INPLASY

HEPCIDIN-INFORMED ANEMIA MANAGEMENT IN PERIOPERATIVE AND CRITICAL CARE: A SYSTEMATIC REVIEW

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Alshahrani, A.

Corresponding author:
Abdullah Alshahrani

amobark@kku.edu.sa

Author Affiliation:
King Khalid University.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 February 2026 and was last updated on 18 February 2026.

INTRODUCTION

Review question / Objective In patients with perioperative or critical illness–related anemia, does a hepcidin-guided strategy for iron and erythropoietin therapy improve hemoglobin recovery, transfusion rates, mortality, and clinical outcomes compared with ferritin/transferrin saturation–based or standard care approaches?

Rationale Perioperative and critical illness–associated anemia are linked to increased transfusion, complications, prolonged hospitalization, and mortality. Conventional iron markers such as ferritin and transferrin saturation are often unreliable in inflammatory states, where functional iron deficiency may exist despite normal or elevated ferritin levels. Hepcidin, the central regulator of iron metabolism, integrates iron status and inflammation and may better identify patients who will benefit from iron or erythropoietin therapy. Although hepcidin-guided strategies have been evaluated in critical care and selected screen-and-treat populations, its role in perioperative anemia management remains unclear. This systematic review aims to determine whether hepcidin-guided management improves hemoglobin recovery, transfusion exposure, and clinical outcomes compared with conventional ferritin/TSAT-based approaches.

Condition being studied Perioperative anemia and critical illness–associated anemia, including functional and absolute iron deficiency in inflammatory surgical and intensive care settings.

METHODS

Search strategy A systematic search was conducted in PubMed (MEDLINE), Embase, Cochrane CENTRAL, Scopus, and Web of Science from 1 January 2013 to 1 October 2025. The search combined terms related to hepcidin, anemia, perioperative or critical care settings, and iron therapy or transfusion. No language

restrictions were applied. Reference lists and trial registries were also screened to identify additional eligible studies.

Participant or population Adults or pediatric patients with perioperative or critical illness–associated anemia, including preoperative, postoperative, and intensive care populations, as well as analogous anemia-management contexts where iron therapy is clinically relevant.

Intervention Hepcidin-guided anemia management strategies in which iron therapy and/or erythropoiesis-stimulating agents are initiated, withheld, or adjusted based on measured serum hepcidin levels and predefined thresholds.

Comparator Conventional anemia management based on ferritin and/or transferrin saturation thresholds, standard care protocols, or routine iron supplementation without hepcidin guidance.

Study designs to be included Randomized controlled trials and comparative observational studies evaluating hepcidin-guided anemia management or assessing hepcidin as a predictive biomarker relevant to perioperative or critical care settings.

Eligibility criteria Studies were included if they were randomized controlled trials or comparative observational studies involving perioperative or critical illness–associated anemia, where hepcidin was used to guide treatment decisions or evaluated as a predictive biomarker for iron therapy. Studies had to report at least one relevant clinical outcome (e.g., hemoglobin change, transfusion, mortality, or complications). Non-comparative studies, case reports, animal studies, and conference abstracts without sufficient data were excluded.

Information sources Electronic databases including PubMed (MEDLINE), Embase, Cochrane CENTRAL, Scopus, and Web of Science were searched. Trial registries and reference lists of relevant studies were also screened to identify additional eligible articles.

Main outcome(s) The primary outcomes were hemoglobin response (change in hemoglobin or anemia correction) and red blood cell transfusion requirement. Secondary outcomes included mortality, complications, length of stay, iron/ESA utilization, and adverse events.

Additional outcome(s) Additional outcomes included 30- and 90-day mortality, postoperative or ICU complications, hospital or ICU length of stay, total iron and erythropoietin use, adverse events related to therapy, and patient-reported outcomes such as fatigue where available.

Data management Records were de-duplicated and screened independently by two reviewers. Data were extracted using a standardized, piloted form and cross-verified for accuracy. Discrepancies were resolved through discussion and consensus. Extracted data were organized in structured tables for narrative synthesis and meta-analysis where applicable.

Quality assessment / Risk of bias analysis Methodological quality was assessed independently by two reviewers. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, and observational studies were assessed using the ROBINS-I tool. Disagreements were resolved by consensus.

Strategy of data synthesis Data were synthesized narratively according to clinical context (perioperative, critical care, and analogous settings). When at least two studies reported comparable outcomes, random-effects meta-analysis was performed. Heterogeneity was assessed using the I^2 statistic, and certainty of evidence was evaluated using the GRADE approach.

Subgroup analysis Subgroup analyses were conducted based on clinical context (high vs low inflammation), type of iron deficiency (functional vs absolute), and differences in hepcidin thresholds or treatment algorithms where data were available.

Sensitivity analysis Sensitivity analyses were performed by restricting pooled estimates to randomized controlled trials and by comparing fixed-effect and random-effects models to assess the robustness of the findings.

Language restriction Studies in English were Included.

Country(ies) involved Saudi Arabia.

Other relevant information The review followed PRISMA 2020 guidelines and included duplicate screening, data extraction, and risk-of-bias assessment. Due to clinical heterogeneity across settings, meta-analysis was limited to comparable outcomes. Certainty of evidence was evaluated using the GRADE approach. This registration is

retrospective, as the review was completed prior to registration.

Keywords Hepcidin , Perioperative anemia, Critical illness ,Iron deficiency ,Patient blood management, Intravenous iron, Transfusion, Erythropoietin.

Dissemination plans The findings of this review will be submitted for publication in a peer-reviewed medical journal and presented at relevant scientific conferences. Results will also inform patient blood management strategies and future clinical research in perioperative and critical care settings.

Contributions of each author

Author 1 - Abdullah Alshahrani - Conceptualization, Methodology , Drafting , and Final Reviewing.
Email: amobark@kku.edu.sa