ($p = 0.008$). Blood loss and transfusion data are presented in Table 3. SMDs confirmed moderate baseline imbalances in these covariates (Table S2 in the Supplementary Material). The percentage of the patient's estimated blood volume loss was approximately 39% lower in the TXA group compared to the non-TXA group (Fig. 1).

In the multivariable linear regression model (Table 4), TXA use was associated with a lower percentage of estimated blood volume loss (β = -12.7, 95% CI -21.0 to -4.4;

Table 3 Blood loss parameters and blood transfusion of adolescents who underwent surgery for idiopathic scoliosis with or without Tranexamic Acid (TXA).

		Non TXA (n = 116)	TXA (n = 71)	*p*-value
EBL/EBV × 100 (%)		38.5 [24.0—57.1]	24.3 [15.9—37.0]	< 0.001[a]
EBL (mL)		1437.5 [957.5—2025.5]	900.0 [600.0—1313.0]	< 0.002[a]
Transfusion PRBC intraoperative (n° patients)	No	50 (43.1%)	59 (83.1%)	< 0.001[b]
	Yes	66 (56.9%)	12 (16.9%)	
Transfusion PRBC postoperative (n° patients)	No	52 (44.8%)	42 (59.2%)	0.057[b]
	Yes	64 (55.2%)	29 (40.8%)	
Cumulative transfusion (n° patients)	No	24 (20.7%)	33 (46.5%)	< 0.001[b]
	Yes	92 (79.3%)	38 (53.5%)	

Values are expressed as medians [interquartile range] for continuous variables and numbers (percentages) for categorical variables. Statistical test: [a]Wilcoxon rank-sum test; [b](Mann-Whitney); χ^2 test. EBL, Estimated Blood Loss; EBV, Estimated Blood Volume; PRBC, Packed Red Blood Cell.

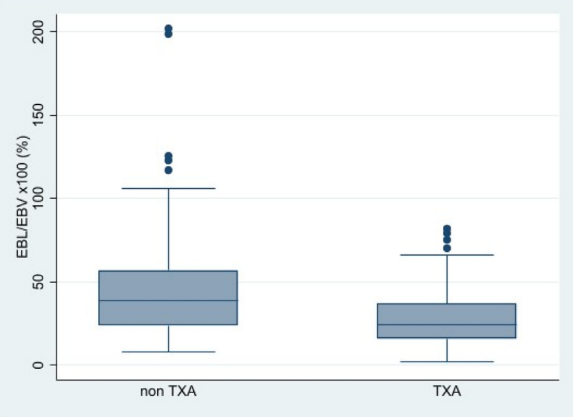

Figure. 1 Box plot representing intraoperative blood loss (mL) in the non-Tranexamic Acid (TXA) group versus the TXA group. Outliers are represented as data dots 1.5 times the interquartile range.

p = 0.003). Greater body weight was associated with increased blood loss ($p < 0.001$). Male sex was also associated with greater blood loss (p = 0.021) (Table 4). Operative factors showed strong associations with blood loss: each additional fused level was associated with a 4.8% increase in estimated blood volume loss (β = 4.8, 95% CI 2.0 to 7.6; p = 0.001), and longer surgical duration was associated with higher blood loss (β = 0.2, 95% CI 0.1 to 0.3; p = 0.004). Age (p = 0.97) and Cobb angle (p = 0.27) were not significantly associated with blood loss. In the unadjusted analysis, TXA use was associated with lower perioperative blood loss expressed as percentage volemia loss (-17.4, 95% CI -24.7 to -10.1; $p < 0.001$). In the primary multivariable linear regression model adjusting for prespecified clinical and surgical covariates, TXA use remained negatively associated with percentage volemia loss (-12.7, 95% CI -19.7 to -5.8; $p < 0.001$) (Fig. S2–S3 in the Supplementary Material).

Graphical assessment of residuals demonstrated mild deviations from normality and non-constant variance across fitted values. The Breusch-Pagan/Cook-Weisberg test provided evidence of heteroscedasticity (χ^2 = 101, $p < 0.001$). Accordingly, all models are reported using heteroscedasticity-consistent (robust) standard errors (Fig. S8 in the Supplementary Material). Coefficient estimates were unchanged compared with conventional models, but robust variance estimation was considered more appropriate given the observed error structure.

Given baseline imbalances in the number of fused levels and number of pedicle screws, the three sensitivity models fitted, the association between TXA use and percentage volemia loss remained consistently negative with overlapping confidence intervals, supporting the robustness of the primary findings (Fig. S4–S6 in the Supplementary Material).

Propensity scores for TXA use were estimated based on clinically relevant variables. Kernel density plots demonstrated adequate overlap between TXA and non-TXA groups (Fig. S9 in the Supplementary Material). The stabilized inverse probability of IPTW was then applied. In the marginal IPTW model including TXA only, TXA use remained associated with a lower percentage volemia loss (-18.5, 95% CI -33.8 to -3.2; p = 0.018). (Fig. S10 in the Supplementary Material) In

Table 4 Univariable and multivariable regression analysis of factors associated with percentage estimated blood loss volume (EBL/EBV × 100).

Variable	Univariable analysis			Multivariable analysis		
	Coefficient	(95% CI)	*p*-value	Coefficient	(95% CI)	*p*-value
TXA						
Non TXA	Reference	–	–	Reference	–	–
TXA	−17.4	(−24.7; -10.1)	< 0.001	−12.7	(−21.0; -4.4)	0.003
Age (years)	−1.7	(−4.0; 0.6)	0.140	0.0	(−2.3; 2.3)	0.972
Weight (kg)	−0.7	(−1.0; -0.4)	< 0.001	−0.8	(−1.1; -0.4)	< 0.001
Gender						
Female	Reference	–	–	Reference	–	–
Male	4.8	(−10.6; 20.3)	0.538	15.0	(2.3; 27.7)	0.021
ASA						
ASA I	Reference	–	–	Reference	–	–
ASA II	−8.3	(−16.5; -0.1)	0.049	−9.1	(−16.3; -1.8)	0.015
ASA III	−8.3	(−24.9; 8.3)	0.327	−25.0	(−48.1; -1.9)	0.034
Cobb angle (degrees)	0.4	(0.1; 0.6)	0.008	0.2	(−0.1; 0.4)	0.269
Number of fused levels	4.7	(1.8; 7.5)	0.001	4.8	(2.0; 7.6)	0.001
Number of screws	−0.5	(−1.8; 0.8)	0.469	−1.3	(−2.8; 0.1)	0.076
Surgery duration (min)	0.2	(0.1; 0.4)	< 0.001	0.2	(0.1; 0.3)	0.004
Type of curve						
Dorsal	Reference	–	–	Reference	–	–
Lumbar	−11.8	(−20.4; -3.2)	0.007	−13.6	(−24.9; -2.2)	0.019
Dorsolumbar	−7.9	(−17.3; 1.5)	0.097	−6.5	(−16.4; 3.5)	0.200

Values of the regression are from linear models fitted with robust standard errors. The multivariable model includes Tranexamic Acid (TXA), age, weight, gender, ASA status, Cobb angle, number of fused levels, number of screws, duration of surgery, and scoliosis type.

the doubly robust IPTW model, additionally adjusting for the same covariates as the primary analysis, the association persisted with a similar direction and magnitude (-13.4, 95% CI -19.9 to -6.8; $p < 0.001$). Weight distributions are shown in Fig. S10 in the Supplementary Material. Together, these analyses indicate that the association between TXA use and lower percentage volemia loss is robust across regression-based and propensity-score-weighted approaches (Fig. S9–S12 in the Supplementary Material).

Discussion

This study is the first that we are aware of to provide evidence that a low dose regimen for TXA for AIS 39% reduction in blood loss and in PRBC transfused. The use of a homogeneous patient population and a consistent team of surgeons and anesthesiologists helped reduce clinical and procedural variability, thereby limiting potential confounding in this retrospective observational cohort study evaluating the association between tranexamic acid use and clinical outcomes. When the patient cohort is uniform in terms of baseline characteristics (such as age, comorbidities, and surgical indication), and the surgical and anesthetic management is standardized by the same team, the likelihood that differences in outcomes are due to factors other than the intervention (low dose of TXA) is substantially reduced. Previous studies have aimed to identify predictive factors for blood loss in AIS surgery. In our cohort study, we investigated the factors influencing blood loss in surgical patients and found significant correlations with the use of TXA, ASA physical status, lumbar curve, the number of levels fused, and operation duration. After adjustment for patient and surgical factors, TXA was associated with a 12.7% absolute reduction in estimated blood volume loss compared with no TXA. These findings contribute to the growing body of evidence supporting the efficacy of TXA in reducing the percentage of intraoperative estimated blood loss and highlight the importance of considering multiple variables in managing surgical blood loss.

Halpern et al. found that TXA, along with sex, surgical duration, and major coronal curve, was associated with blood loss in PSF, explaining 24% of the variation.[16] Hasan et al. observed that surgical blood loss increased with male sex, each vertebral level fused, and additional surgical time.[17] Goobie et al., using a dose of 50 $mg.kg^{-1}$ bolus and 10 $mg.kg^{-1}.h^{-1}$ infusion, found that TXA, duration of surgery, and the number of spinal levels fused were significant predictors of blood loss, with TXA reducing blood loss by 223 mL.[18] Four studies using very high doses of TXA (100 $mg.kg^{-1}$ loading and 10 $mg.kg^{-1}.h^{-1}$ maintenance) showed significant reductions in EBL and transfusion requirements in idiopathic and neuromuscular scoliosis patients. Xu's study with a 20 $mg.kg^{-1}$ loading dose and 10 $mg.kg^{-1}.h^{-1}$ maintenance dose demonstrated significant decreases in EBL and transfusion needs.[19-21] Lastly, two authors reported that a low-dose TXA regimen (10 $mg.kg^{-1}$ loading, 1 $mg.kg^{-1}.h^{-1}$ maintenance) significantly decreased total blood loss and blood product transfusion, though not specifically PRBCs.[22,23]

Since TXA demonstrates a ceiling effect, and side effects are dose-dependent, dose optimization is essential. High doses, especially in cardiac surgery, increase seizure risk. Lecker et al. emphasized dose-dependent neurotoxicit.[24] Balancing efficacy and safety is therefore critical. Before TXA, transfusion rates ranged from 36%—75% in spinal surgery. In our study, low-dose TXA reduced both blood loss and transfusion requirements during AIS surgery.

TXA has been used in different combinations of loading dose and maintenance doses, varied by a factor of 10, with loading doses ranging from 2—100 $mg.kg^{-1}$, associated with a 2—100 $mg.kg^{-1}$ continuous infusion. We found that there is a large variability in dose schemes observed among the different studies, with no rationale for using certain specific doses. The doses used in those trials are not based on pharmacokinetics studies, which have not been assessed for this specific population and setting. However, pharmacokinetic evidence suggests the use of a 10—15 $mg.kg^{-1}$ loading dose, followed by an infusion of 1 $mg.kg^{-1}.h^{-1}$ or a repeated dose. The same dose is also recommended in the ESAIC 2023[25]. Initiating a low-dose TXA protocol for routine use is scientifically supported by evidence demonstrating that low-dose regimens are effective in reducing perioperative blood loss and transfusion requirements, while maintaining a favorable safety profile.[26-30] Therefore, we decided to use a 10 $mg.kg^{-1}$ bolus for 15 minutes, plus 1 $mg.kg^{-1}.h^{-1}$ from incision up to surgical wound closure after surgery. The same was done by Neilipovitz et al. where they prospectively randomized children scheduled for scoliosis surgery to receive 10 $mg.kg^{-1}$ TXA followed by a continuous infusion of 1 $mg.mL^{-1}.h^{-1}$ or the same infusion scheme with saline. The authors reported that 28% less blood was given in the TXA group compared with the placebo.[23] Verma et al. also demonstrated that lower doses of TXA reduced blood loss but not transfusion rate.[22] On the other hand, Sethna et al. and Lykissas et al. demonstrated that using high doses of TXA at 100 $mg.kg^{-1}$ load followed by 10 $mg.kg^{-1}.h^{-1}$ significantly decreased the total blood loss when compared with placebo; however, the transfusion requirement did not significantly decrease.[19-21] Grant et al. compared two doses of TXA, demonstrated that higher-dose TXA is likely effective at reducing perioperative transfusion requirements for children undergoing posterior instrumentations and fusion surgery for idiopathic scoliosis (50%).[31] Although only adolescent idiopathic scoliosis patients were examined, the number of patients included in the study was too low, and the surgeries were performed by different surgeons. In our cohort study, we have always had the same team of orthopedic surgeons, and 116 patients received TXA compared to the control group (71 patients non-TXA). Meanwhile, Johnson et al. described that high-dose TXA is more effective than low-dose TXA in reducing blood loss and transfusion requirements in pediatric idiopathic scoliosis patients undergoing surgery.[32] Burney et al. described that since the introduction of TXA, no patient has required intraoperative or postoperative allogeneic blood product transfusion.[33] The main issue is that all the studies were performed with different doses of bolus and perfusion of TXA. Despite varied regimens, all studies show patient benefit; in our series, blood volume loss fell by approximately 39% with low-dose TXA.

Furthermore, considering the etiology of the disorder, secondary scoliosis, neuromuscular, or other congenital conditions are associated with substantial intraoperative blood loss compared to AIS. Factors implicated in the main blood loss include seizure medication, poor nutritional status,

depletion of clotting factors, and abnormality in platelet aggregation.[20] Shapiro et al. found a 46% decrease in blood loss and a 46% decrease in transfusion volumes in a retrospective study examining blood loss in spinal fusions secondary to Duchenne muscular dystrophy.[20] Antifibrinolytics were effective in decreasing intraoperative blood loss during posterior spinal fusion and instrumentation in children with cerebral palsy; in fact, TXA was found to be more efficacious than EACA.

The Cochrane database review of antifibrinolytic agents for reducing blood loss in scoliosis surgery in children stated that antifibrinolytics reduce blood loss and blood transfusion in scoliosis surgery. However, the fact that only six studies met their inclusion criteria and no comment on dosing regimens was made shows that there is scope for further research in this area.[34,35]

The major concern surrounding the use of TXA is the potential increased risk of thromboembolic events. Thromboembolic complications after spinal fusion are a relatively rare event in children. The risk of venous thromboembolic events in children who undergo spinal fusion with a diagnosis of AIS was found to be approximately 0.04%.[36] TXA does not alter blood clotting, but rather slows the dissolution of the blood clots. Reports of dose-dependent side effects from TXA on clinical seizures mandate the lowest effective dose possible to maximize efficacy while limiting adverse events. All patients were evaluated during a routine orthopedic follow-up visit two weeks after hospital discharge, and no complications were reported; however, because no standardized protocol for systematic adverse-event screening was in place and safety assessment relied on routine clinical practice in this retrospective setting, some complications, particularly subclinical or delayed events, may have been under-detected. However, the study lacked sufficient statistical power to support any conclusions regarding safety. While some predictive factors, such as gender and the number of levels fused, are not modifiable, male sex emerged as an independent predictor of greater blood loss in our cohort. This finding is consistent with the results of Lalenti et al,[4] who also identified male sex as a significant predictor of increased blood loss in posterior spinal fusion procedures. The concordance between these results supports the hypothesis that sex-related anatomical or physiological differences, such as greater muscle mass and soft tissue dissection in male patients, may contribute to increased intraoperative bleeding.[4] Although the exact mechanisms remain speculative, our findings reinforce the relevance of sex as a clinically meaningful factor when estimating perioperative blood loss risk.

Similar to previous studies, our study supports the findings that blood loss increased with fused vertebrae and longer operative time.[4,37] The number of fused levels showed a strong dose-response relationship with bleeding, with each additional level associated with an average 4.8% increase in estimated blood volume loss. Surgical duration was also an important determinant, with each additional unit of operative time associated with a 0.2% increase in blood volume lost. These findings are clinically intuitive and highlight that procedural complexity and operative exposure substantially influence blood loss risk, reinforcing the need to account for these factors when evaluating the effect of antifibrinolytic therapy. Thompson et al. identified factors correlated with massive hematic losses; the number of instrumented levels was the variable with the greatest impact, especially in surgeries with 12 instrumented levels. Yu et al. correlated low weight, a Cobb angle above 50%, more than 6 instrumented levels, and the introduction of osteotomy with massive loss (> 30% of blood volume) that occurred in 59.9% of their patients.[38] However, our study did not find a correlation between blood loss and Cobb angle.

Our study has some limitations. The main limitation of this study is its retrospective design; because treatment was not randomized, differences in baseline characteristics and clinical decision-making may have influenced both TXA administration and blood loss. In our study, the difference in the number of patients between the two groups can be attributed to the temporal aspect of data collection. As data were collected over a period, variations in patient inclusion naturally occurred. To address group imbalance and potential confounding, we applied multivariable regression with heteroscedasticity-consistent standard errors and conducted prespecified sensitivity analyses based on alternative model specifications and propensity score weighting. The consistency of results across these approaches supports the robustness of the primary findings. By doing so, we aimed to balance the groups and mitigate the impact of any confounding variables, ensuring a more accurate and unbiased association estimates in our analysis.

Other limitation was the number of TXA-treated patients who received a transfusion was small, limiting statistical power and increasing uncertainty around transfusion-related estimates. Residual confounding remains possible despite prespecified covariate adjustment and multiple sensitivity analyses. Several surgically relevant variables were imbalanced at baseline, and although alternative model specifications and propensity score-weighted analyses yielded consistent results, unmeasured confounding cannot be excluded. The use of complete-case analysis may also have introduced selection bias, and some linear model assumptions were only partially satisfied despite the application of robust variance estimators. Another limitation is that the indications for transfusion were not defined with objective parameters. The restrictive policy may be one of the most important measures missed in this study. Lacroix et al showed that a restrictive policy with a threshold below 7 g. dL^{-1} applied to children hospitalized in intensive care units significantly reduced transfusions with no increase in morbidity and mortality.[39] Anesthesiologists, however, followed common practice triggers such as an intraoperative hemoglobin level less than 8 $g.dL^{-1}$. Our study reflects real-world practice, where transfusion is often guided by clinical assessment and general recommendations rather than rigid criteria, introducing variability in transfusion rates and potentially confounding the evaluation of tranexamic acid efficacy. For example, the study by Sui et al. retrospectively reviewed adolescent idiopathic scoliosis patients and reported transfusion requirements and blood loss, but did not specify a strict transfusion protocol; instead, transfusion was administered according to clinical indications, which typically follow international guidelines but allow for provider discretion.[40] Similarly, Johnson et al. conducted a retrospective cohort study comparing high-dose and low-dose tranexamic acid in pediatric scoliosis surgery, with transfusion decisions made by the clinical team rather than by a

fixed hemoglobin threshold.[32] Blood loss calculations were estimated by a uniform method.

Conclusion

This study indicates that low-dose TXA use was associated with a lower percentage of intraoperative estimated blood volume loss and transfusion requirements, with no observed increase in thrombotic events. Independent predictors of blood loss included TXA use, surgery duration, and the number of fused spinal levels. These findings highlight the role of tranexamic acid in blood loss management while underscoring the need for further research to develop predictive models and improve outcomes in scoliosis surgery. Future prospective, randomized controlled trials are warranted to confirm these results and to further define the role of low-dose tranexamic acid within patient blood management strategies for adolescent idiopathic scoliosis surgery.

Ethics

The study was approved by the Ethical Research Committee on 2015/6/5 of Hospital de Santo António, Centro Hospitalar Universitário de Santo António, Unidade Local de Saúde de Santo António (Santo António), Porto, Portugal, with the registration number 2015.083 (077-DEFI/072-CES).

AI assistance disclosure

The authors confirm that no artificial intelligence tools were used in the preparation, writing, analysis, or editing of this manuscript.

Data availability statement

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

Authors' contributions

Paula Alexandra Sá: Conceptualization; methodology; formal analysis; investigation; resources; data curation; writing-original draft; writing-review & editing; visualization; project administration; funding acquisition.

Filipa Pereira: Conceptualization; methodology; investigation; data curation; writing-review & editing.

Daniel Soares: Conceptualization; methodology; investigation; data curation; writing-review & editing.

António Oliveira: Conceptualization; methodology; validation; writing-review & editing; supervision.

Eugénia Cruz: Conceptualization; methodology; validation; writing-review & editing; supervision.

Sibylle Langenecker: Conceptualization; methodology; validation; writing-review & editing; supervision.

All authors approved the final manuscript.

Funding

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

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

Authors would like to thank to Joana Dias (Faculty of Medicine — University of Porto), for her assistance with the statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844746.

Editor

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Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Accuracy of a point-of-care CoaguChek test versus standard laboratory coagulation monitoring in cardiac surgery involving cardiopulmonary bypass: randomized clinical trial

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Received 3 March 2025; accepted 7 November 2025
Available online 22 November 2025

KEYWORDS
Blood coagulation tests;
Cardiopulmonary bypass;
Diagnostic, point of care;
International normalized ratio

Abstract
Background: Intraoperative coagulopathies are common in complex surgeries, and timely coagulation monitoring is crucial. We assessed the accuracy of the point-of-care CoaguChek XS test against standard laboratory measurements in patients undergoing cardiac surgery with Cardiopulmonary Bypass (CPB).
Methods: We conducted a single-center, diagnostic accuracy study to assess the coagulation profile of 50 participants before and after CPB. The index test was the CoaguChek XS device and the reference test was the standard laboratory assay. The primary outcome was the accuracy of the CoaguChek device in measuring the International Normalized Ratio (INR). We pre-specified a tolerance range of $\pm$ 0.5 INR units. Secondary outcomes included accuracy in measuring prothrombin time and prothrombin activity.
Results: We included 50 patients undergoing cardiac surgery with CPB between October 2023 and January 2024. The mean (standard deviation) age was 59.2 (12.3) years, and 32 participants (64%) were male. For INR values, Lin's coefficient was 0.72 (95% CI: 0.60–0.82) pre-CPB and 0.66 (95% CI: 0.50–0.77) post-CPB, both indicating good agreement. In the pre-CPB period, on average, the index test readings exceeded reference readings by 0.045 INR units (95% CI: 0.030–0.059, $p < 0.001$), while in post-CPB period, index readings were, on average, 0.064 INR units lower (95% CI: -0.09 to -0.04, $p < 0.001$). Although statistically significant differences were observed, they fell within predefined tolerance range and were considered clinically irrelevant. Analyses of secondary outcomes were consistent with the primary outcome findings.

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https://doi.org/10.1016/j.bjane.2025.844714

Conclusion: In patients undergoing cardiac surgery with cardiopulmonary bypass, CoaguChek XS provided results comparable to standard laboratory coagulation monitoring, both pre-and post-cardiopulmonary bypass.
Research Board Approval: Plataforma Brasil CAAE 70266023.8.0000.5553.
Clinical Trials Registration: (https://clinicaltrials.gov/study/NCT06037720) NCT06037720, 14/09/2023.

Introduction

Effective monitoring of blood coagulation is essential in perioperative care, particularly during surgeries with a high risk of bleeding. While intraoperative fluid replacement is often necessary, it can dilute coagulation factors, potentially worsening bleeding and increasing the need for transfusions. This dynamic highlights the need for improved, rapid coagulation assessment methods.[1] The Prothrombin Time (PT) test is used to diagnose and manage bleeding, and it can be performed either through standard laboratory tests or point-of-care devices. PT assesses the integrity of the extrinsic and common coagulation pathways. The International Normalized Ratio (INR), calculated from the PT, standardizes results across laboratories, regardless of reagents used.[2]

Point-of-care coagulation tests have been recommended in the perioperative setting.[3] However, in Brazil, standard laboratory assays remain more commonly used due to their wider availability and lower cost, despite their longer turnaround times.[4] Regarding the devices licensed in Brazil, CoaguChek devices have been recommended for the follow-up of patients after cardiac surgery, due to their practicality.[5,6] Nevertheless, the accuracy of Coaguchek compared with standard laboratory methods for PT and INR measurement in cardiac surgery, especially in patients undergoing cardiopulmonary bypass, has not been well established.[7,8]

In this study, our general objective was to evaluate the accuracy and agreement between the CoaguChek XS device and traditional laboratory methods. Our specific objectives were to assess the performance of the point-of-care test in measuring INR, prothrombin time, and prothrombin activity in Brazilian patients undergoing elective cardiac surgery with cardiopulmonary bypass.

Methods

Study design

This was a prospectively planned, single-center, cross-sectional, diagnostic accuracy study conducted between October 01, 2023, and January 10, 2024. The study was conducted at the Hospital de Base do Distrito Federal, Brasília, Brazil, a tertiary, public reference center for cardiac surgeries. All methods were pre-specified (ClinicalTrials.gov registration: NCT06037720). The study was approved by the local Research Ethics Committee (Research Ethics Committee of the Strategic Health Management Institute of the Federal District) on August 10, 2023, under approval number 6.232.031, CAAE 70266023.8.0000.5553. All participants provided written informed consent. We adhered to the STARD guidelines for diagnostic accuracy studies to report our results.[9]

Participants

We included consecutive participants of both sexes aged 18 years or older, undergoing elective cardiac surgery (coronary artery bypass grafting, valve replacement, and aortic surgery) with cardiopulmonary bypass. To be included, participants had to have an American Society of Anesthesiologists (ASA) physical status classification of I to III and baseline hemoglobin levels greater than 10 $g.dL^{-1}$. Patients with liver or hematological diseases, conditions affecting coagulation (hemophilia, factor VII deficiency and others), or those participating in other studies were excluded.

Test methods

Index test

The index test was the portable CoaguChek XS device (Roche, Switzerland), which uses an International Sensitivity Index (ISI) value close to 1.0 and measures the international normalized ratio within an analytical range of 0.8 to 8.0. A single device was used throughout the study, and it was pre-calibrated by the manufacturer; no additional calibration was required. All measurements were performed according to the manufacturer's instructions by trained investigators. The device's readings were obtained without knowledge of the reference test results. All measurements were successfully completed, and no invalid or indeterminate results occurred.

Reference test

The reference test was a standard laboratory-based assay conducted by a central hospital laboratory, using the same sample as the index test. All measurements were performed at the same facility, which is accredited by the Brazilian Society of Clinical Pathology/Laboratory Medicine (SBPC/ML) and adheres to relevant local standards and guidelines. Laboratory personnel were blinded to clinical information and index test results. According to the laboratorý s internal quality protocol, samples were processed immediately after collection, and the interval between blood collection and the reference assay did not exceed 30 minutes. the collection tubes were specifically designed to maintain sample integrity for coagulation testing during this period. All measurements were successfully completed, and no invalid or indeterminate results occurred.

Procedures

After the induction of anesthesia (Web-Appendix 1), trained phlebotomists drew venous blood samples (03 mL) using standard techniques into 0.5 mL (3.2%) sodium citrate tubes. The samples were used to measure Activated Clotting Time (ACT) and blood gases. From the same sample, Prothrombin Time (PT) and International Normalized Ratio (INR) were assessed using both the index and reference tests. All tests were repeated 10 minutes after protamine administration and after the completion of the cardiopulmonary bypass. Blinding to the standard laboratory assay results was ensured by performing the index test immediately after blood collection, and before the reference test results were available.

Outcomes

Our primary outcome was the accuracy of the index test in measuring the International Normalized Ratio (INR) compared with the standard laboratory method. We pre-specified a tolerance range of $\pm$ 0.5 INR units. This cutoff has been used in prior validation studies of point-of-care INR devices and aligns with recommendations that differences $\leq$ 0.5 INR units do not typically alter clinical management.[10] Secondary outcomes included the agreement between index and reference measurements of Prothrombin Time (PT, in seconds) and prothrombin activity (PA, in %). Agreement between the index and reference tests was assessed both pre- and post-operatively to capture performance under distinct coagulation states. These time points reflect baseline and altered hemostasis conditions, ensuring a comprehensive evaluation of test accuracy. Central laboratory outcome measurements were blinded to participant status, study objectives, and prior point-of-care results.

Sample size

The sample size was determined based on the primary outcome during the post-cardiopulmonary bypass period. This decision was informed by pilot data from 26 patients at the same center, which showed a larger standard deviation for the difference between the index and standard tests in the post-cardiopulmonary bypass period compared to the pre-cardiopulmonary bypass period. By focusing on the period with the greatest variation, we ensured that the final sample size was adequately powered in both periods. Agreement between the index and reference tests was assessed both pre- and post-operatively to capture performance under distinct coagulation states. These time points reflect baseline and altered hemostasis conditions, ensuring a comprehensive evaluation of test accuracy. For the calculations, we used the Bland-Altman limits of agreement, following the method developed by Lu et al. (2016). This test is a statistical method used to simultaneously assess the agreement between two measurement methods by evaluating both the mean and variance differences. Based on previous studies and our pilot data, we assumed a mean difference between the index test and the laboratory assay of -0.126 units, with a standard deviation of 0.132. Additionally, based on clinical criteria, we considered that an absolute difference greater than 0.5 unit would be clinically relevant. In other words, the maximum allowable difference (Δ) that would not affect clinical management was $\pm$ 0.5 units (i.e., differences within the range of -0.5 to 0.5 were considered clinically irrelevant). Assuming a 5% significance level (α) and 95% Confidence Intervals around the Bland-Altman limits of agreement, 43 participants were required to ensure 90% statistical power to demonstrate agreement between the two tests. To account for a potential 15% dropout or missing data rate, we increased the final sample size to 50 patients. This adjustment was made a priori, before data collection began, to preserve statistical power in case of incomplete observations. No interim or adaptive analyses were performed, and all data were analyzed after study completion.

Statistical analysis

We conducted all statistical analyses following the Guidelines for Reporting Reliability and Agreement Studies and the recommendations by Gerke (2020).[11,12] We presented continuous variables with approximately normal distributions as mean (Standard Deviation, SD), and those with a skewed distribution as median (Interquartile Range, IQR). Categorical variables were expressed as numbers (percentages).

The index and the reference tests were compared graphically using Bland-Altman plots. We assessed the normality of the differences between tests through graphical inspection. We used Lin's concordance correlation coefficient to evaluate the statistical agreement between the tests. This coefficient ranges from -1 to +1, with higher absolute values indicating stronger agreement. For Lin's coefficient (absolute values), we adopted the following pre-specified criteria:[13] $\leq$ 0.4 indicates poor agreement, 0.41—0.60 moderate agreement, 0.61—0.80 good agreement, and $>$ 0.81 excellent agreement. The cut-offs recommended by McBride were deemed less applicable to the clinical context of the present study.[14] To assess whether the range of measurements was sufficiently broad, we applied the Preiss-Fisher procedure with 10,000 random resamplings.

The Bradley-Blackwood test was used to evaluate the global hypothesis of differences in means and/or variances between the two tests. When the Bradley-Blackwood test was statistically significant, we used Student's paired *t*-test to determine if the index and reference tests differed in their mean measurements. Subsequently, the Pitman-Morgan test was applied to assess whether the index and reference tests differed in their variability. All analyses were conducted using Stata (version 18, StataCorp, College Station, USA); p-values $<$ 0.05 (two-tailed) were considered statistically significant.

Results

Between October 01, 2023, and January 10, 2024, we assessed 61 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass, of whom 50 were included in the final analysis. All measurements yielded valid results for both the index and reference tests, with no indeterminate or invalid readings observed. Figure 1 shows details of the study selection process. Table 1 summarizes the main clinical and demographic characteristics of the 50 included participants. The mean age (SD) was 59.2 (12.3) years, and

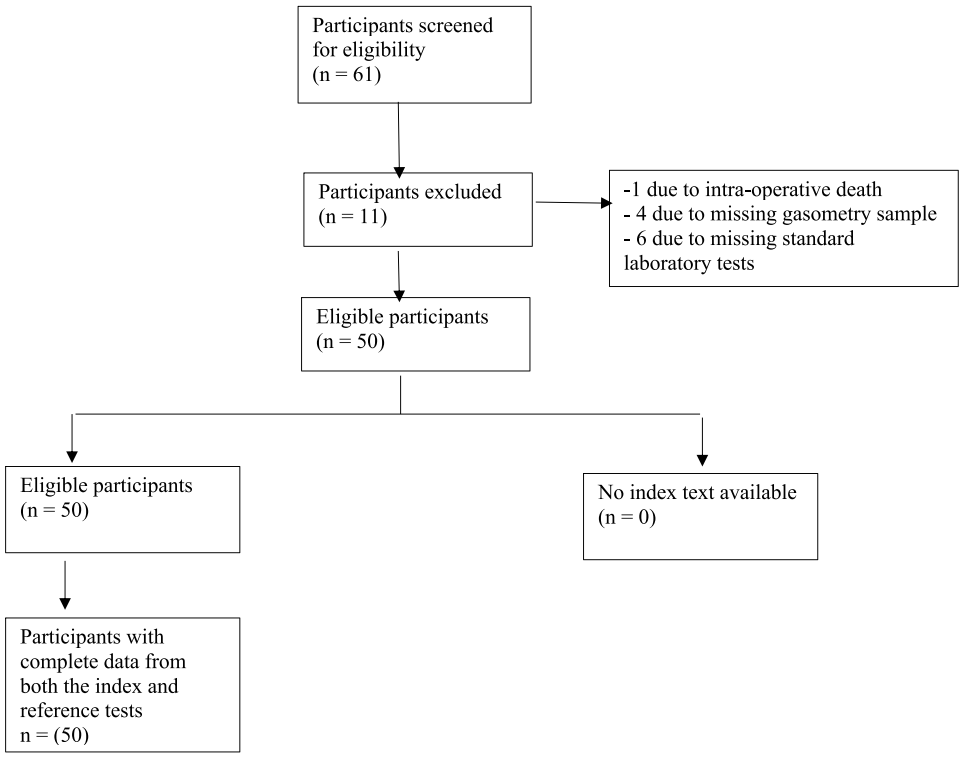

Figure 1 Flowchart summarizing the study selection process.

32 participants (64%) were male. The most common diagnosis was angina, affecting 18 participants (36%).

All graphical assessments revealed no major concerns regarding the normality of the differences between the index and reference tests. The Preiss-Fisher procedure confirmed that the measurement range was sufficiently wide for all outcomes (Web-Appendix 2).

Agreement between the index and reference test — Pre-cardiopulmonary bypass

Figure 2 (panels A–C) presents the Bland-Altman plots comparing the index and reference tests for INR, Prothrombin Time (PT), and Prothrombin Activity (PA) levels before cardiopulmonary bypass. Lin's concordance correlation coefficients were 0.72 for INR (95% CI: 0.60 to 0.82), 0.66 for PT (95% CI: 0.51 to 0.78), and 0.69 for PA (95% CI: 0.57 to 0.80), indicating good concordance across all parameters. For INR, the index test showed a mean ± SD of 1.098 ± 0.089 and the reference test showed 1.053 ± 0.082, with a statistically significant difference in means ($p < 0.001$) but not in variability ($p = 0.31$). The mean difference was 0.045 units (95% CI: 0.030 to 0.059, $p < 0.001$), falling within the predefined tolerance range of ± 0.5 INR units. For PT, the index test showed a mean of 13.2 ± 1.10 seconds and the reference test 13 ± 1.53 seconds, with no significant difference in means ($p = 0.21$), although the variability differed statistically ($p = 0.002$). The mean difference was 0.2 seconds (95% CI: -0.11 to 0.51, $p = 0.21$), with limits of agreement ranging from -1.95 to 2.35 seconds. For PA, the index test showed a mean of 86% ± 11.4% and the reference test 92.7% ± 13%, with a statistically significant difference in means ($p < 0.001$), but not in variability ($p = 0.12$). Index test values were, on average, 6.65 percentage points lower than the reference (95% CI: -8.85 to -4.44, $p < 0.001$), falling within the Bland-Altman limits of agreement (-22.41 to 8.57 percentage points). For all three biomarkers, most participants had differences within the limits of agreement, with only a few measurements exceeding the boundaries: 2 participants (4%) for INR, 5 (10%) for PT, and 1 (2%) for PA.

Agreement between the index and reference test — Post-cardiopulmonary bypass

Figure 3 (panels A–C) presents the Bland-Altman plots comparing the index and reference tests for INR, PT, and PA levels after cardiopulmonary bypass. Lin's concordance correlation coefficients were 0.66 for INR (95% CI: 0.50 to 0.77), 0.55 for PT (95% CI: 0.37 to 0.69), and 0.70 for PA (95% CI: 0.54 to 0.82), indicating moderate to good concordance between the tests. For INR, the index test had a mean of 1.170 ± 0.116 and the reference test 1.234 ± 0.147, with statistically significant differences in both the mean ($p < 0.001$) and variability ($p = 0.02$). The average difference was -0.064 units (95% CI: -0.09 to -0.04, $p < 0.001$), falling within the tolerance range of ± 0.5 units. One participant (2%) exceeded the upper limit of agreement and 1 (2%) fell below the lower limit. For PT, the index test had a mean of 14.1± 1.30 seconds and the reference test 15.1 ± 1.73 seconds. Both mean ($p < 0.001$) and variability ($p = 0.008$) differed

Table 1 Baseline characteristics of participants, and biochemical and hematological parameters during the pre- and post-cardiopulmonary bypass periods (n = 50).

Variable	Estimate
Age, mean (SD)	59.2 (12.3)
Female sex, n (%)	32 (64)
Body mass index (kg.m^{-2}), mean (SD)	26.3 (4.5)
Arterial hypertension, n (%)[a]	38 (81%)
Ejection fraction (%), mean (SD)[b]	56.3 (14.5)
Initial body temperature (°C), mean (SD)	
Hypothermia, n (%)	
Mild	42 (84%)
Moderate	8 (16%)
Clamp time (minutes), median (IQR)	92 (72 to 120)
Cardiopulmonary bypass time (minutes), median (IQR)	108.5 (88 to 148)
Pre-cardiopulmonary bypass period	
pH, mean (SD)	7.36 (0.05)
Bicarbonate, median (IQR)	23.4 (22.2 to 25.7)
Base excess, median (IQR)[a]	-1.7 (-2.5 to -0.3)
Hemoglobin, median (IQR)	11 (9.9 to 12.4)
Hematocrit, median (IQR)	34.9 (32 to 39.5)
Glucose, median (IQR)	111.5 (96.9 to 139)
Lactate, median (IQR)	1.39 (1.09 to 1.9)
Post-cardiopulmonary bypass period	
pH, mean (SD)	7.32 (0.05)
Bicarbonate, median (IQR)	21.9 (20.4 to 23.8)
Base excess, median (IQR)[a]	-3.85 (-5.3 to -2.2)
Hemoglobin, median (IQR)	9.3 (8.9 to 10.1)
Hematocrit, median (IQR)	28.8 (27.2 to 31.3)
Glucose, median (IQR)	142 (128 to 62)
Lactate, median (IQR)	3.48 (2.29 to 4.35)

IQR, Interquartile Range; SD, Standard Deviation.
[a] Based on 47 participants (3 with missing data).
[b] Based on 49 participants (1 with missing data).
At the onset of the cardiopulmonary bypass period.

statistically. The index test values were on average 0.92 seconds lower than those of the reference test (95% CI: -1.29 to -0.56, $p < 0.001$), with limits of agreement from -3.51 to 1.57 seconds. None of the participants exceeded the upper limit, while 2 (4%) fell below the lower limit. For PA, the index test had a mean of 76.4% ± 12.8% and the reference test 72.4% ± 13.3%; this difference was statistically significant ($p = 0.004$). There was no significant difference in variability ($p = 0.73$). On average, the index test measurements were 4.03 percentage points higher than those of the reference test (95% CI: 1.34 to 6.73, $p < 0.001$). Limits of agreement ranged from -15.22 to 22.63 percentage points. One participant (2%) exceeded the upper limit, and none fell below the lower limit.

Discussion

Main findings

In this prospectively planned, single-center, diagnostic accuracy study, we evaluated the accuracy of a point-of-care test for rapid assessment of the coagulation profile of patients undergoing cardiac surgery involving cardiopulmonary bypass. We found moderate to good agreement between the point-of-care and standard laboratory assays for the three coagulation markers examined (INR, PT, and PA). Although some statistically significant differences were observed between the index and reference test readings, they were not considered clinically significant and are unlikely to affect clinical decision-making.

Comparison to previous studies

Previous studies have examined the agreement between point-of-care tests and conventional laboratory assays for rapid assessment of coagulation profiles in patients undergoing major surgery. These findings help contextualize our results.[15,16]

Our results are consistent with those reported by Urwyler et al. (2009), who assessed the accuracy of the CoaguChek in measuring prothrombin time compared with the standard laboratory assay in adult patients who underwent major surgeries. The device showed a sensitivity and specificity of 0.95, with an area under the ROC curve of 0.988, indicating equivalence between the point-of-care and laboratory tests. Overall, CoaguChek was considered a rapid and accurate method for intraoperative monitoring of prothrombin time in cases of suspected coagulopathy.[16]

Similarly, Meesters et al. (2016) assessed the agreement between the point-of-care CoaguChek and the standard laboratory assay in 50 adult patients undergoing cardiothoracic surgery with cardiopulmonary bypass. High agreement for INR values was observed before bypass, but discrepancies emerged at 3, 6, and 10 minutes post-protamine administration, with CoaguChek readings averaging 0.22 INR units lower than the standard laboratory assay. Nevertheless, the differences were not clinically significant for transfusion decisions, as INR discrepancies up to 0.5 are generally considered acceptable. These findings support the use of point-of-care testing in cardiac surgery and align closely with our results, reinforcing the value of rapid-result testing in this setting.[17]

In our study, although some comparisons reached statistical significance, the differences between CoaguChek and laboratory INR values remained within clinically acceptable limits and are unlikely to influence decision-making in practice. Given the sample size, statistical overpowering may have occurred, leading to the detection of statistical differences without clinical relevance. This highlights the importance of interpreting statistical findings within a real-world clinical context.

Okabayashi et al. (2018) also found that point-of-care devices such as the CoaguChek XS (Roche Diagnostics) provided clinically comparable results for PT and INR while enabling faster result acquisition in patients undergoing cardiac surgery and receiving warfarin therapy. Of note, the study indicated that heparin administration significantly prolonged PT/INR values in laboratory assays, with similar effects observed across different point-of-care devices, including the CoaguChek XS, Hemochron Jr., and DRIHEMATO PT (non-heparin neutralized). Both the CoaguChek XS and Hemochron Jr. use thromboplastin reagents with an ISI close to 1.0, resulting in a strong correlation with standard

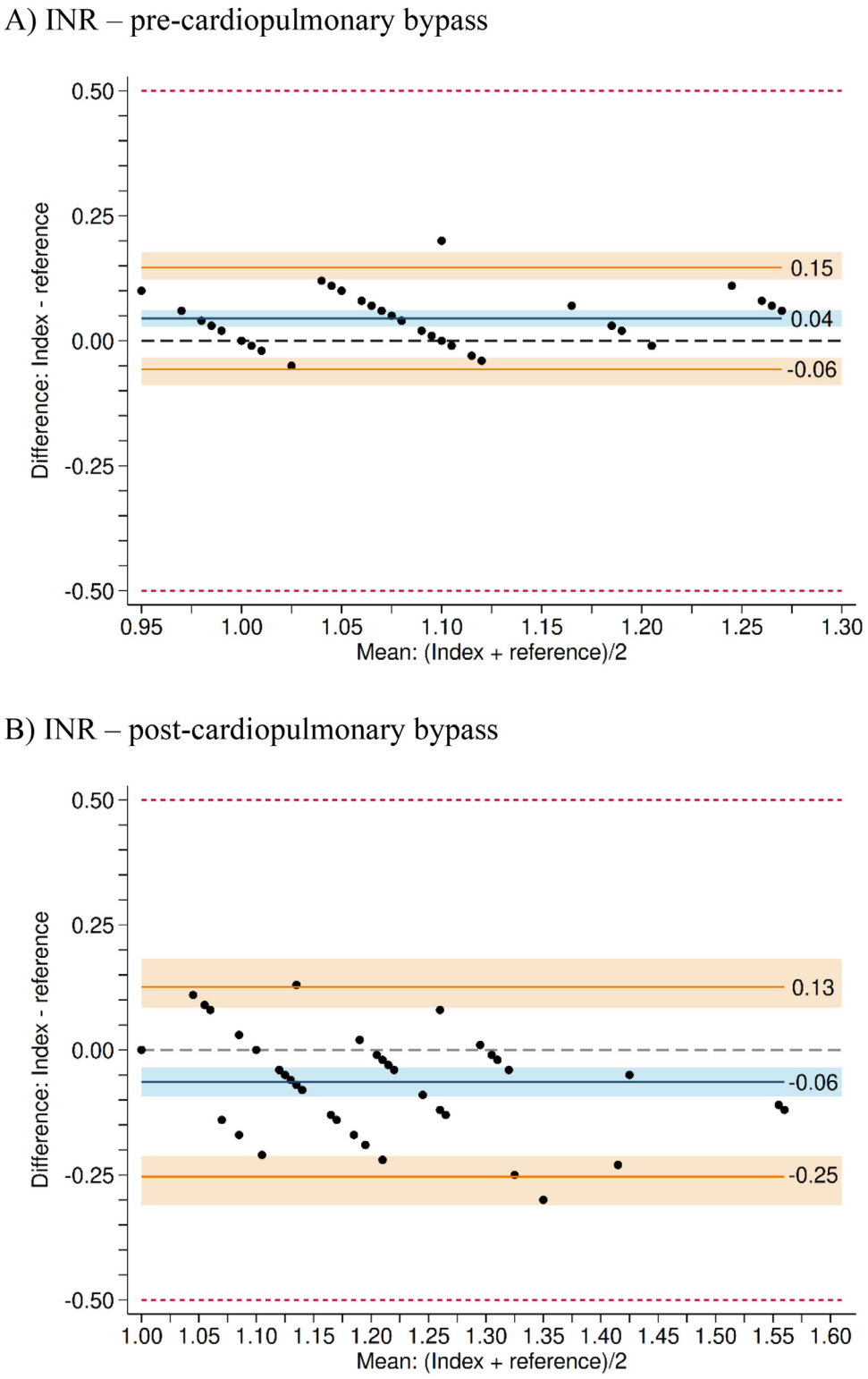

Figure 2 Agreement between the index and reference test for International Normalized Ratio (INR). Results are based on 50 participants. Points represent the measurements for each participant. The blue line represents the mean difference between the tests (in INR units). The orange lines represent the limits of agreement. It is expected that 95% of individuals will fall within these limits. The 95% Confidence Intervals are represented by the shaded areas (in blue and orange). The dashed line centered at zero (vertical axis) represents perfect agreement between the index and reference tests. When the blue region does not overlap with this line, we can conclude that the index test is associated with a statistically significant overestimation or underestimation relative to the reference test measurements. In panel A, a statistically significant overestimation is observed, while in panel B, a statistically significant underestimation is noted. The red dashed lines at -0.5 and 0.5 represent the pre-specified tolerance range. Differences within this tolerance range were not considered clinically relevant.

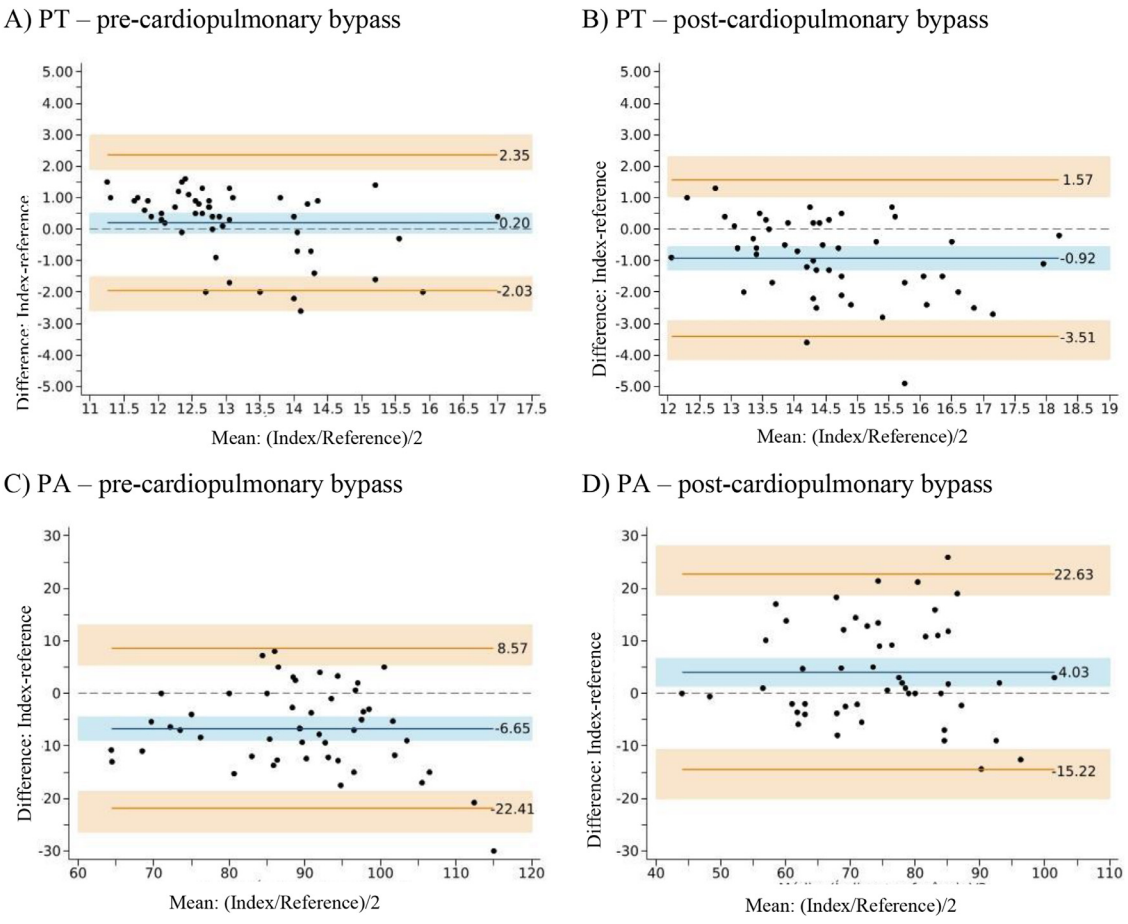

Figure 3 Secondary outcomes: Prothrombin Time (PT) and Prothrombin Activity (PA). All results are based on 50 participants. Comparison between the index test (CoaguChek) and the reference test (standard laboratory assay). Panels A and B show the results for PT (in minutes). Panels C and D show the results for PA (in percentage). Black dots represent the measurements for each of the 50 participants. The blue line represents the mean difference between the tests. The orange lines represent the limits of agreement. It is expected that 95% of patients will fall within these limits. The 95% Confidence Intervals are represented by the shaded areas (in blue and orange). The dashed line centered at zero (horizontal axis) represents perfect agreement between the index and reference tests. When the blue region does not overlap with this line, we can conclude that the index test shows a statistically significant overestimation or underestimation relative to the reference test measurements.

thromboplastin reagents used in clinical laboratories for plasma PT/INR. According to Okabayashi et al. (2018), PT/INR results obtained using the CoaguChek XS during cardiopulmonary bypass, in the range of 2.1 to 6.0, may overestimate the need for plasma transfusion. However, the number of participants with INR values above 2.0 was insufficient to draw definitive conclusions.[15]

From an economic point of view, CoaguChek appears to be cost-effective when compared with the standard laboratory assay. Hoel et al. evaluated the efficacy of the device in patients undergoing hemodialysis and found that the cost of the point-of-care test was lower than that of conventional laboratory tests.[18] In addition, the time between test execution and result release is significantly shorter with the point-of-care device.

Limitations

Our study has some limitations that should be acknowledged. First, although the sample size was determined based on a priori calculations to ensure sufficient statistical power for the primary outcome, the study was conducted in a single center with a specific patient profile, which may limit the external validity of the findings. Second, our statistical approach treated the pre- and post-cardiopulmonary bypass measurements as independent, rather than modeling them jointly. More sophisticated approaches, such as mixed-effects models, Deming regression, or Bayesian concordance models, could have been applied to assess agreement while accounting for repeated measures or measurement error in both tests. However, with only two observations per participant, these models would not provide additional value and could introduce instability or overfitting. Third, the time interval between the index (first) and reference tests was, on average, 30 minutes. Although this delay could have contributed to measurement differences, its impact was likely minimal due to the stability provided by the specialized collection tubes. Fourth, although viscoelastic tests are considered the gold standard for assessing coagulation in cardiac surgery,[19] they were not included for comparison with

CoaguChek in this study. The high cost and limited availability in many centers across the country were important limiting factors.

Conclusion

CoaguChek XS demonstrated moderate to good agreement with standard laboratory assays for INR, PT and PA in adult patients undergoing elective cardiac surgery, supporting its clinical applicability for perioperative coagulation monitoring.

Authors' contributions

Idealization: Sergio Honorato de Matos. Executing and writing: Larissa Goveia Moreira, Igor Louza Pereira, Lorenzo Leite Dino, Matheus Beserra Braga. Results: Fabrício Tavares Mendonça. Revision: Gustavo Henrique dos Santos Dias.

Data availability statement

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

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.2025.844714.

Associate Editor

Luiz Marcelo Malbouisson

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Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Independent preoperative predictors of day-of-surgery red cell transfusion in major orthopedic surgery: a six-year retrospective cohort of 7072 patients

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Received 2 March 2025; accepted 11 September 2025
Available online 11 October 2025

KEYWORDS
Anesthesia;
Blood transfusion;
Orthopedic surgery

Abstract

Background: Major Orthopedic Surgery (MOS) is frequently associated with significant blood loss, potentially resulting in perioperative anemia and the need for allogeneic blood transfusion, which carries inherent risks. This study aimed to identify independent preoperative predictors of early Packed Red Blood Cell (PRBC) transfusion in patients undergoing MOS.

Methods: We analyzed, retrospectively, data from 7072 patients who underwent MOS. The variables assessed included age, sex, weight, height, Body Mass Index (BMI), ASA (American Society of Anesthesiologists) physical status classification, surgical category (hip, knee, spine), type of procedure (primary or revision total hip/knee arthroplasty, spinal arthrodesis, scoliosis surgery), preoperative hemoglobin levels and levels at 8:00 AM on postoperative day 1, hemoglobin thresholds (> 13, < 13, < 12, < 11, and < 10 g.dL^{-1}), administration of tranexamic acid, and the requirement for PRBC transfusion.

Results: The overall transfusion rate was 4.8 % (3.6 % for hip, 2.7 % for knee, and 15.0 % for spine surgery). Independent predictors of PRBC transfusion included: preoperative hemoglobin < 13 g.dL^{-1} (Relative Risk [RR] 6.55), high-risk surgical procedures (RR = 7.40), ASA physical status III–IV (RR = 2.00), absence of tranexamic acid use (RR = 2.52), and, to a lesser extent, age > 75 years (RR = 1.50). The combination of all identified risk factors was associated with a markedly increased transfusion risk (RR = 14.55; $p < 0.0001$).

Conclusion: These findings have informed modifications to our clinical practice, aimed at enhancing quality standards through the implementation of more effective Patient Blood Management (PBM) strategies.

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https://doi.org/10.1016/j.bjane.2025.844685

Introduction

Major Orthopedic Surgery (MOS) often requires allogeneic Blood Transfusion (BT), which is associated with various complications,[1] including transmission of infectious diseases, venous thromboembolism, pulmonary embolism, myocardial infarction,[2] transfusion-related acute lung injury, increased risk of surgical site infection,[2–4] prolonged hospital stay,[2] and elevated morbidity and mortality rates.[5]

The implementation of blood-sparing strategies, optimization of Patient Blood Management (PBM) protocols,[6] routine use of Tranexamic Acid (TXA),[7] advancements in surgical techniques, and updated transfusion thresholds and clinical guidelines[8,9] have all contributed to a decline in transfusion rates in recent years. Concurrently, increasing life expectancy and the demand for higher healthcare standards have led to a growing volume of major orthopedic procedures. The primary goal of elective orthopedic surgery is to restore patients' functional status without increasing the incidence of postoperative complications.[10] However, patient-specific characteristics must always be considered in perioperative planning.[11]

The first 24 hours following surgery represent a critical window for determining the ultimate surgical outcome. During this period, the extent of bleeding and the requirement for transfusion are key factors, given the potential for coexisting complications such as hemodynamic instability, oliguria, impaired tissue perfusion, and acidosis, along with the inherent risks of transfusion.

Several specific characteristics of our center are relevant to this study:

- Our hospital is located in a rural area, 16 km from the nearest tertiary care center.
- It is a specialized, elective orthopedic surgery facility with dedicated teams for knee, hip, and spine procedures.
- There is no emergency department or trauma admissions (e.g., fractures).
- Staffing and laboratory resources are limited, particularly during on-call shifts.
- Due to these constraints, patients remain in the Post-Anesthesia Care Unit (PACU) for enhanced monitoring throughout the day of surgery.
- The anesthesia department maintains a prospectively updated database that records all clinical events occurring in the PACU during the first 24 postoperative hours.
- Hospital policy regarding the preoperative reservation of Packed Red Blood Cells (PRBC) for orthopedic procedures has been revised to be more restrictive.

Given these contextual factors, the primary objective of this study is to identify independent Preoperative Risk Factors for PRBC Transfusion (PRF-PRBC-T) within the first 24 hours following MOS. Identifying these predictors will support informed preoperative counseling and enable the implementation of targeted strategies aimed at reducing transfusion rates and improving perioperative outcomes.

Study design and methods

This was a six-year observational study with retrospective follow-up, including a total of 7072 patients who underwent surgery between March 2018 and April 2024. The study was approved by the Clinical Research Ethics Committee of Navarra on April 28, 2023 (Registry n° PI_2023/32), and by the Managing Director of the University Hospital of Navarra on May 2, 2023 (Registry n° 465).

Inclusion criteria encompassed the following procedures: Total Knee Arthroplasty (TKA), TKA Revision (TKAR), Total Hip Arthroplasty (THA), THA Revision (THAR), Spine Arthrodesis (SA), and Scoliosis Surgery (SS).

Exclusion criteria included amputations, tumor-related surgeries, and major upper limb procedures.

All data were obtained from a prospectively maintained institutional database with no missing values. The variables analyzed included: age, sex, weight, height, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) physical status classification, type of surgery, preoperative and postoperative hemoglobin values (measured at 8:00 AM on the first postoperative day), use of Tranexamic Acid (TXA), and requirement for PRBC transfusion.

The TXA using protocol during the study period was: hip and knee surgery 10 $mg.kg^{-1}$ IV and 2.5 g locally infiltrated; spine surgery initial bolus of 10 $mg.kg^{-1}$ IV and infusion of 1 $mg.kg^{-1}.h^{-1}$ during surgery. The use of TXA in the PACU was at the discretion of the attending physician.

Based on institutional experience and unpublished internal data, TKAR, THAR, and SS were classified as high-risk procedures for transfusion (more than 10 % of patients transfused). Our historical transfusion rates were: TKAR 10.79 %, THAR 12.70 %, and SS 69.81 %.

Statistics

Normality of data distribution was assessed using histograms and the Kolmogorov-Smirnov test. Homogeneity of variances was evaluated with Levene's test. Continuous variables are presented as mean ± Standard Deviation (SD) and 95 % Confidence Interval (95 % CI). Between-group differences were assessed using Student's *t*-test for normally distributed data, or the Mann-Whitney *U* and Kruskal-Wallis tests for non-normally distributed data. The unequal variance *t*-test (Welch *t* Test) was used rather than Student's *t*-test when the sample sizes for each group differed (significant different variances).

Categorical variables are reported as relative frequencies (percentages) and ranges. Group comparisons for categorical variables were conducted using Pearson's chi-squared test or Fisher's exact test, as appropriate.

Correlation between continuous variables was assessed using Pearson's correlation coefficient; for ordinal or non-normally distributed variables, Spearman's correlation coefficient was used.

Univariate logistic regression was performed to identify potential predictors of blood transfusion. Variables with $p < 0.10$ in univariate analysis were included in a multivariate logistic regression model (forward stepwise) to identify independent predictors and control for confounding. Model significance was assessed using the omnibus test of model coefficients, and goodness of fit was evaluated using the

Hosmer-Lemeshow test. Predictive performance was further assessed using Receiver Operating Characteristic (ROC) curve analysis.

Youden's J statistic and Odds Ratios (ORs) with 95 % Confidence Intervals (95 % CIs) were calculated to determine optimal threshold values for sensitivity and specificity in distinguishing transfused versus non-transfused patients.

Preoperative hemoglobin levels were recoded using the Youden index-derived cutoff value to calculate Relative Risks (RRs) via the MedCalc online tool (https://www.medcalc.org/calc/).

All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at a two-tailed *p*-value of 0.05.

Results

Preoperative values and corresponding transfusion rates by surgical group and procedure type are presented in Table 1 and Table 2, respectively.

The mean first-day hemoglobin loss, defined as the difference between preoperative hemoglobin and hemoglobin measured at 8:00 AM on postoperative day 1, was -2.9 ± 1.0 g.dL^{-1}. Significant differences were observed among surgical groups: hip -2.8 ± 1.0, knee -2.9 ± 0.9, and spine -3.2 ± 1.3 g.dL^{-1} ($p < 0.0001$), as well as among specific procedures: THA -2.8 ± 1.0, THAR -3.0 ± 1.3, TKA -2.8 ± 0.8, TKAR -3.4 ± 1.1, SA -3.2 ± 1.2, and SS -3.2 ± 2.3 g.dL^{-1} ($p < 0.0001$). Notably, scoliosis surgery patients often receive transfusions on the first postoperative day, which likely underestimates true hemoglobin loss in this group.

The mean first-day hemoglobin loss was -2.9 ± 1.0 g.dL^{-1} for both men and women. Hemoglobin loss was similar between sexes for hip (-2.8 ± 1.0 vs. -2.9 ± 1.1 g.dL^{-1}) and knee surgeries (-3.0 ± 1.0 vs. -2.9 ± 0.9 g.dL^{-1}) but differed in spine surgery (-3.4 ± 1.3 vs. -3.1 ± 1.4 g.dL^{-1}). Stratifying by procedure and sex, hemoglobin loss was comparable for THA (-2.8 ± 1.0 g.dL^{-1} in both sexes), THAR (-3.0 ± 1.2 vs. -3.0 ± 1.4), and TKA (-2.9 ± 0.9 vs. -2.8 ± 0.9), while men experienced greater hemoglobin loss in TKAR (-3.6 ± 1.2 vs. -3.2 ± 1.0), SA (-3.4 ± 1.2 vs. -3.2 ± 3.0), and SS (-4.2 ± 2.5 vs. -3.0 ± 2.2 g.dL^{-1}).

Table 3 summarizes demographic characteristics and hemoglobin values for transfused and non-transfused patients. Significant correlations with transfusion requirement were found for sex, weight, height, BMI, BMI category, type of surgery, preoperative hemoglobin, hemoglobin thresholds (< 13, < 12, < 11, and < 10 g.dL^{-1}), use of Tranexamic Acid (TXA), and high-risk surgical classification (all $p < 0.0001$, Spearman's rho).

A binary logistic regression using the enter method identified potential predictors of transfusion. Variables with $p < 0.10$ (age $p = 0.014$, sex $p = 0.029$, ASA class $p < 0.0001$, surgical group $p < 0.0001$, procedure type $p < 0.0001$, preoperative hemoglobin $p < 0.0001$, TXA use $p < 0.0001$, and high-risk surgical category $p < 0.0001$) were included in a multivariate logistic regression using forward stepwise (likelihood ratio) selection (Table 4). In the final model, sex was excluded as an independent predictor ($p = 0.424$).

Receiver Operating Characteristic (ROC) curve analyses were conducted to evaluate predictive accuracy and determine optimal cutoff points via Youden's index. The full model exposed in Table 4 had an overall quality of 0.75 (Youden's index = 0.456; AUC = 0.779 ± 0.016, $p < 0.0001$, 95 % CI 0.747–0.811; ROC curve in Figure 1 and precision-recall curve in Figure 2). The Brier score of the full model was 0.03, indicating that the probabilistic prediction model is very good, since it predicts probabilities that closely match the observed outcomes. The Events-Per-Variable (EPV) ratio was 48, well above the recommended minimum of 10, indicating that the model was robust and the estimates for each predictor were reliable.

The variable with the highest predictive value was preoperative hemoglobin (Youden's index = 0.49; AUC 0.817 ± 0.014, $p < 0.0001$, 95 % CI 0.790–0.844). This was followed by procedure type (Youden's index = 0.65; AUC 0.689 ± 0.020, $p < 0.0001$, 95 % CI 0.650–0.729) and classification as high-risk surgery (Youden's index = 0.65; AUC 0.688 ± 0.020, $p < 0.0001$, 95 % CI 0.649–0.726). Lower predictive values were observed for ASA classification (Youden's index = 0.55; AUC 0.591 ± 0.020, $p < 0.0001$, 95 % CI 0.551–0.631), TXA use (Youden's index = 0.54; AUC 0.582 ± 0.019, $p < 0.0001$, 95 % CI 0.544–0.620), and age (Youden's index = 0.47; AUC 0.503 ± 0.019, $p = 0.862$, 95 % CI 0.465–0.541).

The most significant PRF-PRBC-T are related either to patient characteristics, namely, preoperative hemoglobin < 13.15 g.dL^{-1}, ASA class III or higher and age > 75.5 years – or to surgical factors, such as undergoing a procedure with high transfusion risk or having contraindications to TXA use.

Preoperative hemoglobin < 13.15 g.dL^{-1} (cutoff per ROC, Youden's index = 0.490, RR = 6.55, $p < 0.0001$ and OR = 7.59, $p < 0.0001$) demonstrated the highest predictive power for transfusion, with a ROC curve showing excellent discriminative ability.[12]

The optimal ASA class cutoff value was 2.5 (Youden's index = 0.178), corresponding to the threshold between ASA II and ASA III. Patients classified as ASA III or IV had a transfusion RR = 2.00 ($p < 0.0001$) and OR = 2.07 ($p < 0.0001$).

Age also showed a significant association, with a cutoff of > 75.5 years (Youden's index = 0.084) yielding an RR of 1.50 ($p = 0.0002$) and OR = 1.54 ($p = 0.0002$).

The presence of all three demographic risk factors (hemoglobin < 13.15 g.dL^{-1}, ASA > III and age > 75.5 years) conferred a cumulative transfusion RR of 4.45 ($p < 0.0001$) and OR = 5.18 ($p < 0.0001$).

Regarding surgical factors, patients undergoing a high-risk procedure had an RR of 7.40 ($p < 0.0001$) and OR = 9.21 ($p < 0.0001$), while those not receiving TXA had an RR of 2.52 ($p < 0.0001$) and OR = 2.67 ($p < 0.0001$). The combination of both surgical risk factors resulted in a transfusion RR of 6.13 ($p < 0.0001$) and OR = 7.87 ($p < 0.0001$).

When all five risk factors – both demographic and surgical – were present, the cumulative risk of transfusion increased markedly, with a relative risk of 14.55 ($p < 0.0001$) and OR = 38.27 ($p < 0.0001$).

Discussion

BT is associated with a range of postoperative complications in MOS,[1] including increased risk of wound infection, venous thromboembolism, pulmonary embolism, myocardial infarction, and prolonged hospital stay – particularly in spine

Table 1 Preoperative characteristics by surgical group (hip, knee, and spine).

	Hip	Knee	Spine	Total	*p*
n	2737	3344	991	7072	
%	38.7	47.3	14.0	100	
Age	66.2 ± 11.8 [65.8 – 66.7]	70.3 ± 8.6 [70.0 – 70.6]	57.7 ± 17.2 [56.6 – 58.9]	67.0 ± 12.1 [66.7 – 67.3]	< 0.0001
Sex					< 0.0001
Male	59.9	49.7	45.5	53.1	
Female	40.1	50.3	54.5	46.9	
Weight	78.9 ± 15.7 [78.1 – 79.4]	81.2 ± 15.1 [80.7 – 81.8]	75.4 ± 16.8 [74.4 – 76.6]	79.5 ± 15.7 [79.1 – 79.9]	< 0.0001
Height	166.0 ± 9.7 [165.6 – 166.4]	163.2 ± 9.5 [162.9 – 163.6]	164.4 ± 10.0 [163.9 – 165.2]	164.4 ± 9.7 [164.2 – 164.7]	< 0.0001
BMI	28.5 ± 4.8 [28.3 – 28.7]	30.4 ± 5.1 [30.3 – 30.6]	27.8 ± 5.4 [27.4 – 28.2]	29.3 ± 5.1 [29.2 – 29.5]	0.009
BMI class					< 0.0001
UW	0.6	0.1	4.5	0.9	
HW	22.5	11.9	24.6	17.7	
OW	42.2	38.6	38.6	40.0	
O-I	25.7	32.2	23.3	28.4	
O-II	6.9	12.3	7.0	9.5	
O-III	2.0	4.9	2.1	3.4	
ASA	2.3 ± 0.6 [2.3 – 2.4]	2.5 ± 0.6 [2.5–2.6]	2.3 ± 0.7 [2.3 – 2.4]	2.4 ± 0.6 [2.4 – 2.5]	< 0.0001
I	8.6	2.9	11.1	6.3	
II	47.7	45.1	44.8	46.1	
III	39.9	48.7	40.6	44.1	
IV	3.8	3.4	3.6	3.5	
Hb	14.4 ± 1.3 [14.4 – 14.5]	14.2 ± 1.2 [14.2 – 14.3]	13.8 ± 1.7 [13.8 – 14.0]	14.2 ± 1.3 [14.2 – 14.3]	< 0.0001
Hb					
> 13	87.1	85.3	74.8	84.6	< 0.0001
< 13	12.9	14.7	25.2	15.4	< 0.0001
< 12	3.0	3.2	11.3	4.3	< 0.0001
< 11	0.8	0.9	6.3	1.5	< 0.0001
< 10	0.3	0.3	3.7	0.8	< 0.0001
TXA use	87.1	82.4	85.2	84.6	< 0. 0001

Age (yr), weight (kg), height (cm), Body Mass Index (BMI, $kg.m^{-2}$), ASA, American Society of Anesthesiologists physical status category) and preoperative Hemoglobin (Hb) ($g.dL^{-1}$) are expressed as mean ± standard deviation.

Continuous variables – age (years), weight (kg), height (cm), Body Mass Index (BMI, $kg{\cdot}m^{-2}$), ASA physical status classification, and preoperative hemoglobin (Hb, $g.dL^{-1}$) – are presented as mean ± standard deviation and [95 % Confidence Interval].

Categorical variables – surgical group (hip, knee, spine), sex, BMI classification according to the World Health Organization [Underweight (UW), Healthy Weight (HW), Overweight (OW), Class I Obesity (O-I), Class II Obesity (O-II), Class III Obesity (O-III)], ASA classification, preoperative hemoglobin categories (< 13 to < 10 $g{\cdot}dL^{-1}$), and Tranexamic Acid (TXA) use – are expressed as percentages.

Table 2 Preoperative characteristics by type of surgery.

	THA	THAR	TKA	TKAR	SA	SS	*p*
n	2549	188	2962	382	885	106	
%	36.0	2.7	41.9	5.4	12.5	1.5	
Age	66.1 ± 11.7 [65.7 – 66.6]	67.7 ± 13.1 [65.7 – 69.7]	70.1 ± 8.6 [69.8 – 70.5]	71.6 ± 9.0 [70.7 – 72.6]	60.8 ± 13.1 [59.9 – 61.7]	32.4 ± 24.6 [25.6 – 31.6]	< 0.0001
Sex							
Male	59.9	60.6	48.9	55.6	48.4	21.7	
Female	40.1	39.4	51.1	44.4	51.6	78.3	< 0.0001
Weight	78.8 ± 15.7 [78.2 – 79.5]	77.4 ± 15.4 [75.0 – 79.8]	81.2 ± 15.1 [80.7 – 81.8]	81.1 ± 14.8 [79.6 – 82.7]	78.0 ± 15.5 [76.9 – 79.1]	54.2 ± 10.7 [51.5 – 55.8]	< 0.0001
Height	166.1 ± 9.7 [165.7 – 166.5]	164.2 ± 9.5 [162.8 – 165.7]	163.2 ± 9.5 [162.9 – 163.6]	163.2 ± 9.5 [162.2 – 164.2]	164.8 ± 10.0 [164.2 – 165.6]	160.8 ± 9.4 [159.6 – 163.5]	< 0.0001
BMI	28.5 ± 4.8 [28.3 – 28.7]	28.5 ± 4.5 [27.8 – 29.2]	30.4 ± 5.1 [30.2 – 30.7]	30.4 ± 5.1 [29.9 – 31.0]	28.6 ± 4.9 [28.3 – 29.0]	21.1 ± 4.7 [19.7 – 21.6]	< 0.0001
BMI class							< 0.0001
UW	0.6	0.6	0.6	0.0	0.6	36.8	
HW	22.9	17.8	17.8	13.1	21.8	47.4	
OW	42.0	44.8	44.8	38.0	41.9	10.5	
O-I	25.4	30.1	30.1	30.2	25.7	3.2	
O-II	7.0	5.5	5.5	13.7	7.5	2.1	
O-III	2.1	1.2	4.9	5.0	2.4	0.0	
ASA	2.3 ± 0.6 [2.3 – 2.4]	2.6 ± 0.7 [2.5 – 2.7]	2.5 ± 0.6 [2.4 – 2.5]	2.6 ± 0.6 [2.6 – 2.7]	2.4 ± 0.6 [2.4 – 2.5]	2.0 ± 0.9 [1.8 – 2.2]	< 0.0001
I	8.9	4.9	3.0	2.1	7.4	41.5	
II	48.7	34.8	46.3	35.3	47.4	22.6	
III	39.2	49.5	47.5	57.4	41.6	32.1	
IV	3.2	10.9	3.1	5.3	3.5	3.8	
Hb	14.4 ± 1.2 [14.4 – 14.5]	13.7 ± 1.6 [13.5 – 14.0]	14.3 ± 1.2 [14.3 – 14.4]	13.9 ± 1.5 [13.7 – 14.0]	14.0 ± 1.5 [14.0 – 14.2]	12.0 ± 2.3 [11.4 – 12.5]	< 0.0001
Hb							
> 13	88.2	73.4	86.4	77.0	78.4	44.3	< 0.0001
< 13	11.8	26.6	13.6	23.0	21.6	55.7	< 0.0001
< 12	2.2	13.3	2.5	8.4	8.0	38.7	< 0.0001
< 11	0.4	5.9	0.4	3.4	3.6	28.3	< 0.0001
< 10	0.2	1.6	0.1	1.6	1.9	18.9	< 0.0001
TXA use	88.1	72.1	83.4	74.3	84.8	89.6	< 0.0001

Continuous variables – age (years), weight (kg), height (cm), Body Mass Index (BMI, $kg{\cdot}m^{-2}$), ASA physical status classification, and preoperative hemoglobin (Hb, $g.dL^{-1}$) – are expressed as mean ± standard deviation and [95 % Confidence interval].

Categorical variables – including surgical procedures [Total Hip Arthroplasty (THA), Total Hip Arthroplasty Revision (THAR), Total Knee Arthroplasty (TKA), Total Knee Arthroplasty Revision (TKAR), Spine Arthrodesis (SA), and Scoliosis Surgery (SS)], sex, BMI classification according to the World Health Organization [Underweight (UW), Healthy Weight (HW), Overweight (OW), Class I Obesity (O-I), Class II Obesity (O-II), Class III Obesity (O-III)], ASA classification, hemoglobin categories (< 13 to < 10 $g.dL^{-1}$), and tranexamic acid (TXA) use – are expressed as percentages.

Table 3 Demographic and preoperative hemoglobin characteristics by transfusion status.

	Transfused	Non-transfused	*p*
n	337	6735	
%	4.8	95.2	
Age	62.0 ± 23.3 [58.7 − 64.4]	67.1 ± 11.4 [67.0 − 67.6]	< 0.0001
Sex			< 0.0001
Male	3.1	96.9	
Female	6.7	93.3	
Weight	68.2 ± 16.2 [66.0 − 69.9]	79.9 ± 15.3 [79.6 − 80.4]	< 0.0001
Height	160.4 ± 9.6 [159.2 − 161.6]	164.6 ± 9.6 [164.4 − 164.9]	< 0.0001
BMI	26.5 ± 5.9 [25.7 − 27.1]	29.4 ± 5.0 [29.3 − 29.6]	< 0.0001
BMI class			< 0.0001
UW	10.5	0.5	
HW	28.5	17.3	
OW	35.7	40.2	
O-I	16.6	29.0	
O-II	6.9	9.6	
O-III	1.8	3.5	
ASA	2.6 ± 0.8 [2.6 − 2.8]	2.4 ± 0.6 [2.4 − 2.5]	< 0.0001
I	11.9	6	
II	23.5	47.2	
III	51.5	43.8	
IV	13.1	3.1	
Hb	12.4 ± 1.8 [12.2 − 12.7]	14.3 ± 1.3 [14.3 − 14.4]	< 0.0001
Hb			
> 13	4.8	95.2	< 0.0001
< 13	16.9	83.1	< 0.0001
< 12	34.2	65.8	< 0.0001
< 11	49.1	50.9	< 0.0001
< 10	55.6	44.4	< 0.0001
TXA use	3.5	96.5	< 0.0001
Hip	3.6	96.4	< 0.0001
THA	2.9	97.1	
THAR	13.8	86.2	
Knee	2.7	97.3	< 0.0001
TKA	1.5	98.5	
TKAR	11.5	88.5	
Spine	15.0	85.0	< 0.0001
SA	8.0	92	
SS	73.6	26.4	

Continuous variables – age (years), weight (kg), height (cm), Body Mass Index (BMI, $kg.m^{-2}$), ASA physical status classification, and preoperative hemoglobin (Hb, $g{\cdot}dL^{-1}$) – are expressed as mean ± standard deviation and [95 % Confidence interval].
Categorical variables – including type of surgery (hip, knee, or spine), sex, BMI classification based on the World Health Organization [Underweight (UW), Healthy Weight (HW), Overweight (OW), Class I Obesity (O-I), Class II Obesity (O-II), Class III Obesity (O-III)], ASA classification, hemoglobin categories (< 13 to < 10 $g{\cdot}dL^{-1}$), Tranexamic Acid (TXA) use, and transfusion rates – are reported as percentages.

fusion surgery (n = 13,695).[2] Therefore, identifying Preoperative Risk Factors for Packed Red Blood Cell Transfusion (PRF-PRBC-T) is essential for improving preoperative patient stratification, enabling inclusion in Patient Blood Management (PBM) programs, and offering personalized risk information.

Moreover, recognizing PRF-PRBC-T contributes to reducing the healthcare system's burden by decreasing postoperative complications and optimizing resource utilization. This includes tailoring PBM interventions, rationalizing preoperative crossmatching, considering autologous blood donation, implementing perioperative blood salvage systems,[13] and limiting postoperative hemoglobin testing to patients at higher risk.[14]

Ideally, PRF-PRBC-T should be identifiable during preoperative evaluation through patient history, physical examination, and standard blood tests. We evaluated age, sex, height, weight, BMI, ASA physical status, hemoglobin concentration, surgery type, and TXA use.

Advanced age (≥ 60 years) has been widely recognized as a transfusion risk factor in MOS,[2,14–18] while in pediatric spinal fusion, younger age has been associated with increased risk.[19] In our cohort, the mean age of transfused patients (62.0 years) was paradoxically lower than that of non-transfused patients (67.1 years), due to the younger age distribution of the scoliosis surgery group, which also had the highest transfusion rate. Nevertheless, age > 75.5 years was independently associated with increased transfusion risk.

Table 4 Binary logistic regression analysis using the stepwise forward likelihood ratio method to identify independent predictors of blood transfusion.

	β	SE β	Wald's χ^2	df	Wald test *p*-value	OR	95 % CI	
							Inferior	Superior
Age	0.013	0.006	5.411	1	0.020	1.013	1.002	1.025
ASA	−0.415	0.119	12.127	1	< 0.0001	0.661	0.523	0.834
Group	0.710	0.088	64.799	1	< 0.0001	2.033	1.711	2.417
Surgery	−0.676	0.069	94.864	1	< 0.0001	0.509	0.444	0.583
Hb	0.747	0.054	192.816	1	< 0.0001	2.110	1.899	2.345
TXA	−0.793	0.171	21.448	1	< 0.0001	0.453	0.324	0.633
High risk	1.481	0.155	91.113	1	< 0.0001	4.399	3.245	5.963
Constant predictor	−7.639	0.874	76.359	1	< 0.0001	0.000	NA	NA
Omnibus test of model coefficients			744.085	7	< 0.0001			
Goodness-of-fit test: Hosmer-Lemeshow test			7.979	8	0.436			

Model performance is indicated by Cox and Snell R^2 = 0.110; Nagelkerke R^2 = 0.374.
Regression outputs include: β (regression coefficient), SE β (standard error of β), df (degrees of freedom), OR (Odds Ratio), and 95 % CI (95 % Confidence Interval).
Predictors analyzed: age, ASA classification (American Society of Anesthesiologists physical status), surgical group (hip, knee, or spine), specific surgical procedure [Total Hip Arthroplasty (THA), Total Hip Arthroplasty Revision (THAR), Total Knee Arthroplasty (TKA), Total Knee Arthroplasty Revision (TKAR), Spine Arthrodesis (SA), Scoliosis Surgery (SS)], preoperative Hemoglobin (Hb), Tranexamic Acid (TXA) use, and classification as high-risk surgery for transfusion.

Several studies have identified female sex as a risk factor for BT in orthopedic procedures[18] including TKA,[20] Total Joint Arthroplasty (TJA = TKA + THA),[17,21] and pediatric spine fusion.[19] However, sex was not an independent predictor in our analysis and in another study.[16] While women had higher transfusion rates (Table 3), this was likely due to lower baseline hemoglobin levels (13.6 ± 1.1 g.dL^{-1} in women vs. 14.8 ± 1.2 g.dL^{-1} in men), despite similar hemoglobin declines postoperatively (mean drop: −2.9 ± 1.0 g.dL^{-1}).

The influence of weight, height, and BMI on transfusion risk remains controversial. Low body weight and low BMI have been reported as PRF-PRBC-T,[15,16,19,22] whereas high BMI has been associated with reduced transfusion rates in TJA,[17,23] and some studies have shown no association.[24] In our cohort, BMI was not an independent risk factor.

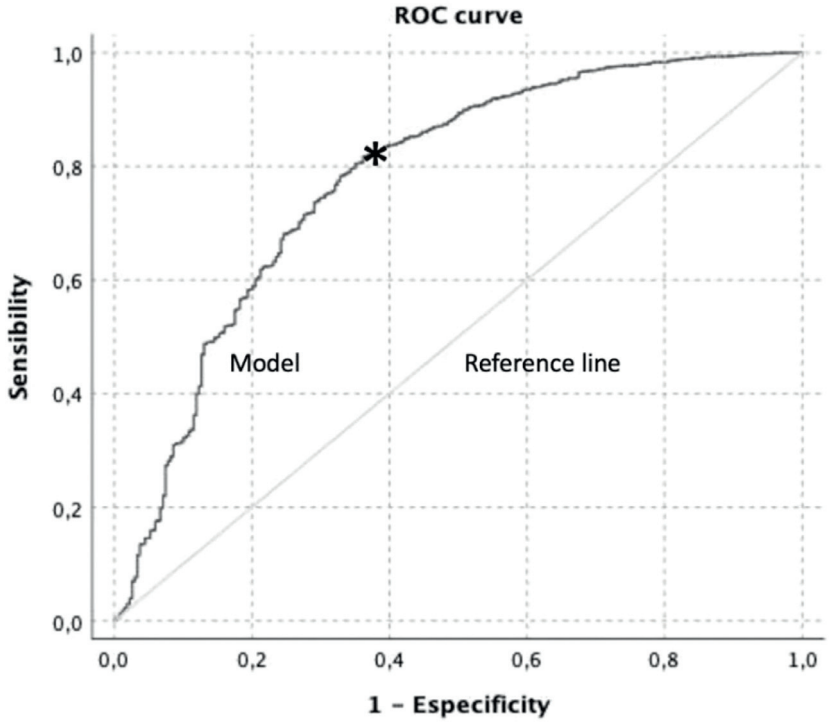

Figure 1 Receiver Operating Characteristic (ROC) curve for the Table 4 full model as predictor of blood transfusion.

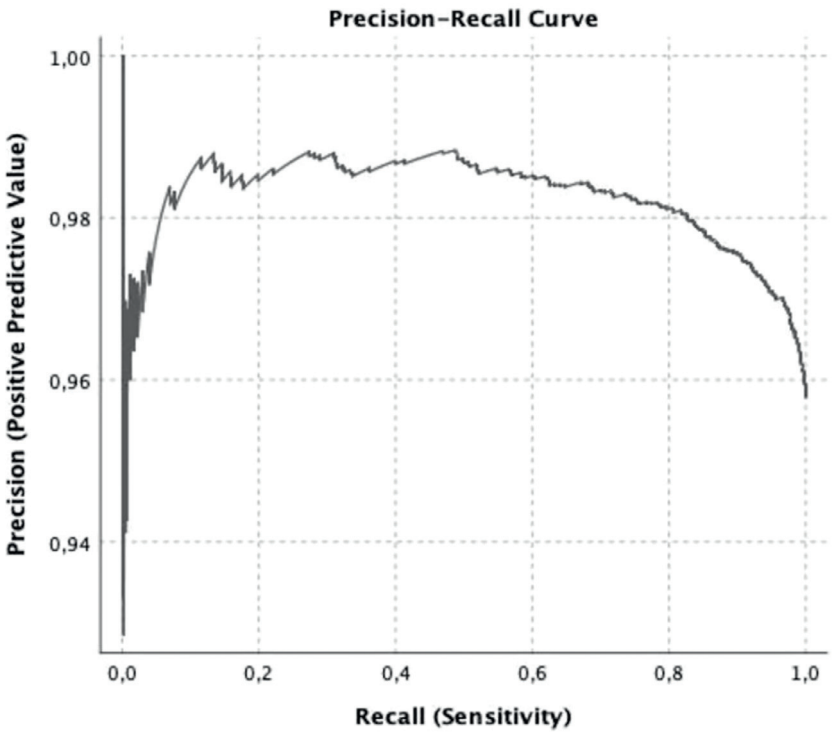

Figure 2 Precision-recall curve of the model of the Table 4 full model as predictor of blood transfusion.

Although race has been identified as a PRF-PRBC-T in children undergoing spinal fusion,[19] it was not analyzed in our study due to the homogeneity of our patient population (Southern European).

Comorbidity burden, as reflected by ASA classification, has consistently been shown to predict transfusion risk across orthopedic procedures.[2,17–20] In our study, ASA class III or higher was independently associated with increased transfusion risk.

Surgical complexity – such as revision TJA, multilevel spine fusion, scoliosis correction, and tumor resections – is another well-known determinant of transfusion risk.[2,16,18,19,25,26]

PBM strategies target three main pillars – optimizing erythropoiesis, minimizing blood loss, and improving physiologic tolerance to anemia – across the pre-, intra-, and postoperative periods. We focused on preoperative variables and one intraoperative factor (TXA use). All patients had routine preoperative lab tests. Low hemoglobin was a strong predictor of transfusion, in line with previous studies.[14–16,18,19,21,22,25–27] In fact, hemoglobin and age are often cited as the two most important predictors.[14,18] However, we argue that surgical type and ASA classification can, in some cases, outweigh the impact of age. Notably, our cutoff for age (75.5 years) was higher than in prior studies, where thresholds of 60 years were more common.[15]

Numerous studies have proposed a hemoglobin threshold of 13 $g.dL^{-1}$ to reduce transfusion risk. Some recommend 12 $g.dL^{-1}$ as the minimum for THA.[28] Regardless of the exact value, higher hemoglobin levels are consistently associated with lower transfusion rates.[17] Although the transfusion threshold is commonly set at 7 $g.dL^{-1}$, real-world decisions must consider broader clinical context, especially in older patients with comorbidities and acute bleeding.

In our study, the optimal preoperative hemoglobin cutoff for predicting transfusion was 13.15 $g.dL^{-1}$, which closely aligns with the widely accepted minimum of 13 $g.dL^{-1}$. The average hemoglobin loss within the first 24 hours postoperatively was approximately 3 $g.dL^{-1}$, underscoring the clinical relevance of this threshold. Patients with preoperative hemoglobin < 13 $g.dL^{-1}$ had significantly higher transfusion rates (Table 3).

At our institution, a perioperative PBM program has substantially reduced transfusion rates. Patients with preoperative hemoglobin < 13 $g.dL^{-1}$ undergo automated iron studies, and their lab results are reviewed by Internal Medicine for appropriate management with iron, folate, erythropoietin, or combination therapy. In our country, anemia is detected in 6.6 % of patients scheduled for arthroplasty, with 14.5 % having suboptimal hemoglobin (< 13 $g.dL^{-1}$), and 32.4 % having iron deficiency.[29] In our series, 15.4 % had suboptimal hemoglobin, highlighting the opportunity for preoperative optimization.

Regarding intraoperative blood conservation, TXA has proven effective in reducing blood loss in MOS (n = 4921),[7] and is recommended for all patients undergoing TJA regardless of preoperative hemoglobin.[30] Although TXA use is often planned in advance, individual clinical decisions may evolve intraoperatively.

Given the high prevalence and clinical burden of MOS, identifying transfusion risk factors is essential for guiding clinical decisions and improving patient outcomes. Our study has several strengths: it includes a large sample size (n = 7072), uses prospectively updated perioperative data, and focuses on transfusion risk within the first 24 hours postoperatively – a period associated with significant hemodynamic instability and adverse outcomes.

However, the study has limitations. It was conducted at a specialized orthopedic hospital with dedicated surgical teams, which may not reflect transfusion rates in general hospitals. Still, our center treats complex referral cases, often at higher risk of bleeding. Furthermore, our findings may not be generalizable to non-Southern European populations due to differences in demographics and baseline hemoglobin levels.

This study has several strengths and limitations that warrant discussion. Although retrospective in nature, it is based on data extracted from a continuously updated database that records multiple perioperative variables in real time. Therefore, it is not merely a review of potentially incomplete medical records. As a result, no cases were missed in our analysis. Moreover, the large sample size (n = 7072) provides substantial statistical power for validation and enhances the generalizability of the findings.

Geographic location – used here as a proxy for population ethnicity[19] – is another factor to consider when extrapolating these results to other populations. In this context, it is important to highlight that this study contributes valuable data from a Southern European population, complementing the existing literature, which predominantly focuses on Asian cohorts.

The study was conducted in a specialized orthopedic surgery hospital, where all staff members are exclusively dedicated to orthopedic procedures. This may result in lower transfusion rates compared to general hospitals. However, it should also be noted that, as a referral center, this institution often handles more complex surgical cases, which are inherently associated with a higher risk of bleeding.

An important limitation to acknowledge is that this study only addresses transfusion risk within the first 24 hours postoperatively. Although some patients may require transfusion later during their hospital stay, there is a paucity of data focusing specifically on the immediate postoperative period – when the greatest hemodynamic compromise typically occurs. This represents an added value of our study, particularly given that patients undergoing MOS are often elderly and present with comorbidities that limit their physiological reserve and tolerance to acute blood loss.

We are currently operating in a clinical landscape where patients increasingly demand both comprehensive information about procedural risks and optimal levels of postoperative well-being outcomes – sometimes with unrealistic expectations. It is imperative, therefore, to provide the most accurate and individualized risk assessments possible. Patients should be informed of their specific risks based on their physical status and the nature of the planned procedure, including the likelihood of requiring a blood transfusion.

Clinical data must be systematically collected and analyzed in accordance with evidence-based medicine principles to generate reliable conclusions that can guide improvements in care quality. Understanding these data enables the implementation of perioperative strategies aimed at reducing transfusion requirements and postoperative complications in high-risk patients. Those identified with multiple transfusion risk factors should undergo thorough preoperative assessment and optimization to minimize avoidable and unnecessary risks.

Conclusion

Preoperative hemoglobin < 13 g·dL^{-1}, high-risk surgical procedures, ASA class III–IV, absence of TXA use, and age > 75 years are independent predictors of transfusion risk within the first 24 hours after major orthopedic surgery.

Identifying these factors preoperatively allows for targeted PBM interventions and improved perioperative planning. Given demographic and healthcare system variability, conducting local studies is advisable to guide context-specific clinical practice.

Data availability statement

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

Authors' contributions

All authors contributed equally to the conception, design, data analysis, drafting, and critical revision of the manuscript. All authors have read and approved the final version. The authors affirm that they meet the criteria for authorship as defined by the International Committee of Medical Journal Editors.

Funding and resources

The authors report no external funding or sponsor involvement that could have influenced the outcomes of this research.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors express their sincere gratitude to the staff of the Anesthesiology Department for their collaboration and support throughout this study.

Associate Editor

Luís Vicente Garcia

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Brazilian Journal of Anesthesiology 2026;76(2): 844731

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Effectiveness and safety of antifibrinolytic agents in off-pump coronary artery bypass grafting: a systematic review and meta-analysis

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Received 23 June 2025; accepted 4 January 2026
Available online 24 January 2026

KEYWORDS
Antifibrinolytic agents;
Aprotinin;
Myocardial revascularization;
Tranexamic acid

Abstract
Background: Coronary Artery Bypass Grafting (CABG) is the most widely used cardiac intervention and can be accomplished without an extracorporeal circulation off-pump. The benefits of antifibrinolytics in off-pump CABG have yet to be demonstrated.
Methods: Randomized Controlled Trials (RCTs) and observational studies comparing the use of antifibrinolytic agents (tranexamic acid, aprotinin, and epsilon-aminocaproic) versus controls in patients undergoing off-pump CABG were searched in the PubMed, Embase, and Cochrane databases. Outcomes included thromboembolic events, in-hospital mortality, overall mortality, bleeding, Intensive Care Unit (ICU) length of stay, and blood product transfusions. Meta-analyses were conducted using the Inverse Variance method under a random-effects model, with $p < 0.05$ considered statistically significant.
Results: Of the 23,149 patients in 20 RCTs and seven observational studies, 51% received antifibrinolytic agents (tranexamic acid or aprotinin). Observational and randomized designs were analyzed separately in primary subgroup analyses. Significant reduction was found for overall mortality (RR = 0.72; [95% CI 0.54—0.95]) in the RCT subgroup. Red-blood-cell transfusion requirements were reduced (RR = 0.65; [95% CI 0.53, 0.78]) as well as Platelets (RR = 0.59; [95% CI 0.41, 0.84]) and fresh-frozen-plasma (RR = 0.39; [95% CI 0.36, 0.42]) transfusion requirement. The RCT subgroup showed a reduction in thromboembolic events (RR = 0.55; [95% CI 0.39, 0.79]).
Conclusions: In *off-pump* CABG, antifibrinolytics reduced the need for blood transfusion while reducing thromboembolic events and overall mortality in RCT subgroups, while pooled analyses combining RCTs and observational studies did not demonstrate significant reductions.
Prospero Link: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024545640

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https://doi.org/10.1016/j.bjane.2026.844731

Introduction

Coronary Artery Bypass Grafting (CABG) is the most commonly performed cardiac procedure worldwide, with the possibility of being carried out with the use of Cardiopulmonary Bypass (CPB), referred to as "on-pump", or without it, referred to as "off-pump".[1] On-pump CABG allows greater stabilization of the anastomosis site, enhanced myocardial protection achieved through cardioplegia, and improved handling of the heart by surgeons. However, blood contact with the CPB circuit can activate clotting, exhaust coagulation factors, and cause platelet dysfunction and excessive fibrinolysis.[2] Off-pump CABG is an alternative for patients undergoing CPB and aortic clamping, particularly those with heavily calcified or atheromatous aortas, or those at a high risk of dissection or embolization. While avoiding CPB-related risks, including blood exposure, hypothermia, acidosis, and tissue trauma, cardiac surgeries inherently carry a high risk of perioperative bleeding.[3] This raises specific concerns regarding hemostasis, as reducing blood loss is crucial for preventing worse patient outcomes.[2]

In this context, the use of antifibrinolytic agents to improve hemostasis is a viable approach for both on- and off-pump cardiac surgery. The clinical relevance of these agents is centered on mitigating perioperative bleeding and consequently reducing the need for allogeneic blood transfusions, which are independent risk factors for postoperative morbidity and mortality. Although off-pump CABG prevents systemic coagulopathy induced by cardiopulmonary bypass, extensive surgical trauma can trigger major fibrinolysis. Acknowledging this risk, prophylactic antifibrinolytic administration has become a cornerstone of modern blood conservation strategies, a practice strongly advocated by major clinical practice guidelines.[4,5]

Antifibrinolytic agents act primarily by inhibiting plasminogen activation and plasmin activity but differ in specificity and potency. Tranexamic Acid (TXA) and Epsilon-Aminocaproic Acid (EACA) are synthetic lysine analogs that competitively block plasminogen binding to fibrin, thereby preventing its conversion to plasmin and reducing fibrin clot degradation. In contrast, aprotinin is a serine protease inhibitor that directly blocks plasmin, kallikrein, and trypsin. Thus, while TXA and EACA primarily interfere with plasminogen activation, aprotinin provides more potent and pleiotropic inhibition of fibrinolysis.

The use of antifibrinolytics in on-pump CABG has been well established.[6] However, it remains uncertain whether off-pump CABG offers significant clinical benefits. In CABG, the absence of cardiopulmonary bypass reduces blood contact with extracorporeal circuits, leading to lower inflammatory activation, attenuated fibrinolysis, and decreased consumption of coagulation factors compared with on-pump surgery. Consequently, bleeding risk and transfusion requirements are reduced. Under these conditions, the effect of lysine analogs such as TXA and EACA may be less pronounced, as their antifibrinolytic action is most evident in settings of hyperfibrinolysis. Aprotinin, with its broader antifibrinolytic profile, effectively reduces the need for blood product transfusion; however, its additional effects have limited its use due to safety concerns. Previous meta-analyses have demonstrated the ability of these drugs to reduce perioperative bleeding and, consequently, the number of transfusions.[7] However, currently available studies and observational studies were excluded from the analyses. This systematic review and meta-analysis aimed to provide a comprehensive and current evaluation of antifibrinolytic use in off-pump CABG. It incorporates more Randomized Controlled Trials (RCTs) and includes observational studies that contribute to a substantial number of patients, facilitating comparisons with smaller RCTs, as well as including studies published after the most recent meta-analysis on the topic. In addition, compared with the most recently published meta-analysis, the present study evaluated mortality and thromboembolic events as independent outcomes, evaluated each thromboembolic outcome individually, and further divided mortality into in-hospital and overall mortality subgroups, thereby enabling more accurate interpretation of the data.[7]

Methods

This study was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Cochrane Guidelines.[8] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; identifier: CRD42024545640) on May 24, 2024.

Eligibility criteria

Inclusion and exclusion criteria were defined according to the prospectively defined PICOTT framework: P — Adult patients undergoing off-pump CABG; I — Anti-fibrinolytic therapy; C — Placebo or no intervention; O — Overall mortality, thromboembolic events, ICU length-of-stay, blood transfusion requirements, and intraoperative blood loss; T — Randomized controlled trials and observational studies; and T — No time constraints in this study.

The inclusion in this systematic review and meta-analysis was restricted to studies with the following eligibility criteria: 1) RCTs or non-RCTs; 2) Patients who underwent off-pump CABG; and 3) Comparison of antifibrinolytics (TXA, EACA, or aprotinin) with placebo or no intervention. Studies were included only if they had at least one previously determined outcome, and no limits were established for the follow-up duration.

The following study designs were excluded: 1) Reviews; 2) Meta-analyses; 3) Guidelines; and 4) Communications. Additionally, studies were excluded if they involved population overlap, lacked a control group, did not consider antifibrinolytic use, were available only as abstracts, or assessed mediastinal antifibrinolytic application.

Search strategy and data extraction

We systematically searched PubMed, Embase, and Cochrane for studies published up to July 18, 2024, without language restriction, with the following search strategy: ("off pump" OR "off-pump" OR "op-cab" OR opcab) AND ("Tranexamic acid" OR Antifibrinolytic OR "Antifibrinolytics" OR cyklokapron OR transamin OR amcha OR TXA OR "epsilon-

aminocaproic acid" OR "epsilon aminocaproic acid" OR aprotinin). The complete search strategy for each database is provided in the Supplementary Material. Two authors (JLW and MS) independently extracted the data using predefined search criteria and quality assessments. Disagreements between the two reviewers were resolved through discussion with a third reviewer (DW). After removing duplicates, all the studies were screened based on their titles and abstracts. The remaining articles were then thoroughly read. A Zotero Tool was manually used to perform this process. If the number of patients in the outcomes was expressed as a percentage and the conversion for absolute numbers resulted in a decimal number, the number was approximated to the closest integer.[9-12]

Endpoints and subgroup analyses

Outcomes included overall mortality, intrahospital mortality, thromboembolic events, time spent in the Intensive Care Unit (ICU), platelet transfusion, plasma transfusion, red blood cell transfusion, and intraoperative blood loss. Transfusion was quantified by the number of patients who received blood components. In some cases, RCTs and non-RCTs were analyzed independently to better elucidate the outcomes.

In addition, the impact of different anti-fibrinolytics was investigated by conducting a subgroup analysis, as shown in the. Sensitivity analyses were conducted by excluding high-impact studies. If an outcome of interest was described as a secondary outcome in the original trial, it still was included in the analysis to avoid selection bias. Studies that did not report outcome data were excluded from meta-analysis. No multiple imputation methods were applied to handle missing data.

In this review, overall mortality, intrahospital mortality and thromboembolic events were considered primary endpoints, whereas ICU length-of-stay, blood transfusion requirements, and intraoperative blood loss were considered secondary outcomes.

Quality assessment

The risk of bias was evaluated in randomized studies using the second version of the Cochrane Risk-of-Bias assessment tool (RoB2), whereas non-randomized studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions Tool (ROBINS-I) (Fig. S15).[13,14] Two independent authors (JLW and EC) independently completed the risk-of-bias assessment. Disagreements were resolved through discussions with a third author (MS). The final figure was generated using robvis, a visualization tool designed for risk of bias assessment in systematic reviews.[15] Publication bias was investigated using Egger's tests and funnel plot analyses of effect measures in relation to study weights, which are available in the Supplementary Appendix.

Statistical analysis

Random-effects inverse variance meta-analyses were conducted with restricted maximum likelihood estimates of tau^2 and Hartung-Knapp confidence intervals. As between-study heterogeneity was expected, the individual true effect for each study could differ from the overall true effect; therefore, random-effects modeling was preferred. Heterogeneity was assessed using the *Q* test (α = 0.10) and described by the I^2 statistic. The thresholds of 25%, 50% and 75% were used to define low, moderate and high heterogeneity, respectively. Estimates were reported as Relative Risks (RR) for dichotomous outcomes and Mean Differences (MD) for discrete variables with 95% Confidence Intervals. Subgroup analyses moderated by study design were conducted, and differences were tested by standard χ^2 tests.

A standard continuity correction (addition of 0.5 to zero-value cells on both arms) was applied to the outcomes of interest to prevent null denominator analysis. Trials that did not report specific analyzed outcomes were excluded from the respective meta-analyses to which they could not contribute data. Analyses were performed using *R* version 4.3.3, employing the meta, ggplot2, dplyr, robvis packages and Review Manager version 5.4.[16]

Certainty of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the level of certainty of the evidence. This system consists of five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall quality was classified as high, moderate, low, or very low. The quality of all outcomes was assessed by two independent reviewers (JLW and MS), and any disagreements were resolved through discussion among all authors.

Results

Study selection and baseline characteristics

The initial search yielded 399 results. After removing 128 duplicate records, 208 studies were excluded from the title/abstract analysis. Thus, 63 studies remained and were full-text reviewed based on the inclusion criteria (Fig. 1). Of these, 27 studies were included, including 23,149 patients from 20 RTCs and 7 non-randomized cohorts. A total of 11,899 (51%) patients received antifibrinolytics, and 11,250 (49%) received placebo or no intervention. In the antifibrinolytic group, 11,208 (94%) patients received TXA and 691 (6%) received aprotinin. The dose regimen presented significant variability among studies, but in the vast majority, it consisted of a bolus at the beginning of surgery, followed by an infusion until the end of surgery. Due to the specific type of patient with highly developed coronary disease that undergoes off-pump CABG, the populations in the different studies did not show a significant difference. Other characteristics, such as the type of control group, presence of a cell saver, operation time, and number of grafts, are shown in Table 1. Studies including EACA compared it with other antifibrinolytics, and no trials assessing EACA versus placebo were available. Therefore, this meta-analysis was restricted to TXA and/or aprotinin versus placebo.

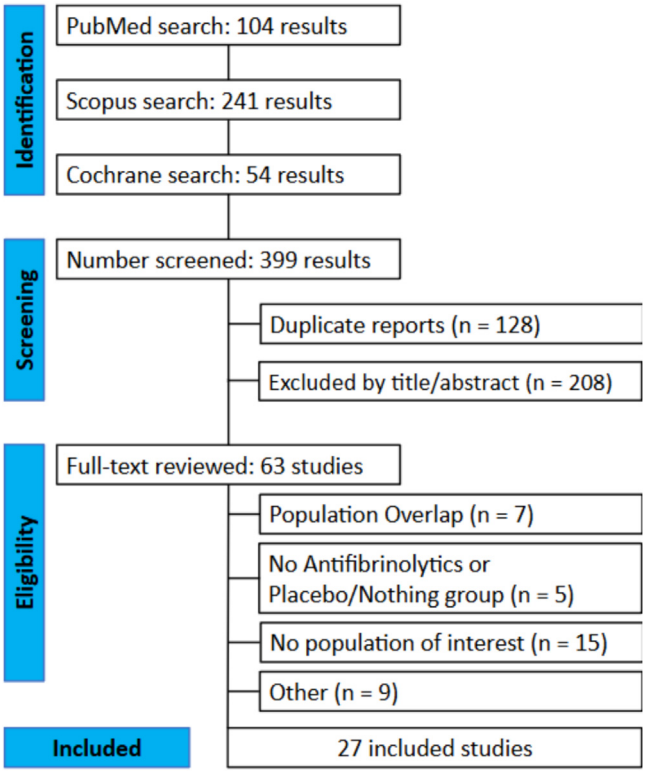

Figure 1 PRISMA flow diagram of study screening and selection. Study flow diagram.

Pooled analyses

Reduction of the intraoperative blood loss (MD = -17.47; [95% CI -77.82 to 42.88]; $p > 0.05$; $I^2 = 38\%$) or in time until the discharge of the intensive care unit (MD = 0.8; [95% CI -2.08 to 3.68]; $p > 0.05$; $I^2 = 89\%$) were not observed (Fig. S15). The number of patients who underwent packed red blood cell transfusion reduced significantly (RR = 0.59; [95% CI 0.53 to 0.67]; $p < 0.05$; $I^2 = 5\%$) similar to fresh frozen plasma (RR = 0.50; [95% CI 0.31 to 0.82); $p < 0.05$; $I^2 = 93\%$) and platelets (RR = 0.60; [95% CI 0.42 to 0.85]; $p < 0.05$; $I^2 = 0\%$) (Fig. 2). There was no change in either overall mortality (RR = 1.04; [95% CI 0.87 to 1.24]; $p = 0.65$; $I^2 = 0\%$) or in-hospital mortality (RR = 1.08; [95% CI 0.90 to 1.29]; $p = 0.35$; $I^2 = 0\%$] (Fig. 3). Regarding thromboembolic outcomes, a non-significant result was observed (RR = 0.96; [95% CI 0.77, 1.19]; $p = 0.70$; $I^2 = 0\%$] (Fig. 4).

Subgroup analyses

The result of packed red blood cells was reduced in both randomized studies (RR = 0.74; [95% CI 0.60 to 0.91]; $p < 0.05$; $I^2 = 0\%$) and non-randomized studies (RR = 0.55; [95% CI 0.51 to 0.60]; $p < 0.05$; $I^2 = 0\%$). Intra-hospital mortality did not decrease in RCTs (RR = 0.64; [95% CI 0.29 to 1.41]; $p = 0.54$; $I^2 = 0\%$), unlike in non-RCTs (RR = 1.12; [95% CI 0.93 to 1.35]; $p = 0.16$; $I^2 = 0\%$). Overall mortality showed different results between RCTs (RR = 0.72; [95% CI 0.54 to 0.95]; $p < 0.05$; $I^2 = 0\%$) and observational studies (RR = 1.18; [95% CI 0.98; 1.41]; $p = 0.07$). Thromboembolic events showed a diverged result, with RCTs showing a reduction (RR = 0.55; [95% CI 0.39 to 0.79]; $p < 0.05$; $I^2 = 0\%$] and observational studies showing an increase (RR = 1.2; [95% CI 1.06; 1.35]; $p = 0.02$). Given the controversies surrounding the availability of aprotinin, a stratified analysis was performed across the antifibrinolytic agents: overall mortality was not reduced in RCTs for either TXA (RR = 0.58; [95% CI 0.20 to 1.65]; $p = 0.19$; $I^2 = 0\%$) or aprotinin (RR = 0.74; [95% CI 0.51 to 1.07]; $p = 0.09$; $I^2 = 0\%$) subgroups. In-hospital mortality was not reduced in RCTs for TXA (RR = 0.58; [95% CI 0.20 to 1.65]; $p = 0.19$; $I^2 = 0\%$]. Thromboembolic events were reduced in RCTs with aprotinin (RR = 0.44; [95% CI 0.23 to 0.86]; $p = 0.02$; $I^2 = 0\%$), while no changes were observed with TXA (RR = 0.78; [95% CI 0.60 to 1.01]; $p = 0.05$; $I^2 = 0\%$).

Quality assessment

Rob-2 and ROBINS-I were used for quality assessment, as shown in Fig. S15. Three studies had a high risk of bias.[11,17,18] Vijay et al.[18] did not fully describe these methods. Durand et al.[11] and Weingarten et al.[17] reported a high bias due to participant selection, and only Weingarten et al.[17] reported a high bias due to confounding factors. In the funnel plot analysis (Supplementary Appendix), studies occupied a symmetrical distribution according to weight and tended towards the pooled effect as their weight increased, except for the thromboembolic event outcome, which indicated a significant publication bias, confirmed by Egger's test.

Discussion

In this systematic review and meta-analysis of 27 studies and 23,149 patients, we compared antifibrinolytic use with placebo or no use during off-pump CABG. The leading findings with antifibrinolytics include: 1) A reduction in the need for blood component transfusions; 2) A lower risk of overall death in RCTs; 3) A lower incidence of thromboembolic events in RCTs; 4) No change in overall mortality across all studies; 5) No change in thromboembolic events in any study, and 6) A higher incidence of thromboembolic events in observational studies. These differences between RCTs and non-RCTs were confirmed via meta-regression (Supplementary Appendix).

CABG surgeries are associated with an increased risk of bleeding and the need for blood transfusions, with fibrinolysis playing an important role in this context.[19] Antifibrinolytic agents such as TXA and aprotinin have a great capacity for hemostasis in cardiac surgery. However, when using these drugs, there is concern about an increased risk of thromboembolic events. The use of these agents in on-pump CABG is well established, which is not the case with off-pump CABG, for which it remains unclear whether the clinical outcomes are beneficial.[6,20] A previous meta-analysis included only randomized studies in its methodology and lacked statistical power to determine the results, especially regarding postoperative thromboembolic complications, combining thromboembolic events and mortality into a single composite outcome.[7] This study aimed to carry out a more comprehensive analysis that allows for the comparison of observational studies, including a larger patient number, with RCTs, while also investigating the effects of the antifibrinolytic class

Table 1 Baseline characteristics of included studies.

Study	Design	AF	Patients AF/PB	Control Group	Cell Saver	Male, % AF/PB	Age†, y AF/PB	BMI AF/PB	Operation Time	Preoperative Antiplatelet Agents AF/PB	Number of Grafts AF/PB	Ejection Fraction AF/PB
Ahn, 2012	RCT	TXA	38/38	Placebo	For all patients	60/47	69 ± 7 / 67 ± 7	NA	250 ± 47 / 246 ± 51	All agents interrupted 5 days before surgery	3.1 ± 0.6	60 ± 13 / 64 ± 10
Bert, 2008	RCT	Aprotinin	25/25	No AF	NA	80/80	65.7 ± 10.2 / 67.8 ± 10	NA	242.2 ± 51.5 / 260.9 ± 53.5	NA	NA	NA
Bittner, 2008	Non-RCT	Aprotinin	391/370	No AF	For all patients	81.1%	68.5 ± 9.3 / 67.8 ± 10	27.6 /27.5	163 ± 43 / 168 ± 51	337/320 (aspirin)	NA	NA
Casati, 2001	RCT	TXA	20/20	Placebo	NA	85/75	64 ± 13 / 62 ± 11	NA	NA	6/8 (aspirin)	NA	42 ± 14 / 45 ± 12
Casati, 2004	RCT	TXA	26/25	Placebo	Not for all	76/84	64 ± 12 / 61 ± 11	NA	NA	6/7 (aspirin)	NA	43 ± 14 / 46 ± 13
Chakravarthy, 2012	RCT	TXA	50/48	No AF	NA	78/81	NA	NA	300 ± 0.5 / 300 ± 0.5	All agents interrupted 7 days before surgery	7/6	NA
Desai, 2009	RCT	Aprotinin	37/38	Placebo	For all patients	NA	NA	NA	NA	Aspirin for all patients	NA	NA
Durand, 2006	Non-RCT	Aprotinin	40/40	No AF	NA	NA	67 ± 12 / 66 ± 12	NA	193 ± 49 / 156 ± 43	Aspirin for all patients	2.6 ± 0.7 / 2 ± 0.8	58 ± 15 / 55 ± 20
Englberger, 2002	RCT	Aprotinin	22/25	Placebo	NA	72/76	63.9 ± 10.8 / 66.4 ± 9	74.6 ± 14.1 / 77.1 ± 8.6	176 ± 40 / 177 ± 56	18/23 (aspirin)	2.9 ± 1 / 2.8 ± 1.2	65 ± 13 / 60 ± 13
Grant, 2008	RCT	Aprotinin	59/61	Placebo	For all patients	NA	NA	NA	NA	Aspirin	3.0 ± 0.8 / 2.8 ± 0.9	NA
Hosseini, 2014	RCT	TXA	35/36	Placebo	NA	NA	NA	NA	NA	NA	NA	NA
Hulde, 2019	Non-RCT	TXA	2249/2249	No AF	NA	81/79	67.2 ± 9.9 / 67.5 ± 9.6	28.2 ± 4.4 / 28.1 ± 4.4	NA	1696/1655 (aspirin)	2.9 ± 0.8 / 2.8 ± 0.8	56.5 ± 11 / 56.7 ± 11.3
Khadanga, 2020	Non-RCT	TXA	30/30	No AF	NA	NA	57.5 ± 7.8 / 57.9 ± 7.6	NA	NA	Aspirin interrupted on the day of surgery	NA	50.0 ± 7.8 / 50.2 ± 6.9
Kim, 2004	RCT	Aprotinin	15/15	Placebo	NA	46/60	66 ± 7.4 / 59.7 ± 6.8	NA	320 ± 64.3 / 345 ± 50.5	NA	2.7 ± 0.6 / 2.6 ± 0.4	57.2 ± 10.6 / 52.7 ± 11.1
Mehr-Aein, 2007	RCT	TXA	33/33	Placebo	No	36/45	44 ± 10 / 45 ± 10	23.4 ± 2.6 / 23.4 ± 3.3	NA	Suspended 7 days before operation	2.4 ± 0.3 / 2.3 ± 0.7	45 ± 8 / 40 ± 10
Mouton, 2008	Non-RCT	TXA	2140/1532	No AF	NA	80/81	65.3 ± 9.1 / 64.1 ± 9.6	NA	NA	NA	NA	NA

Table 1 (*Continued*)

Study	Design	AF	Patients AF/PB	Control Group	Cell Saver	Male, % AF/PB	Age†, y AF/PB	BMI AF/PB	Operation Time	Preoperative Antiplatelet Agents AF/PB	Number of Grafts AF/PB	Ejection Fraction AF/PB
Murphy, 2006	RCT	TXA	50/50	Placebo	For all patients	74/84	64.9 ± 7 / 65.8 ± 8.7	27.3 ± 4.35 / 28.6 ± 4.49	210/240	5 patients treated with aspirin or heparin	3/3	NA
Nurözler et al; 2008	RCT	Aprotinin	25/26	Placebo	NA	76/69	63.1 ± 8.8 / 64.6 ± 6.7	28.1 ± 4.1 / 26.9 ± 3.7	NA	6/8 (aspirin)	NA	43.8 ± 6.2 / 42.3 ± 5.3
Poston et al., 2006	RCT	Aprotinin	29/31	Placebo	For all patients	NA	NA	NA	NA	All patients received aspirin	3.1 ± 0.3 / 3.3 ± 0.4	NA
Taghaddomi, 2008	RCT	TXA	50/50	Placebo	NA	76/68	54.7 ± 10.9 / 60.3 ± 10.2	NA	176.5 ± 44.7 / 174.4 ± 32.6	88/92 (aspirin)	3.7/3.8	52.7 ± 11.1 / 54.1 ± 9
Vanek et al., 2005	RCT	TXA	61/30	Placebo	NA	59/73	67.3/68.9	NA	141.7/152.1	Aspirin suspended 5 days before surgery	1.8/1.8	NA
Wang et al., 2022	Non-RCT	TXA	6184/6184	Placebo	NA	77/77	61.5 ± 8.7 / 61.6 ± 8.8	25.7 ± 3.1 / 25.7 ± 3.0	NA	NA	NA	NA
Vijay at al., 2023	RCT	TXA	30/30	Placebo	NA	66/60	NA	NA	NA	NA	NA	NA
Wei et al., 2006	RCT	Aprotinin	36/40	Placebo	NA	77/80	61.4 ± 7.5 / 60.7 ± 8	NA	195 ± 34.3 / 203.4 ± 29.4	Aspirin suspended 5–7 days before surgery	3 ± 0.8 / 2.6 ± 0.6	63.5 ± 8.9 / 62.40 ± 9.4
Wei et al., 2006	RCT	TXA	36/40	Placebo	NA	77/80	62.8 ± 7.9 / 60.7 ± 8	NA	191.3 ± 47.1 / 203.4 ±29.4	Aspirin suspended 5–7 days before surgery	2.8 ± 0.6 / 2.6 ± 0.6	61 ± 8.9 / 62.4 ± 9.4
Weingarten, 2021	Non-RCT	TXA	176/172	Placebo	NA	46/73	66.6 ± 9.7 / 65.6 ± 10.4	29.3/27.8	338 ± 66.5 / 326 ± 64.7	NA	NA	NA
Yang et al., 2003	RCT	Aprotinin	NA	Placebo	NA	NA	NA	NA	NA	NA	NA	NA

AF, Antifibrinolytics; PB, Placebo; BMI, Body Mass Index; RCT, Randomized Controlled Trial; Non-RCT, Observational Studies; NA, Not Available.

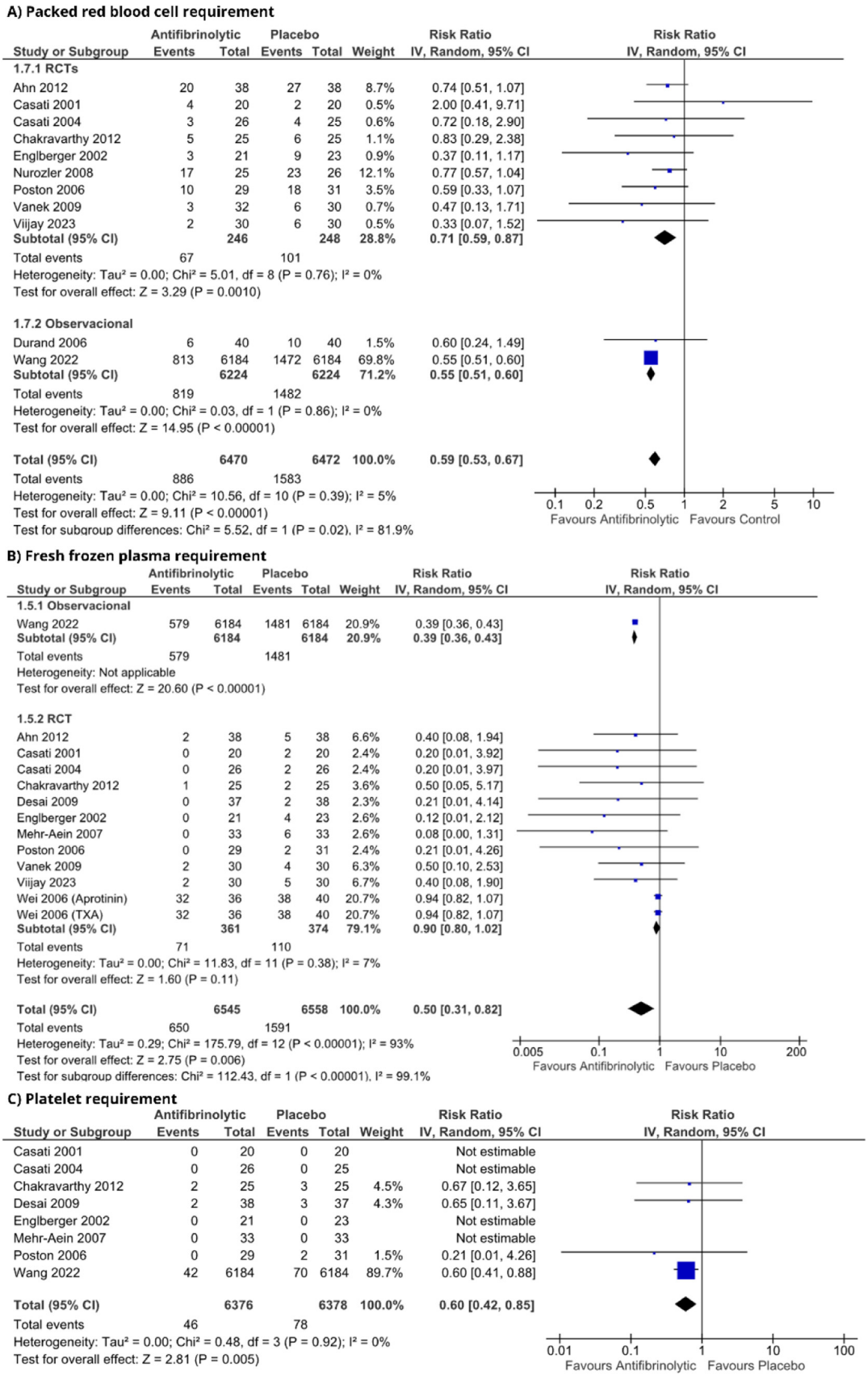

Figure 2 Blood transfusion requirement forest plots. (A) Packed red blood cell requirement; (B) Fresh frozen plasma requirement; (C) Platelet requirement. IV, Inverse Variance; RCT, Randomized Controlled Trial; CI, Confidence Interval.

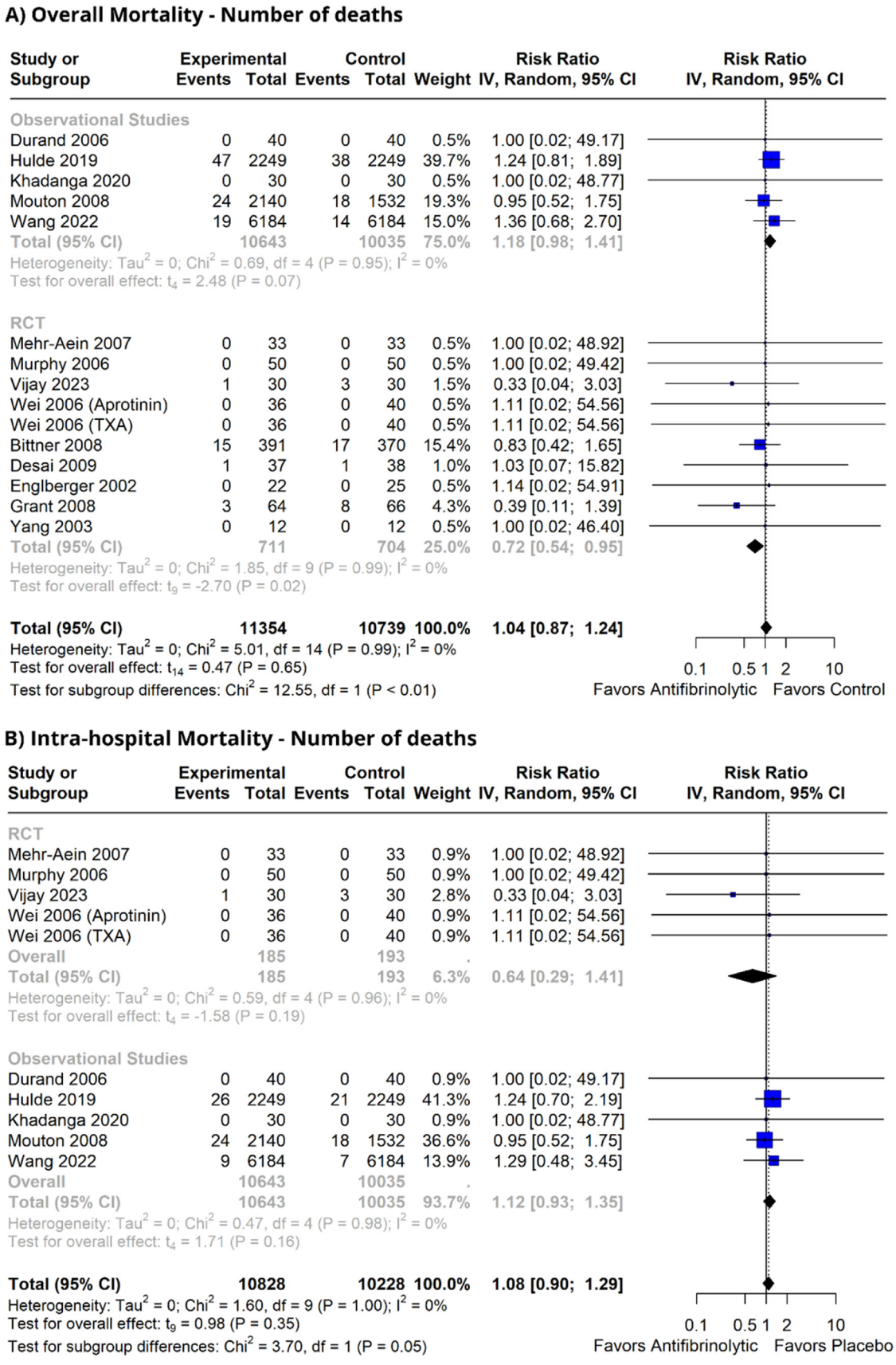

Figure 3 Overall mortality forest plots. Number of deaths. (A) Overall mortality with number of deaths. (B) Intra-hospital with number of deaths. IV, Inverse Variance; RCT, Randomized Controlled Trial; CI, Confidence Interval.

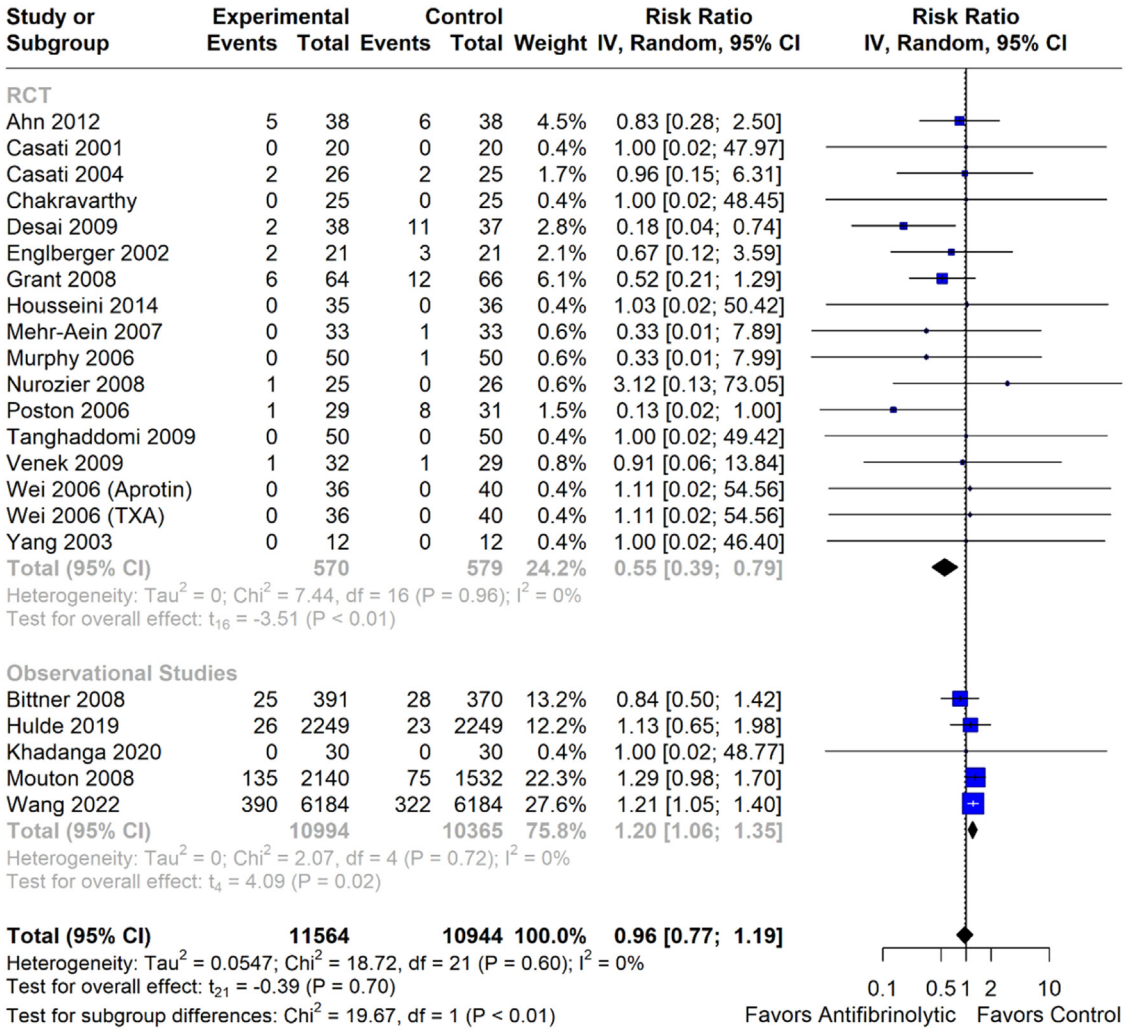

Figure 4 Thromboembolic events. Number of events. IV, Inverse Variance; RCT, Randomized Controlled Trial; CI, Confidence Interval.

beyond tranexamic acid. The inclusion of observational studies in this meta-analysis was based on methodological and clinical considerations. First, the RCTs available on the use of antifibrinolytic agents in off-pump CABG involved relatively small sample sizes, limiting statistical power, particularly for rare outcomes such as thromboembolic events. Moreover, their inclusion enables data capture from more heterogeneous populations and diverse clinical settings, thus reflecting better real-world practice than the more restrictive inclusion criteria of RCTs. This approach also made it possible to assess consistency across different study designs, identify potential sources of heterogeneity, and address evidence gaps in outcomes or subgroups that are underrepresented in RCTs. Wang et al.[20] present us with the analysis of 18,380 patients in a retrospective cohort from 2009 to 2019, highlighting this importance.

The results of this meta-analysis are consistent with those of previous meta-analyses regarding the hemostatic potential of antifibrinolytics and their ability to reduce blood product transfusions.[7,21] However, the relationship between their use and thromboembolic outcomes or mortality was a new milestone in this study. The subgroup analysis of RCTs demonstrated a significant reduction in overall mortality, as well as a significant reduction in thromboembolic events. It is important to highlight that overall mortality represents an outcome with a lower level of bias than thromboembolic events in this study, since it is less heterogeneous. Mortality was assessed in a substantial proportion of the included studies with the assurance that it was evaluated during patient follow-up; however, the assessment and reporting of thromboembolic events remained unclear in the descriptions of the included studies.

It is important to emphasize that the small sample sizes in these studies and the rarity of the outcome required the use of a composite outcome in thromboembolic events. This composite grouped endpoints such as stroke, renal ischemia, pulmonary embolism, myocardial ischemia, deep vein thrombosis, and major neurological dysfunction across the analyzed studies. When comparing the outcomes of thromboembolic events, substantial heterogeneity was observed in the assessments. Some studies evaluated complications only within the first 24 hours, such as Casati et al.[22] and Casati et al.,[23] whereas others, such as Desai et al.,[12] assessed complications up to 72 hours postoperatively,

illustrating differences in follow-up duration. Moreover, different composite outcomes involving thromboembolic events were present within individual studies, as in Grant et al.[24] Additionally, significant publication bias was identified, further complicating the analysis of the results herein reported for this outcome, which should be interpreted with caution. There was also heterogeneity and lack of information regarding the diagnostic criteria for each complication, as most dealt with clinical subjectivity, such as pulmonary embolism and renal dysfunction in Mehr-Aein et al.,[25] or cerebral complications, as reported by Wei et al.[26] Consequently, there was heterogeneity in the diagnostic criteria, thromboembolic outcomes assessed, or follow-up period. For a more thorough analysis, in an attempt to decrease residual heterogeneity, the thromboembolic outcomes were stratified according to the type of composite outcome employed in each primary investigation, revealing results consistent with those observed in the non-stratified analyses, as shown in the Supplementary Materials.

Consequently, we observed discrepancies wherein observational studies reported distinct findings regarding overall mortality and divergent results for thromboembolic events. Several hypotheses have been proposed to explain these discrepancies. First, the study by Wang et al.,[20] in the sensitivity analysis presented in the Supplementary Material, showed a strong influence on increasing the risk ratio for thromboembolic events. In addition, the lack of methodological robustness and homogeneity in the assessment of thromboembolic outcomes across the included studies introduced potential biases that could have led to misleading results, thereby warranting cautious finding interpretations. Additionally, the RCTs included were prospective in design but generally featured relatively short follow-up periods compared to retrospective observational studies, which are better suited for capturing long-term morbidity outcomes. Lastly, given that thromboembolic events have relatively low-incidence outcomes and that RCTs had relatively limited sample sizes, the substantially larger patient populations in observational studies increase the likelihood of detecting these events. This disparity in sample size may partly explain the higher incidence of thromboembolic events reported by observational cohorts. Taken together, these factors underscore the need for careful consideration when comparing results across study designs and highlight the importance of standardized follow-ups in future research.

Observational studies evaluating antifibrinolytic use are susceptible to confounding by indication, wherein treatment assignment is influenced by a patient's baseline characteristics and prognosis. Institutional protocols or clinician judgment may lead to sicker patients at a higher risk of bleeding being more likely to receive an antifibrinolytic, or conversely, patients with a high risk of thrombosis or renal injury being more likely to avoid them. This can introduce a significant bias, potentially skewing the results. To mitigate this, the observational estimates included in this review were adjusted using various statistical methods. Several of the larger retrospective studies explicitly used Propensity Score Matching (PSM) or propensity-adjusted multivariate logistic regression to balance dozens of baseline covariates between the treatment and control groups, thereby creating more comparable cohorts for analysis. For example, Wang et al.[20] used PSM to balance 32 patient and treatment factors, including comorbidities, preoperative medications, and surgical variables. Other studies used direct matching on a smaller set of variables such as age and gender or presented unadjusted estimates while acknowledging the lack of control for confounding as a major limitation. It is important to emphasize that, despite the limitations of unadjusted characteristics, patients undergoing this type of procedure have similar medical profiles, with cardiovascular comorbidities and advanced age.

Despite the presence of well-designed randomized studies with a low risk of bias, analyzing the off-pump CABG management landscape presents inherent challenges when comparing different articles. Significant heterogeneity was evident in intraoperative blood loss comparisons, which may be attributed to calculation methods and biases introduced by heterogeneous team preferences, such as varying degrees of accidental fluid mixing during aspiration or blood absorption by clothes from surgical drapes and gauzes. Therefore, the outcomes of blood product transfusions were used. This provides greater precision and objectivity in assessing the level of blood loss than measuring blood loss alone. Moreover, it serves as a clinically significant marker because excessive bleeding is often accompanied by the need for transfusion. Additionally, dosing regimens varied across studies despite commonly involving an initial bolus followed by continuous infusion, adding another layer of uncertainty to the analysis.

Furthermore, there were differences in how the studies defined transfusion triggers for blood products, with each medical service applying its own criteria (Supplementary Table S1). For example, Vanek et al.[27] initiated red blood cell transfusion when hemoglobin dropped below 8.5 $g.dL^{-1}$ and/or the hematocrit level, while transfusion of fresh frozen plasma was initiated to correct suspected coagulation factor deficiencies when chest drain bleeding exceeded > 150 $mL.h^{-1}$ or > 100 $mL.h^{-1}$ for two consecutive hours. Casati et al.,[23] on the other hand, used the presence of hypovolemia signs or symptoms (hypotension or tachycardia) or diffuse bleeding as criteria for transfusion.

The use of systemic aprotinin is limited by critical safety issues, primarily increased mortality risk as demonstrated by the BART clinical trial, which compared it to safer lysine analogues.[28] These adverse findings led to a global market suspension of the drug in 2007. Within this context, a stratified analysis of the results between aprotinin and lysine analogs was performed. Regarding overall mortality, although individual RCTs investigating TXA and aprotinin did not show a reduction, decreased overall risk was observed when the subgroups were pooled, as shown in Supplementary Figure S6. This finding raises hypotheses to be considered, such as the limited sample sizes and the heterogeneity of institutional protocols. Confirming previous evidence, for in-hospital mortality, there was increased risk of death in the aprotinin subgroup, although the number of available studies limits data reliability; and it should be noted that only one RCT evaluating aprotinin for in-hospital mortality was available, whereas the other two trials were observational. For thrombotic events, RCTs employing aprotinin demonstrated a risk reduction, whereas RCTs which used TXA showed a borderline result that warrants watchful interpretation. The analysis suggested a trend toward reduced risk (RR = 0.78; 95% CI 0.60—1.01; p = 0.055), although the confidence interval indicated non-significance. The absence of heterogeneity (I^2 = 0%) supports consistency across studies,

although there were few occurrences of the outcome and the borderline p-value raises concerns regarding the robustness of the finding. Conversely, the analysis of observational studies employing TXA found increased risk of thrombotic events. As such, there is significant heterogeneity in the current literature and caution must be exerted when interpreting the results. All meta-analyses involving the stratification of antifibrinolytics by outcome can be accessed in the Supplementary Material.

The present study had several limitations. However, these were not sufficient to discredit the findings of our study, as all analyzed outcomes, except ICU stay duration, fresh frozen plasma requirement, and intraoperative blood loss, showed low calculated heterogeneity. Of the 27 included studies, 20 were randomized[9,12,18,22-27,29–38] and seven were observational.[11,17,20,39–42] To minimize the bias introduced by including nonrandomized studies, we conducted several sub-analyses of their results, which provided a better understanding of their effect on the overall sample. This approach allowed the comparison of a large patient population derived from these studies with a smaller population of randomized studies, thereby enabling hypothesis generation to explain the differences and discrepancies between the methodologies. This finding highlights the need for further analysis in yet-to-be published studies.

Finally, an overall optimistic safety profile emerges for the use of antifibrinolytics in off-pump CABG. Reductions in mortality, thromboembolic outcomes, and the need for blood product transfusion suggest tangible benefits for both patients and the health system. Nevertheless, the evidence base would be strengthened by additional, adequately powered, randomized trials with a more standardized assessment of thromboembolic events and mortality. Notably, the perioperative efficacy of these agents in lowering transfusion requirements is well established.[4,5]

Conclusion

This updated and comprehensive meta-analysis encompassing 23,149 patients presents results consistent with the literature regarding reduction in the need for blood product transfusion, introducing a reduction in overall mortality and thromboembolic events in RCT subgroups as novel findings. Clinical recommendations should focus primarily on lysine analogues, tranexamic acid and ε-aminocaproic acid, not aprotinin. Discrepancies were found when RCT and non-RCT subgroups were compared for thromboembolic events, which may be explained by the previously discussed hypotheses involving heterogeneity and composite outcome limitations. Whereas observational data do not support such reductions in some cases and may suggest harm, hence, clinical decisions should privilege RCT-derived estimates. Further large, contemporary, standardized randomized studies with harmonized thromboembolic definitions are necessary to clarify the outcomes of mortality and thromboembolic events, considering the efficacy and safety benefits observed to date.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

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

Presentation

Preliminary data for this study were presented as an oral-presentation at the Brazilian Congress of Anesthesiology, 13–16 November 2024, Belo Horizonte.

Authors' contributions

All authors have contributed significantly to the preparation of this manuscript and approved the final version.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2026.844731.

Associate Editor

Luiz Guilherme Villares da Costa

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Brazilian Journal of Anesthesiology 2026;76(2): 844719

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Perioperative tranexamic acid in burn surgery: systematic review and meta-analysis of randomized controlled trials

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Received 16 July 2025; accepted 16 December 2025
Available online 24 December 2025

KEYWORDS
Antifibrinolytic;
Blood loss;
Burn patients;
Burn surgeries;
Tranexamic acid

Abstract

Introduction: Burn injuries often require surgery, posing challenges due to significant intraoperative blood loss and transfusion risks. Tranexamic Acid (TXA), an antifibrinolytic agent, stabilizes clots and reduces fibrinolysis, with proven efficacy in various surgical settings. However, the benefits in burn patients are yet to be established.

Methods: We performed a systematic review and meta-analysis. PubMed, Embase, and Cochrane databases were searched for Randomized Clinical Trials (RCTs) comparing TXA versus control in burned patients. Risk Ratios (RR) and Mean Differences (MD) with 95% CIs were computed for binary and continuous outcomes, respectively. The primary endpoint of interest was blood loss. Statistical analyses were performed using RStudio software (version 4.2.2). The certainty of the evidence was evaluated using the GRADE approach.

Results: Four RCTs comprising 204 patients were included, with 102 (50%) assigned to the TXA group. The mean patient age across studies ranged from 32.15 to 39.70 years. TXA significantly reduced total blood loss (MD = -183.93 mL; 95% CI: -278.44 to -89.42; $p < 0.01$), need for packed red blood cell transfusions (RR = 0.42, 95% CI 0.26 to 0.66; $p < 0.01$), while also improving hematocrit (MD = 3.49%; 95% CI: 1.58 to 5.41; $p < 0.01$) and hemoglobin levels (MD = 0.87 $g.dL^{-1}$; 95% CI: 0.35 to 1.39; $p < 0.01$).

Abbreviations: CI, Confidence Interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, Mean Difference; PRBC, Packed Red Blood Cell; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs, Randomized Controlled Trial(s); REML, Restricted Maximum Likelihood; RR, Risk Ratios; TBSA, Total Body Surface Area; TXA, Tranexamic Acid; VTE, Venous Thromboembolic Events..

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https://doi.org/10.1016/j.bjane.2025.844719

Conclusion: In patients with burns, TXA was associated with reduced blood loss and packed cell transfusions. However, certainty is limited by the small number and heterogeneity of available trials.
Registration: PROSPERO ID: CRD420251000356. Registered on 07 March 2025.

Introduction

Burn injuries can cause significant skin damage and often require surgical intervention, which presents a challenge because of substantial perioperative blood loss.[1] In recent years, early excision and grafting techniques have significantly reduced mortality in cases of severe burns.[2] However, despite these advancements and the exploration of new treatment approaches, hemorrhage during surgery remains a major concern, resulting in a demand for blood transfusions.[3,4] Nevertheless, the effectiveness of blood product transfusion in restoring hemodynamic stability remains associated with increased morbidity and mortality due to both infectious and non-infectious risks.[4,5] Currently, intraoperative strategies such as the use of extremity tourniquets, epinephrine, topical thrombin, pre-debridement tumescence with an adrenaline solution, immediate dressing application, and fibrin sealant are available.[6] However, none of these modalities have consistently demonstrated effectiveness in reducing blood loss. Consequently, in the absence of a clearly superior technique to minimize intraoperative bleeding in patients with severe burns, the administration of blood products remains the only available method to compensate for blood loss.[1]

Tranexamic Acid (TXA) is a lysine analog with antifibrinolytic activity. Its mechanism of action involves the competitive inhibition of plasminogen, a protein responsible for preventing plasmin activation and fibrin degradation.[7] Its effectiveness has been widely documented in various surgical settings, particularly in procedures related to traumatic injuries.[8] A meta-analysis evaluating the risk of surgical bleeding across multiple specialties found that TXA significantly reduced perioperative blood loss without increasing the incidence of thromboembolic events.[9] Several studies have examined the use of TXA in excisional surgeries for patients with severe burns, demonstrating its effectiveness in reducing perioperative blood loss.[10,11] Although some meta-analyses have evaluated the intraoperative use of TXA in patients with severe burns, the studies included in these reviews vary in their level of evidence, encompassing a combination of cohort studies and non-Randomized Clinical Trials (RCTs). This study aims to focus exclusively on RCTs, as they provide the highest level of scientific evidence available. In addition to expanding the existing medical literature, our goal is to generate new data to contribute to clinical decision-making.

Therefore, we conducted a systematic review and meta-analysis of RCTs to evaluate whether TXA reduces intraoperative blood loss and transfusion requirements in patients with severe burns. Secondary outcomes included duration of surgical operation and length of hospital stay.

Methods

This systematic review and meta-analysis was conducted and reported in accordance with the guidelines outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[12]

Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met the following eligibility criteria: 1) Randomized controlled trials, 2) Double-blinded design, 3) Comparing TXA versus placebo, 4) Population of burn patients aged over 15 years with at least 20% Total Body Surface Area (TBSA) burned, and 5) Reporting any outcomes of interest. Studies reported as abstracts or conference presentations were excluded.

Outcome measures

The primary outcomes were blood loss and Packed Red Blood Cell Transfusion (PRBC) requirements. Secondary outcomes included perioperative hemoglobin and hematocrit levels, colloid and crystalloid units, length of hospital stay, and duration of surgical operation. The blood loss was extracted as reported in the original studies, based on each trial's predefined definitions and measurement methods. Given the variability in how blood loss was assessed across studies, we compiled a summary of the estimation methods employed by each trial in a supplementary table (Supplemental Methods 1).

Search strategy and data extraction

A comprehensive search was conducted across PubMed, Embase, and Cochrane databases from their inception until February 2025. The following search terms were utilized in all three databases: ("Burn injury" OR "Burn patients" OR "Burn surgery") AND ("Tranexamic acid" OR TXA OR "Antifibrinolytic agent"). The specific search strategy employed for each database can be found in the Supplementary Material.

Additionally, the bibliographies of all included studies and relevant reviews were manually examined for supplementary research. Two researchers (J.C.B and N.F.A) independently evaluated the data using predetermined search criteria and quality assessment techniques. When disagreements arose between these two authors, they were resolved through discussion and consensus, with input from a third author (M.E.M). The protocol for this meta-analysis was registered with PROSPERO on March 7, 2025, and assigned registration number CRD420251000356.

Quality assessment

The risk of bias in each study was evaluated using the tool recommended by the Cochrane Collaboration Handbook.[12] We assessed the risk of bias in RCTs using the Risk of Bias in RCTs (RoB-2) tool.[13] This evaluation was conducted independently by two reviewers (M.E.M and R. H). Additionally, two independent researchers (M.E.M and R.H) assessed the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system via the GRADEpro Guideline Development Tool. Any discrepancies were addressed through discussion among the authors after examining the complete articles, leading to a consensus. As per Cochrane recommendations, funnel plots and Egger's test were not performed due to the number of included studies in each outcome ($n < 10$).[12]

Statistical analysis

To compare continuous outcomes between the TXA and control groups, Mean Differences (MD) with 95% Confidence Intervals (95% CI) were calculated. All outcomes were pooled using the inverse variance method under a random-effects model. Risk Ratios (RR) with 95% CI were calculated to compare the incidence of binary outcomes. To address methodological and demographic heterogeneity among the included studies, we implemented a Restricted Maximum Likelihood (REML) random-effects model for all outcomes. We evaluated heterogeneity using three methods: Cochran's *Q* test, I^2 statistics, and tau-squared. Heterogeneity was reported as low (I^2 = 0%–25%), moderate (I^2 = 26%–50%), or high ($I^2 > 50\%$).[14] Studies with zero events in both arms were excluded from the meta-analysis, in accordance with the Cochrane Handbook.[12]

All statistical analyses were performed using R statistical software (version 4.2.1) using the meta package. Prediction intervals were calculated to account for between-study variability and to provide a range in which the true effect of a future study would be expected to fall. Although not formally included in the GRADE approach, prediction intervals can indirectly inform judgments about imprecision, a key domain in GRADE assessments.

Sensitivity analyses

A leave-one-out sensitivity analysis was performed for all outcomes with at least $I^2 \geq 50\%$ and three or more studies to assess the robustness of findings. In this strategy, each study was omitted, and the pooled MD or RR was recalculated for the remaining studies in the analysis.

Trial sequential analysis

A Trial Sequential Analysis (TSA) was conducted to assess the consistency of the outcomes analyzed, with parameters set at a type 1 error of 5% and a type 2 error of 20%. This analysis was performed using TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen).[15]

Results

Study selection and characteristics

The initial search in our systematic review produced 206 results. Following the elimination of duplicate entries and screening based on titles and abstracts, 7 full-text articles were evaluated for potential inclusion. Ultimately, 4 RCTs met our inclusion criteria and were incorporated into the analysis. These studies encompassed a combined population of 204 participants, with 102 (50%) assigned to the TXA group. Figure 1 illustrates the details of the study selection process.[16]

The studies encompassed participants with a mean age range of 32.15 to 39.7 years, and 124 (60.78%) of the subjects were male. Ajai et al.'s[17] research included individuals with third-degree, chemical, and electrical burns affecting less than 30% of their total body surface area upon presentation. The study by Bhatia et al.[18] focused exclusively on adults with burns covering more than 20% of their total body surface area, excluding those with additional health conditions such as myocardial infarction, unstable angina, or renal/hepatic insufficiency. Cardiel et al.'s[19] investigation was limited to patients undergoing their first surgical debridement for burn injuries. The research conducted by Naderi et al.[20] concentrated on patients with severe burns, defined as those affecting over 20% of the total body surface area. A summary of the population characteristics included in this meta-analysis is presented in Table 1.

Blood loss

In the pooled analysis, TXA was associated with a significant reduction in blood loss compared with the control (MD = -183.93 mL; 95% CI: -278.44 to -89.42; $p < 0.01$; I^2 = 61.5%; Fig. 2). The included studies assessed blood loss at different time points; Bhatia et al.[18] reported intraoperative blood loss, whereas the other trials measured total perioperative blood loss.

Laboratory parameters

In terms of laboratory parameter outcomes, our analysis revealed a statistically significant increase in hemoglobin concentrations following TXA use (MD = 0.87 $g.dL^{-1}$; 95% CI: 0.35 to 1.39; $p < 0.01$; I^2 = 0%; Fig. 3A). As expected, a decrease in hemoglobin levels compared to the baseline was observed after surgery. In the TXA group, variations ranged from -2.06 to -0.69 $g.dL^{-1}$, whereas in the control group, the decline was more pronounced, ranging from -3.02 to -1.24 $g.dL^{-1}$. Similarly, we observed a significant increase in hematocrit levels (MD = 3.49%; 95% CI: 1.58 to 5.41; $p < 0.01$; I^2 = 0%; Fig. 3B).

Fluids

The investigation focused on intraoperative crystalloids and colloids, as well as the need for PRBC transfusions administered during hospitalization. Statistical analyses indicated no significant reduction in the quantity of colloid (MD = -0.25 units; 95% CI: -1.15 to 0.65; p = 0.59; I^2 = 92.7%) (Fig. S1) or crystalloid (MD = 0.10 units; 95% CI: -0.32 to 0.51; p = 0.64;

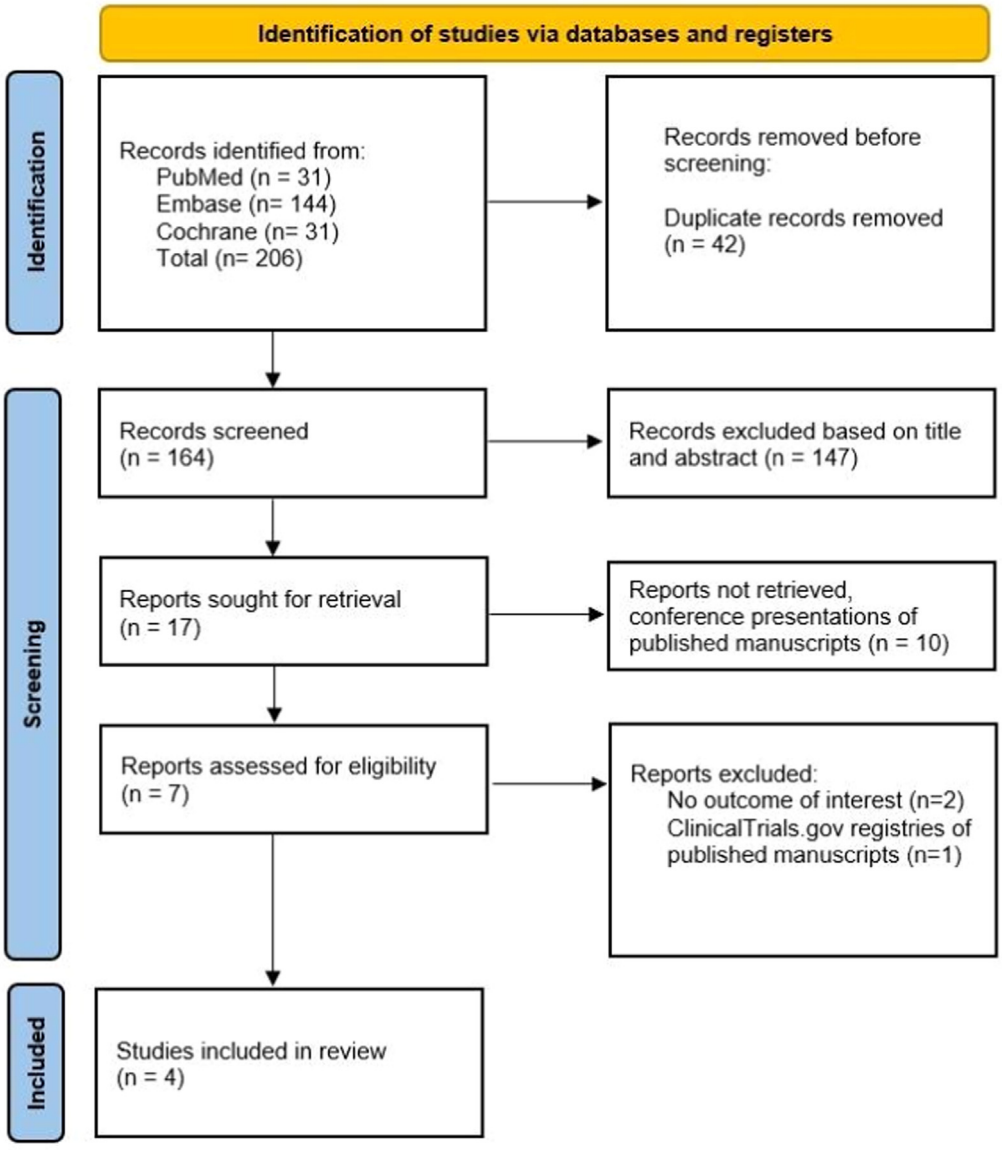

Figure 1 PRISMA flow diagram of study screening and selection.

I^2 = 58%) (Fig. S2). In contrast, a statistically significant decrease was observed in the number of PRBC requirements. (RR = 0.42; 95% CI: 0.26 to 0.66; $p < 0.001$; I^2 = 0%) (Fig. 4).

Length of hospitalization and duration of surgery

The analysis revealed no statistically significant differences in hospitalization stay (MD = -1.56 days; 95% CI: -4.42 to 1.31; p = 0.29; I^2 = 82.3%; Fig. S3). Similarly, the reduction in surgical procedure time was not statistically significant (MD = -6.46 min; 95% CI: -15.94 to 3.02; p = 0.18; I^2 = 47%; Fig. S4).

Safety outcomes

Regarding safety outcomes, the main concerns with TXA involve Venous Thromboembolic Events (VTE), seizures, and renal complications. However, among the included RCTs, none of the studies reported adverse events related to TXA use, except for postoperative infections described by Naderi et al.,[20] in which 11 patients in the TXA group and nine in the control group developed infection after the surgical procedure with no statistically significant difference between groups.

Sensitivity analyses

Sensitivity analyses were performed using a leave-one-out method (Supplemental Table 1). In the analysis of blood loss, the overall effect remained statistically significant in all scenarios, demonstrating the robustness of these findings. Notably, when the study by Bhatia et al.[18] was omitted, heterogeneity decreased to 0%, suggesting that this study contributed substantially to the observed variability, which may be attributable to differences in the timing of blood loss assessment, as most studies analyzed postoperative

Table 1 Baseline characteristics of included studies.

Study	Design	TXA regimen[b]	Control	Patients (n)	Age[a] (Years)		Male (n)		Hb transfusion threshold ($g.dL^{-1}$)	BMI[a] ($kg.m^{-2}$)		Burn-surgery interval (days)	TBSA[a] (%)		Anesthesia type	Follow-up
					TXA	C	TXA	C		TXA	C		TXA	C		
Ajai 2022	RCT	15 $mg.kg^{-1}$ Preoperatively	10 mL saline IV	30	33.6	30.7	12	14	< 8	21.2	20.9	6	28.4	26.7	General anesthesia	3 months postoperatively
Bhatia 2017	RCT	15 $mg.kg^{-1}$ Preoperatively	25 mL saline IV	50	35.1	36.2	15	14	< 7	20.8	21.6	7	38.6	41.8	General anesthesia	Intraoperative and 24 hours postoperatively
Cardiel 2025	RCT	10 $mg.k^{g-1}$ Preoperatively	10 mL saline IV	30	33.8	35.2	9	11	< 10	27.3	26.2	10	26.5	27.1	NA	Intraoperative and 24 hours postoperatively
Naderi 2025	RCT	10 $mg.kg^{-1}$ bolus + 1 mg. kg^{-1} during surgery per hour.	Saline solution IV	94	39.3	40.1	24	25	Exceeding ABL	24.8	24.5	NA	45.6	43.5	General anesthesia	NA

[a] Mean.
[b] Dose of TXA used.
ABL, Allowable Blood Loss; BMI, Body Mass Index; C, Control; Hb, Hemoglobin; NA, Not Available; RCT, Randomized Controlled Trial; TBSA, Total Body Surface Area; TXA, Tranexamic Acid.

bleeding, whereas Bhatia et al.[18] assessed intraoperative bleeding.

The sensitivity analysis demonstrated that the exclusion of Naderi et al.[20] reduced heterogeneity to 0% for both hospital stay and surgery duration outcomes. Nonetheless, this exclusion did not change the overall effect estimates, suggesting that although the Naderi et al.[20] study contributed substantially to statistical heterogeneity, the overall results remained stable and robust (Supplemental Table 1).

Risk of bias assessment

The Cochrane Collaboration's tool for assessing RoB-2[13] was used for quality assessment. No study was considered to have a high risk of bias. Two RCTs were labeled as having some concerns regarding the overall risk of bias.[18,20] One trial[20] demonstrated some concerns regarding missing outcome data due to losses during follow-up. Other concerns were that one trial did not mention any protocol or ethics committee approval[18] and the other had a retrospective protocol registration.[18,20] All other domains were labeled as low risk (Fig. S5). This reflects appropriate randomization, allocation concealment, and blinding of participants, supporting the overall methodological quality of the included trials. The funnel plot analysis was not necessarily due to the number of studies ($n < 10$).

Certainty of evidence

According to the GRADE approach, the certainty of the evidence for the evaluated outcomes was initially rated as high, given that all included studies were randomized controlled trials. However, the certainty was subsequently downgraded based on judgments related to risk of bias, inconsistency, imprecision, and potential publication bias. Our GRADE analysis revealed that most outcomes were supported by low or very low certainty of evidence. For blood loss, the evidence indicates a reduction; however, there was some indirectness due to the timing of TXA administration relative to burn injury, which varied across studies and was imprecise with a wide prediction interval. Regarding transfusion requirements, the presence of studies with some concerns of risk of bias and variability in transfusion thresholds contributed to further downgrading. Hemoglobin outcomes were judged as moderate certainty due to imprecision, while hematocrit was rated as low certainty given very serious imprecision. Finally, hospital stay, and duration of surgery were rated as very low certainty, mainly due to high heterogeneity and wide prediction intervals. The GRADE assessment is displayed in Supplemental Table 2.

Trial sequential analysis

The results were considered conclusive only if the Z-curve crossed the trial sequential monitoring boundaries for benefits or harm. Results that did not cross any of the boundaries indicated that the evidence was insufficient to reach a conclusion, and further studies are warranted. In addition, we documented whether the calculated information size was reached. Outcomes that did not achieve the requisite information size for analysis were noted. A detailed description of TSA analysis is

Figure 2- Blood loss

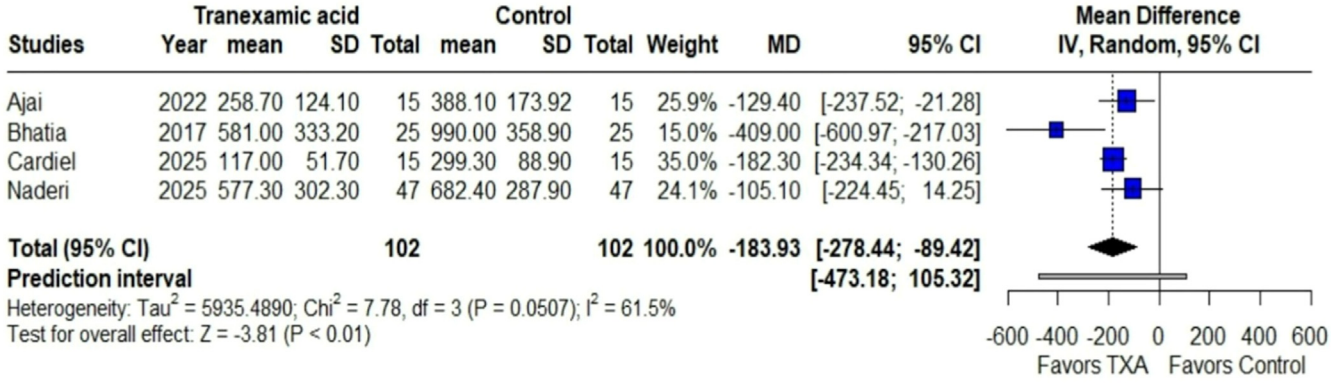

Figure 2 Blood Loss analysis. Comparison of total blood loss between perioperative tranexamic acid administration and control in burn patients undergoing surgical excision. Patients in the TXA group showed a reduced blood loss volume ($p < 0.01$).

Figure 3A- Hemoglobin

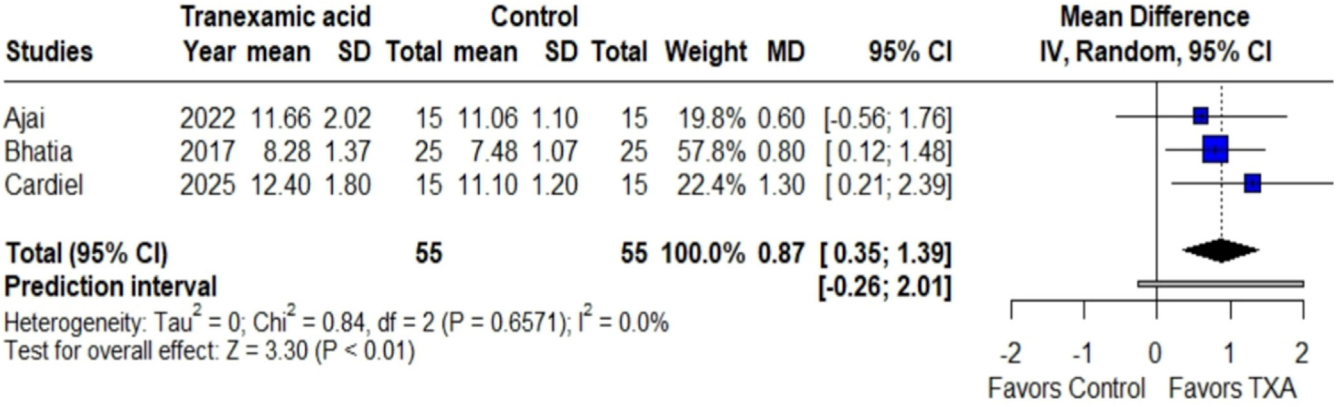

Figure 3B- Hematocrit

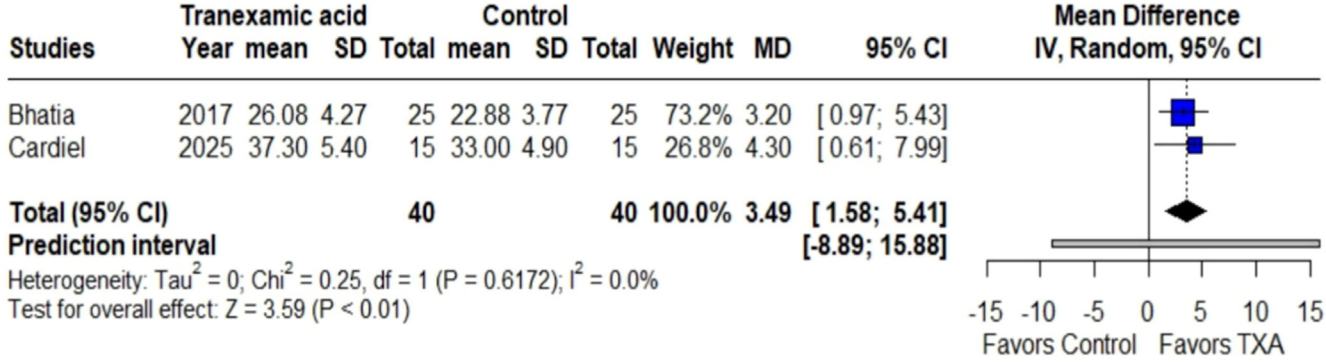

Figure 3 Laboratory parameter analysis. (A) Comparison of hemoglobin ($g.dL^{-1}$) and (B) Hematocrit (%) levels between perioperative tranexamic acid administration and placebo in surgical treatment of burn injuries.

present in the summary of findings table (Table 2). Confirmation was obtained for the results related to reduced blood loss, the need for PRBC requirements, and improved hemoglobin levels. The corresponding images for each TSA analysis are available in the Supplementary Table 3.

Discussion

In this present systematic review and meta-analysis of four RCTs and 204 patients, we evaluated the efficacy of perioperative TXA compared with placebo in patients with burns undergoing surgical treatment. The main findings include: 1)

Figure 4- Packed red blood cells requirements

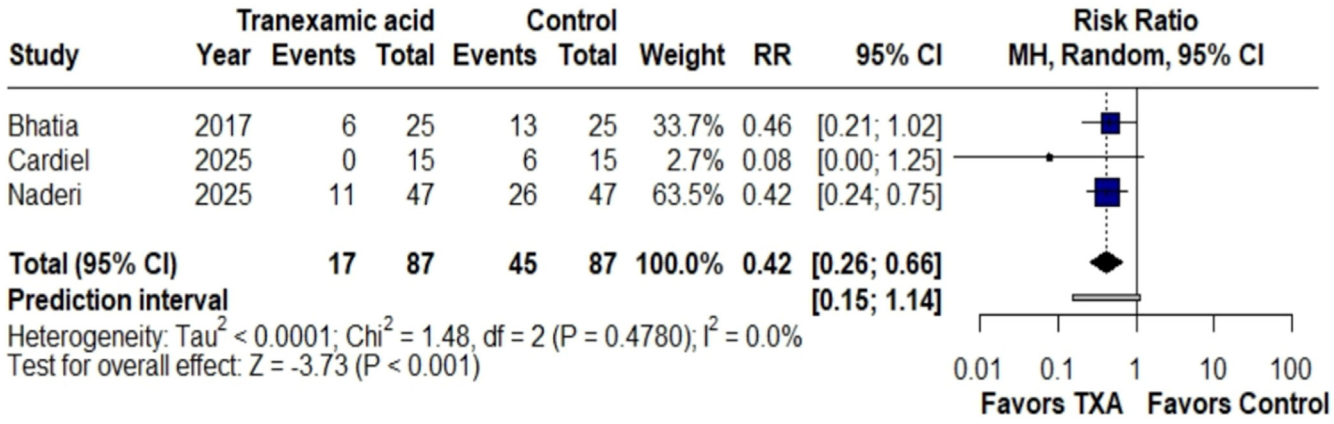

Figure 4 PRBC requirements analysis. Comparison of transfusion requirements between perioperative tranexamic acid administration and placebo in burn surgery. A reduction in transfusion requirements was observed in the TXA group ($p < 0.001$).

Reduced blood loss, 2) Higher hematocrit levels, 3) Increased hemoglobin levels, and 4) Reduction in the need for PRBC transfusions for burn patients. These findings have important implications for perioperative anesthetic and surgical management in burn patients.

The CRASH trial 2 is a landmark study on the use of TXA in trauma, demonstrating a 9% reduction in the risk of death from acute traumatic hemorrhage when administered within three hours of injury.[21] However, the CRASH trial excluded patients with burns from its analysis. The rationale for using TXA is its potent antifibrinolytic activity. TXA acts by blocking the activation of plasminogen into plasmin, thereby reducing the breakdown of fibrin clots and helping to stabilize hemostasis.[22,23] In addition to its antifibrinolytic effect, some studies suggest it may also have anti-inflammatory properties and support endothelial function, although these mechanisms remain secondary and less well established.[24]

The antifibrinolytic action of TXA appears to provide a pharmacological adjunct to optimize perioperative hemostasis. This is reflected in our primary results, with a statistically significant reduction in blood loss volume in milliliters (MD = -183.93 mL). These findings align with those of a meta-analysis by Fijany et al.,[25] who also reported reductions in blood loss; however, their analysis included some cohort studies. In contrast, Slob et al.[26] did not observe a statistically significant reduction in blood loss when analyzing only two RCTs, highlighting how limited sample sizes and methodological heterogeneity can affect pooled estimates. Finally, our TSA confirmed the observed reduction in blood loss as a true positive finding in our meta-analysis, and heterogeneity turned to 0% when excluding Bhatia et al.[18] likely because it measured intraoperative blood loss, overestimating the effect, whereas the other studies assessed across the perioperative period.

It is crucial to note that blood loss can be quantified using different metrics, such as mL/%TBSA or $mL.cm^{-2}$ of excised area. Ajai et al.[17] measured blood loss per excised area, and Bhatia et al.[18] measured blood loss by %TBSA, both showing significant reductions with TXA. Only these two studies used alternative metrics, suggesting that TXA's benefits may extend beyond total blood loss. Focusing solely on the excised surface area could underestimate overall bleeding, whereas broader measures risk overstating the effect. Therefore, future trials should standardize and combine complementary metrics to provide more meaningful clinical insights.

Additionally, TXA was associated with modest but statistically significant improvements in hemoglobin and hematocrit levels, with mean increases of 0.88 $g.dL^{-1}$ and 3.49%, respectively. These laboratory outcomes reflect better perioperative preservation of red cell mass, which may contribute to improved oxygen-carrying capacity and reduced transfusions. Notably, transfusion requirements were reduced by 58%, underscoring TXA's impact on transfusion thresholds and decision-making during anesthetic management, given that more transfusion is related to higher mortality rates.[27,28]

The interval between burn injury and surgery, and consequently TXA administration, is pathophysiologically relevant for interpreting our findings. Following a severe burn, patients progress through distinct physiological phases, with an initial period characterized by profound systemic inflammation, increased capillary permeability, and fluid shifts, followed by a proliferative phase with progressive stabilization of the microvasculature.[29,30] Early surgery during the hyperpermeability phase may be associated with greater intraoperative blood and fluid loss, potentially amplifying the hemostatic benefits of TXA.[31,32] In our analysis, the interval from injury to TXA administration ranged from 6 to $\geq$ 10 days. Therefore, it is important to be careful when interpreting these findings for urgent repairs and later surgeries. The lack of standardized reporting limits assessment of time-dependent effects, highlighting the need for future trials to stratify outcomes by burn phase or time since injury.

Some arguments have emerged against the use of TXA. Its cost-effectiveness has been questioned in the past, although the literature has extensive findings suggesting it is considered a cost-saving alternative. The underlying reason is related to the side effects and clinical and surgical benefits. Furthermore, TXA can reduce the need for blood transfusions, a costly alternative associated with numerous side effects and complications.[33,34] However, despite lowering transfusion requirements, no statistically significant reductions were observed in hospital length of stay, operative

Table 2 Summary of findings.

Perioperative Tranexamic Acid in Burn Surgery: Systematic Review and Meta-Analysis of Randomized Controlled Trials						
Patients: Burn patients. **Intervention:** Perioperative intravenous tranexamic acid. **Comparison:** Control						
Outcomes	**MD or RR (95% CI)**	**Prediction intervals (95% PI)**	**N° of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments***	**Trial sequential analysis**
Blood loss (mL)	MD = −183.93 (−278.44 to −89.42)	−473.18 to 105.32	204 (4 RCTs)	⊕⊕◯◯ Low[a,b,c]	Omitting Bhatia et al. turns I^2 to 0%. The results were consistent and not dependent on any single study.	Confirmed by TSA; RIS achieved
PRBC requirements	RR = 0.42 (0.26 to 0.66)	0.15 to 1.14	174 (3 RCTs)	⊕⊕◯◯ Low[d,e]	The heterogeneity was 0%	Confirmed by TSA; RIS achieved
Hemoglobin	MD = 0.87 (0.35 to 1.39)	−0.26 to 2.01	110 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	The heterogeneity was 0%	Confirmed by TSA; RIS achieved
Hematocrit	MD = 3.49 (1.58 to 5.41)	−8.89 to 15.88	80 (2 RCTs)	⊕⊕◯◯ Low[f]	The heterogeneity was 0%	The required information size was exceeded at the first information fraction, preventing TSA boundary rendering.
Hospital stay	MD = −1.56 (0.19 to 0.52)	−0.16 to 0.88	154 (3 RCTs)	⊕◯◯◯ Very low[g,h]	Omitting Naderi et al. turns I^2 to 0% without altering the non-significant results.	Not confirmed by TSA; RIS not achieved
Duration of surgery	MD = −6.46 (−15.94 to 3.02)	−39.02 to 26.10	174 (3 RCTs)	⊕◯◯◯ Very low[d,h]	Omitting Naderi et al. turns I^2 to 0% without altering the non-significant results.	Not confirmed by TSA; RIS not achieved

The corresponding risk, its 95% Confidence Interval, and its 95% prediction intervals were calculated by R software. CI, Confidence Interval; PI, Prediction Interval; MD, Mean Difference; TSA, Trial Sequential Analysis; RIS, Required Information Size.

[a] Although heterogeneity was high, all trials favored tranexamic acid. Sensitivity analysis showed that exclusion of Bhatia et al. reduced heterogeneity to 0%, likely due to its intraoperative assessment of blood loss, which overestimated the effect compared with the postoperative evaluations of the other trials.

[b] The settings in which the intervention was initiated varied considerably, with differences in the timing of TXA administration relative to burn injury and in the dosing regimens across studies. These variations significantly increase the level of indirectness in our assumptions.

[c] Downgraded once due to the wide prediction interval.

[d] Downgraded once due to risk of bias, as two of the three studies were rated as having some concerns.

[e] The transfusion thresholds applied to define the timing of blood transfusion varied considerably across the included studies, which increases variability and contributes to greater inconsistency in the results.

[f] Downgraded twice due to very serious imprecision.

[g] Downgraded due to high heterogeneity.

[h] Downgraded for imprecision due to the fact that the 95% PI around the effect size was large.

[*] In comments, we describe the results from the leave-one-out analysis.

time, or crystalloid and colloid fluid use. The absence of effects on other cost-related outcomes implies that financial advantage might primarily result from reducing transfusion requirements rather than decreasing the overall use of perioperative resources.[34-36]

Moreover, some authors have raised concerns about increased costs related to the management of potential complications, particularly VTE and seizures.[37] A limitation of our review is that none of the included trials systematically reported adverse events beyond postoperative infection (reported only by Naderi et al.).[20] This probably reflects the small sample sizes and short follow-up periods of the available RCTs, which restrict the ability to detect and quantify such complications. Importantly, the lack of reported events should not be equated with safety evidence, given the pharmacological profile of TXA and the hypercoagulable state in patients with burns.[38,39] Future trials must consistently monitor and report VTE and other clinically relevant adverse events, especially with longer follow-up periods.

Regarding clinical implications, our findings suggest that the use of TXA in burn surgery may help reduce packed cell transfusions with a reduction in blood loss, contributing to more efficient perioperative management. It would be valuable to explore, through future meta-regression analyses, whether factors such as patient age, sex, dose, and extent of TBSA involvement modify the effect of TXA on blood loss. A higher TXA dose or larger burn areas might be associated with greater benefit, but these relationships can only be reliably assessed once a sufficient number of studies (> 10) are available. Thus, its use should be individualized, and further high-quality studies are needed to confirm its efficacy and safety in this population.

This meta-analysis has several limitations that should be acknowledged. First, the small number of included trials and their limited sample sizes reduced the overall robustness, resulting in low statistical power and limiting the strength and generalizability of our findings. Second, substantial heterogeneity in patient characteristics, burn severity, surgical techniques, TXA dosing regimens, and differing transfusion thresholds across studies may have contributed to the variability in the observed effects. Third, the absence of individual patient-level data prevented more granular subgroup evaluations of interest and the exploration of potential effect modifiers through meta-regression analyses. Fourth, the limited number of studies did not allow us to formally assess publication bias using funnel plots or Egger tests. Finally, safety outcomes such as venous thromboembolism and seizures, in addition to other clinically meaningful outcomes such as mortality, were not systematically reported by the included RCTs, thereby limiting our ability to evaluate the safety profile of TXA in patients with burns.

Conclusion

In available RCTs, TXA was associated with reduced intraoperative blood loss, improved hemoglobin and hematocrit levels, and fewer PRBC transfusions in burn surgery. Certainty is limited; further high-quality, adequately powered studies with standardized dosing and comprehensive safety assessments are needed.

Authors' declaration

AI assistance disclosure: No artificial intelligence tools, software, or models were used in the generation, writing, analysis, or review of this manuscript.

Data availability statement

The data associated with the paper are available in PubMed, Cochrane and Embase.

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

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

Funding

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

Authors' contributions

The authors confirm contribution to the paper as follows: Conceptualization: Maria Eduarda Molinari; Formal analysis: Ramon Huntermann, Maria Eduarda Molinari, Julia Cremonini Bernardi, Caroline de Oliveira Fischer Bacca; Methodology: Ramon Huntermann, Nicoly Fiorese Andrade, Maria Eduarda Molinari; Writing — original draft: Gustavo David Barbosa, Nicolas Ramos, Ramon Huntermann, Maria Eduarda Molinari and Caroline de Oliveira Fischer Bacca.

All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2025.844719.

Associate Editor

Lorena Ibiapina Mendes de Carvalho

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LETTER TO THE EDITOR

Response to the Letter to the Editor regarding "Lateral versus posterior quadratus lumborum block in children undergoing open orchiopexy: a double-blind randomized clinical trial"

Dear Editor,

We sincerely thank Dr. Aphale and colleagues for their interest in our study and for their appreciative comments that underscore the value of our study entitled "Lateral versus posterior quadratus lumborum block in children undergoing open orchiopexy: a double-blind randomized clinical trial".[1] Their thoughtful remarks provide an opportunity to clarify the scope and objectives of our research and to emphasize several methodological considerations.[2]

As correctly noted,[2] current systematic reviews and meta-analyses have indicated that Quadratus Lumborum Block (QLB) is an effective and reliable postoperative analgesic technique for children undergoing lower abdominal surgeries, providing longer and superior pain relief compared with caudal anesthesia.[3] Our study, however, was not designed to compare QLB with caudal block or systemic analgesia. The primary aim was to compare the analgesic efficacy of two QLB approaches applied from different anatomical sites – lateral and posterior – in a specific pediatric surgical procedure, open orchiopexy.[1] Therefore, including a control group such as a caudal or systemic analgesic was beyond the scope of our study. Nevertheless, we agree that future randomized controlled studies comparing different QLB approaches with caudal and systemic analgesic techniques in different types of surgeries are warranted to identify the optimal approach and further strengthen clinical practice.

Regarding the comment on the absence of dermatomal mapping,[2] we acknowledge that standardized sensory evaluation could provide additional insight into the spread of the local anesthetic. However, as clearly stated in our manuscript, sensory testing was not feasible in our study population due to the use of general anesthesia and the young age of participants. This limitation was explicitly addressed in the discussion section.[1] In pediatric patients, particularly under general anesthesia, objective sensory assessment poses both practical and ethical challenges; therefore, the dermatomal distribution of local anesthetics cannot be precisely delineated in a clinical setting.

Additionally, we thoroughly discussed that both lateral and posterior QLB may not be sufficient for scrotal incisions because of the complex and variable innervation of this region. As noted in our manuscript, this observation was attributed to anatomical variations in local anesthetic spread and uncovered innervation zones. Nevertheless, there were no statistically significant differences between the two groups regarding the additional analgesic requirements, nor in the duration of analgesic-free intervals.[1]

We also noted the concern regarding parental pain scoring after discharge. As mentioned in our methods and limitations, pain assessment by caregivers is an inherent constraint of pediatric outpatient surgery research.[1] To minimize the limitation parents were pre-instructed on the use of the Wong-Baker Pain Scale, and written guidance was provided before discharge. Similar approaches are widely used in the pediatric anesthesia literature for day-case surgeries, given the impracticality of inpatient follow-up for every patient.[4] Hence, while subjective, parental assessment remains an accepted and pragmatic method for short-term postoperative evaluation in this setting.

We concur that several factors influence the choice of regional anesthesia technique in clinical practice, including the type of surgery, patient positioning, anesthesiologist experience, and anticipated spread of local anesthetic. Our findings demonstrated that lateral and posterior QLB techniques produced comparable analgesic efficacy for open orchiopexy.[1] Thus, given the technical simplicity of the lateral approach, this method may be a reasonable alternative in clinical scenarios where both efficacy and ease of performance are relevant considerations.

Finally, to the best of our knowledge, our study was the first double-blind, prospective, randomized trial comparing lateral and posterior QLB in children. We fully agree that further research is warranted to evaluate the comparative analgesic effectiveness of different QLB approaches across various pediatric surgical procedures. Such studies should ideally incorporate imaging-based confirmation of block spread and consider long-term pain outcomes when ethically and logistically feasible. However, the assessment of long-term outcomes was beyond the scope of our hypothesis. We specifically designed our study to evaluate the first 24 postoperative hours, which represent the period when postoperative pain is most intense.[1,5]

https://doi.org/10.1016/j.bjane.2025.844718

In conclusion, we appreciate the insightful feedback from Dr. Aphale and colleagues.[2] We hope our clarifications reinforce the intended focus of our study and contribute to ongoing efforts to optimize regional anesthesia strategies in children.

Data availability statement

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

Authors' contributions

Ozgecan P. Zanbak Mutlu made substantial contributions to the conception, interpretation, and drafting of the manuscript.

Pinar Kendigelen contributed to revision of the manuscript.

Ayse C. Tutuncu played a key role in the study's conception and critical revision of the manuscript.

Funding

None.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

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Received 10 October 2025; accepted 1 December 2025
Available online 6 December 2025

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Comment on: "Comparison of automatic versus constant CPAP in elderly patients after major abdominal surgery: a randomized noninferiority trial"

Dear Editor,

We read the research article on the comparison of the automatic versus constant Continuous Positive Airway Pressure (CPAP) in elderly patients after major abdominal surgery with great interest.[1] We commend the authors for the wonderful concept of comparing these two techniques. However, the trial design and the interpretation of the results warrant further discussion.

First, Thu et al.[1] published the study as a noninferiority type. Nevertheless, we would like to highlight that a few key elements required to interpret a noninferiority trial were not clearly reported in accordance with the protocol specified for a noninferiority study. Primarily, this type of study should be planned before commencing the study, with calculation of the noninferiority margin (Δ) and the sample size, and these details should be incorporated in the trial registry.[2,3] Thu et al.[1] did not mention the study as "noninferiority" while explaining the study arms in the trial registry, and the Δ-value was also not provided.

Second, the sample size calculation raises an additional concern. Thu et al.[1] did not mention the calculation of the noninferiority margin. This is pivotal for the sample size calculation.[2,3] Consequently, we believe that the sample size calculation may be inaccurate.

Third, reporting of a noninferiority study should ideally include a figure illustrating the position of the confidence interval with the null value and the noninferiority margin.[2] This was not provided in the current study; hence, the results need careful interpretation, especially considering the p-value was significantly lower for the oxygenation and FVC, suggesting a superiority of the constant CPAP group, rather than "non-inferior". We would like to seek clarification from the authors whether the primary outcome was "oxygenation".

In summary, there are many important concepts and protocols to conduct and report a noninferiority study.[2,3] Unfortunately, a few key elements, such as the prespecified primary endpoint, the calculation of noninferiority margin (Δ) and its justification, the position of the confidence interval in relation to Δ, were not presented in the current study as discussed above. As the interpretation of the results, consequently the conclusions, are mainly based on the specific protocols of a noninferiority study,[2,3] we hope that further insights from Thu et al.[1] would clarify the readers on these aspects.

Authors' contributions

RMS: Conceptualization, drafting, reviewing and editing the manuscript. AT, AB: Drafting the manuscript. All authors approved the final version.

Data availability statement

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

Declaration of competing interest

The authors declare no conflicts of interest.

Funding

None.

Editor

Liana Azi

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https://doi.org/10.1016/j.bjane.2026.844744

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Received 30 December 2025; accepted 27 February 2026
Available online 5 March 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Reply to Comment on "Comparison of automatic versus constant CPAP in elderly patients after major abdominal surgery: a randomized noninferiority trial"

Dear Editor,

We thank Sethuraman et al.[1] for their thoughtful comments and the opportunity to further clarify the noninferiority framework of our study.[2]

This trial was prospectively designed to test the noninferiority hypothesis that automatic CPAP is noninferior to constant CPAP in maintaining postoperative arterial oxygenation (PaO_2) in elderly patients after major abdominal surgery. The primary endpoint for this comparison was PaO_2 measured during the predefined early postoperative observation period. The primary aim was therefore not to demonstrate superiority of automatic CPAP over constant CPAP, but rather to determine whether automatic CPAP could maintain postoperative oxygenation within a clinically acceptable margin compared with the standard constant CPAP mode. This noninferiority framework reflects routine clinical practice, in which both CPAP strategies are already well established as superior to conventional low-flow oxygen therapy in preventing early postoperative hypoxemia and respiratory deterioration in elderly patients undergoing major abdominal surgery. Accordingly, the clinically relevant question is whether automatic CPAP can preserve these recognized benefits without a clinically meaningful loss of efficacy, while potentially offering additional advantages in patient comfort and adaptability.

We acknowledge that a formal noninferiority margin was not explicitly prespecified in the published manuscript or in the trial registry, and we recognize this as a limitation in reporting transparency. Although the study was powered based on a clinically meaningful improvement in PaO_2 (approximately 15 mmHg) reported in prior studies comparing CPAP or noninvasive ventilation with conventional oxygen therapy,[3-5] this value should be understood as an assumption used for sample size estimation, rather than as a prespecified noninferiority margin for comparison between automatic and constant CPAP. In retrospect, a clearer distinction between these concepts would have better aligned the report with CONSORT recommendations for noninferiority trials.

Accordingly, the approximately 15 mmHg improvement in PaO_2 associated with CPAP compared with conventional oxygen therapy should not be interpreted as a formal noninferiority margin, but rather as a clinically meaningful reference benchmark for the expected magnitude of benefit of CPAP-based respiratory support. In our trial, mean PaO_2 values were 90.8 $\pm$ 12.3 mmHg with automatic CPAP and 97.5 $\pm$ 10.8 mmHg with constant CPAP, corresponding to a mean between-group difference of -6.7 mmHg (95% Confidence Interval [95% CI], -12.5 to -0.9 mmHg). When interpreted in relation to this clinically meaningful reference, the observed difference remains well within a range suggesting no clinically meaningful loss of CPAP efficacy, despite a small numerical difference between modes.

We further note that statistically significant differences observed at individual time points in repeated-measures analyses should not be interpreted as evidence of superiority in the absence of a prespecified superiority hypothesis. Such analyses primarily describe temporal patterns and within-group changes, and between-group p-values at specific time points indicate statistical differences in trajectories rather than clinically meaningful superiority. In noninferiority trials, conclusions should be guided mainly by the confidence interval of the between-group difference in relation to the noninferiority margin and by clinical relevance, rather than by isolated p-values. Because superiority testing was not prespecified in the protocol, it was therefore not formally undertaken.

Regarding graphical presentation, we agree that figures displaying confidence intervals in relation to a noninferiority margin can facilitate interpretation. However, CONSORT Item 17a notes that such figures "may be useful" rather than mandatory.[6] The absence of such a figure therefore does not invalidate the findings, although clearer visualization might have improved interpretability for readers.

Finally, we acknowledge the concern raised in the Letter to the Editor that the absence of an explicitly stated noninferiority margin in the registry represents an important reporting issue. Prospectively, the trial was planned with a noninferiority objective and a predefined primary outcome, but the margin itself was not explicitly reported or registered. We recognize this as a limitation and appreciate the opportunity to clarify this distinction transparently.

In summary, although aspects of noninferiority reporting required clarification to meet contemporary reporting

https://doi.org/10.1016/j.bjane.2026.844748

expectations, these issues pertain to transparency of presentation rather than to the conduct or validity of the study. Within a clinical context in which both CPAP strategies are known to outperform conventional oxygen therapy, our findings indicate that automatic CPAP preserves postoperative respiratory function within clinically acceptable limits and represents a reasonable alternative to constant CPAP in selected elderly patients after major abdominal surgery.

Data availability statement

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

Authors' contributions

NDT: Conceptualization, drafting, reviewing, and editing the manuscript. NTT, LSN, NNT, NTK: Drafting the manuscript. All authors approved the final version.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 30 January 2026; accepted 15 February 2026
Available online 26 March 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

From the Turing Test to AI detectors: an epistemological mismatch in scholarly publishing

Dear Editor,

Alan Turing's "imitation game" proposed that if a machine's responses were indistinguishable from a human's, even expert judges could not reliably tell the difference.[1] In scholarly publishing, however, there has been a shift from such human-based judgments toward automated AI text detectors that claim to identify machine-generated writing. This shift raises fundamental epistemological concerns. Empirical evidence indicates that, in certain experimental settings, both human experts and some current AI detection systems have been shown to perform only marginally better than chance in distinguishing AI-generated text from human prose.[2] Thus, replacing human judgment with algorithmic detection has not meaningfully improved reliability. Given that advanced AI language models are explicitly optimized to produce human-like text, the assumption that another machine can consistently outperform expert readers appears paradoxical.

AI text detectors do not evaluate meaning; instead, they primarily rely on surface-level linguistic proxies such as stylistic regularity and textual predictability.[3] Consequently, some AI text detectors have been reported to flag a non-trivial proportion of well-written, formally structured academic texts as AI-generated, particularly in specific disciplinary or evaluative contexts.[4] Ironically, clarity, coherence, and disciplined academic style – hallmarks of high-quality scholarly writing – may increase the likelihood of false-positive classifications. This issue disproportionately affects authors using formulaic scientific language or writing in a second language. Notably, detectors have misclassified a majority of genuine academic essays by non-native English writers as AI-generated, with false-positive rates exceeding 60% reported in controlled evaluations of non-native English academic writing samples using multiple widely deployed detection tools.[3] Such findings underscore a fundamental conflict with the indistinguishability principle underlying the Turing Test: if text is genuinely human-like, no simple algorithmic signal can reliably reveal its origin.

The editorial consequences of over-reliance on AI detectors are substantial. False-positive labels risk reputational harm, as allegations of AI authorship are difficult to conclusively refute. Unlike plagiarism, AI-generated content lacks verifiable textual overlap, rendering accusations inherently ambiguous. Experimental studies in specific academic domains have demonstrated that AI detectors may incorrectly flag a significant proportion of authentic journal articles, raising serious concerns about their suitability for editorial decision-making.[4] Moreover, such practices may undermine fairness and diversity in scholarly communication, disproportionately affecting non-native English authors and certain disciplinary writing styles. Excessive dependence on detector scores may also create perverse incentives, encouraging authors to alter otherwise clear prose to avoid suspicion, while offering false reassurance against genuinely AI-generated submissions that evade detection.

In light of these limitations, AI text detectors should be used, at most, as preliminary screening tools rather than definitive arbiters of authorship. Editorial decisions must not hinge on probabilistic detector outputs alone. Even proponents of these technologies caution against their use as sole evidence due to the persistent risk of false positives.[5] Human editorial judgment – grounded in contextual evaluation, scholarly coherence, and transparency – remains indispensable. When detector outputs are considered, their role should be clearly disclosed, interpreted in conjunction with human editorial assessment, and accompanied by a transparent process that allows authors to respond to or contest such findings. Ultimately, Turing's original insight remains instructive: when human and machine outputs become indistinguishable, the solution lies not in increasingly speculative detection, but in clear ethical guidance and balanced editorial oversight. AI detectors may assist the process, but they cannot replace human responsibility in safeguarding scholarly integrity.

For transparency, AI-assisted tools were used only for language editing and structural refinement. All substantive content and arguments were developed by the authors, and no undisclosed AI-generated content or ghostwriting was used.

Data availability statement

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

Authors' contributions

Ahmet Rıdvan Doğan: Conceptualization of the manuscript; clinical and editorial perspective; drafting and critical revision.

https://doi.org/10.1016/j.bjane.2026.844740

Ali İrfan Doğan: Conceptual contribution on artificial intelligence, algorithmic and computational aspects; Literature support, and critical revision of the manuscript.

All authors approved the final version of the manuscript.

Institutional Review Board (IRB) approval

Not applicable. This manuscript is a conceptual Letter to the Editor and does not involve human participants, animals, or identifiable data.

Study registry

Not applicable.

Declaration of generative AI in the write process

During the preparation of this manuscript, the author(s) used generative AI and AI-assisted tools to support language editing, structural organization, and refinement of academic phrasing. All content was carefully reviewed, edited, and verified by the author(s), who take full responsibility for the accuracy, originality, and integrity of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Editor

Liana Azi

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Received 28 January 2026; accepted 15 February 2026
Available online 1 March 2026

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

LETTER TO THE EDITOR

Implementation of a difficult airway rapid response team: a Brazilian experience

Dear Editor,

Failure to obtain a secure airway can escalate within minutes to hypoxemia, cardiac arrest, and devastating neurological injury. Although specialty guidelines provide robust algorithms for managing difficult airways, real-world hospital care often fails at critical interfaces – namely, early recognition, rapid mobilization, and coordinated execution across diverse clinical settings. Motivated by this gap and by international experiences, we designed and implemented a hospital-wide Difficult Airway Rapid Response Team (DART) at Einstein Hospital Israelita, a large private tertiary general hospital in São Paulo, Brazil. The institution features modern infrastructure, 647 beds (including 149 ICU beds), and a high-volume emergency department. We also developed a pragmatic manual to support adoption in similar institutions.

Our program is modeled after the Johns Hopkins DART (Difficult Airway Response Team). This multidisciplinary program was created to improve the emergency management of difficult airways outside the operating room. DART brings together specialists from anesthesiology, emergency medicine, otolaryngology, and trauma surgery, responding through a rapid paging system to critical airway events. The team is equipped with advanced airway carts and follows strict activation criteria, including known or encountered difficult airways that standard code teams are unable to manage. The Johns Hopkins DART program was implemented after root cause analyses identified safety gaps in airway emergencies and includes operational protocols, equipment management, and extensive simulation-based training. Since 2005, this model has enhanced patient safety, ensured more reliable emergency responses, and substantially reduced airway-related adverse events and the need for surgical airways in non-operative hospital settings.[1]

During the COVID-19 pandemic, DARTs were essential for adapting hospital airway management protocols to the increasing numbers of critically ill patients and heightened infection risks for healthcare professionals. These expanded teams, composed mainly of anesthesiologists and ICU specialists, followed strict protocols to maximize intubation success, consistently used Personal Protective Equipment (PPE), and minimized mask ventilation to reduce aerosolization risks. Hospitals redeployed experienced professionals to form rapid airway response teams and implemented standardized processes emphasizing effective communication and equipment preparedness. Healthcare worker protection was prioritized through focused training, exclusion of high-risk staff, and rigorous hygiene practices. This multidisciplinary model improved care coordination and contributed to reducing adverse airway events, making these teams a key component of hospital responses during the COVID-19 outbreak.[2]

Our manual incorporates evidence-based clinical pathways supported by systems engineering principles. Activation criteria were standardized and include: (i) Anticipated difficult airway as judged by the attending clinician; (ii) Persistent hypoxemia during airway management ($SpO_2 < 90\%$); (iii) More than two unsuccessful intubation attempts; or (iv) Tracheostomy displacement. We established a single dedicated call number, set an arrival target of $\leq$ 5-minutes, and ensured hospital-wide coverage across all clinical areas, including ICUs, step-down units, the emergency department, operating rooms, obstetrics, diagnostic units, wards, and nurseries.

The pediatric difficult airway response follows a workflow similar to the adult model. Primary management is performed by the anesthesiologist; however, second-line backup differs, utilizing an adult intensivist for adults and a pediatric intensivist for children. Any healthcare professional involved in patient care may activate the DART. Upon activation, all on-duty members of the multidisciplinary response team are paged and immediately proceed to the event location.

Operational readiness relies on three pillars: (1) Pre-positioned adult and pediatric difficult-airway kits available on every floor and sector; the local team retrieves the kit and brings it to the scene. Each kit contains a checklist of items periodically restocked and checked by the pharmacy team and verified by the sector nursing staff to ensure the availability of all necessary devices in all sizes (videolaryngoscopes, supraglottic devices, bougies/guides, capnography, and surgical airway sets). (2) A clear role map at the scene (unit team lead, anesthesiology lead, anesthesia-practice nurse, and respiratory/physiotherapy support; critical-care physicians act as second-line leaders during off-hours). (3) A concise, mandatory handoff and capnography confirmation of airway

https://doi.org/10.1016/j.bjane.2026.844741

placement. Each event concludes with a 2–5 minute debrief and the completion of a structured electronic record to enable process control.

Training is the cornerstone of the program. We implemented structured onboarding and biannual refresher sessions using skill stations and high-fidelity simulations of high-stress scenarios, including anticipated and unanticipated difficult airways, "Cannot-Intubate/Cannot-Oxygenate" (CICO) situations, and tracheostomy emergencies. Program governance is provided by a multidisciplinary committee (Anesthesiology, Critical Care, Emergency, Nursing, Respiratory Therapy, and Quality/Safety), which oversees audits and continuous improvement using predefined indicators: response time, first-pass success, severe hypoxemia, need for surgical airway, complications, and documentation completeness. These metrics are tracked via a dashboard by hospital leadership.

Implementation revealed several challenges, including adherence to activation criteria, after-hours anesthesiology coverage, intra-hospital transit delays, and incomplete documentation. Mitigation strategies included empowering nursing staff to activate the team, designating intensivists as second-line leaders overnight, prioritizing elevators and transport workflows, and implementing real-time audits with clinician feedback. These countermeasures mirror lessons reported by mature international programs and proved feasible in our context.

Beyond algorithms, our experience highlights that difficult airway safety depends on institutional design, encompassing rapid detection, reliable mobilization, clearly defined roles, standardized equipment, simulation-driven competency, and continuous measurement. We therefore share a concise implementation manual covering governance, activation criteria, call and escalation logistics, equipment checklists, scene roles, stepwise clinical plans (Plan A/B/C with mandatory capnography), documentation templates, training curriculum, and performance targets. The manual is intentionally adaptable to the resource variability common across Brazilian hospitals.[3,4]

Limitations of our report include its single-center nature and the absence, to date, of time-series outcome analysis. We are initiating a before-and-after evaluation and invite collaboration toward a multicenter Brazilian registry focused on process and clinical outcomes (e.g., first-pass success, surgical airway rates, and mortality). Ethics committee approval was waived for this letter due to its retrospective and non-interventional nature.

In summary, a hospital-wide difficult airway rapid response team is feasible and effective when supported by clear activation criteria, rapid mobilization, standardized equipment, simulation-based training, and rigorous governance.

The complete implementation manual is available at the following link in the anesthesia section: https://medicalsuite.einstein.br/pratica-medica/SitePages/pathways.aspx.

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

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Received 24 November 2025; accepted 23 February 2026
Available online 6 March 2026

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Brazilian Journal of Anesthesiology

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