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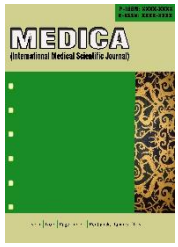

Hospital Management Strategies in Erythropoiesis-Stimulating Agents Therapy for Chronic Kidney Disease: A Systematic Literature Review

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Abstract

Anemia is a severe and costly complication in patients with end-stage Chronic Kidney Disease (CKD) undergoing long-term maintenance hemodialysis. The management of Erythropoiesis-Stimulating Agents (ESAs) therapy frequently faces challenges due to patient variability, dose inertia, and the lack of standardized managerial oversight. This study aims to analyze the strategic role of hospital management in implementing Clinical Practice Guidelines (CPGs) and Standard Operating Procedures (SOPs), evaluating their impact on clinical stability and economic outcomes. The method used is a Systematic Literature Review (SLR) of 21 scientific articles from Scopus, PubMed, and Google Scholar databases published between 2020 and 2025. Study quality, evidence heterogenity, and risk of bias were critically appraised by prioritizing methodological rigor and alignment with clinical implementation. The review results indicate that structured ESA protocols managed by specialist healthcare professionals, such as pharmacists or clinical nurse specialists, exhibit clinical effectiveness equivalent to conventional physician-led care while improving operational efficiency. The implementation of these protocols significantly lowers drug dosages, with studies showing a median weekly ESA dose reduction of up to 34% compared to discretionary care. Furthermore, achieving a high Hemoglobin Time-in-Range (TiR ≥60% within 10.0–11.5 g/dL) strongly correlates with a 19% decline in hospitalization rates and a 43% reduction in blood transfusion requirements. Economically, protocol-driven management demonstrates potential for substantial value; however, exact financial outcome should be interpretedwith caution due to the heterogenity of regional healthcare financing systems. With specific settings, proactive models reported annualized total healthcare cost savings reaching $33,921 per patient, including $6,201 in reduced transfusion costs. The novelty of this research lies in highlighting management systems and process discipline as critical factors influencing therapeutic success. As an implication, the formalization of SOPs and the integration of predictive tools like AI become crucial mandates for hospital management to ensure patient safety while maintaining institutional financial sustainability and ESG accountability.

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1. INTRODUCTION

Chronic Kidney Disease (CKD) has escalated into a public health crisis globally, imposing an enormous burden on healthcare infrastructures and national economies (Zheng et al., 2025) (Sunariyanti et al., 2023). The most resource-intensive phase of this disease is End-Stage Renal Disease (ESRD), where patients require life-sustaining Renal Replacement Therapy (RRT), predominantly in the form of chronic hemodialysis (HD) (Adejumo et al., 2020; Arodiwe et al., 2024; Rao et al., 2025). The cost associated with HD sessions alone represents the overwhelming majority of disease expenditure, often exceeding 86% of the total illness cost in numerous healthcare settings (Rao et al., 2025; Sunariyanti et al., 2023).

Anemia is prevalent in this patient population, largely due to diminished erythropoietin production by the failing kidneys (Muhammad-Baqir et al., 2023). This condition is directly linked to decreased quality of life, increased cardiovascular risk, and elevated mortality rates (Coutinho et al., 2025). Consequently, the administration of Erythropoiesis-Stimulating Agents (ESAs) is a cornerstone intervention, vital for raising Hemoglobin (Hb) levels, alleviating symptoms, and reducing the critical need for blood transfusions (Coutinho et al., 2025; Muhammad-Baqir et al., 2023).

Despite the clear therapeutic necessity, ESA management remains inherently complex. The goal is not merely to raise Hb but to maintain it within a narrow, targeted therapeutic window (10.0−11.5 g/dL) with minimal variability (Coutinho et al., 2025). This precision is essential because both excessively low and excessively high Hb levels correlate with poor outcomes: low levels lead to transfusions and hospitalization, while high levels (e.g., >12 g/dL) carry significant cardiovascular risks and are medically inappropriate (Coutinho et al., 2025; Ingrasciotta et al., 2021). The recently updated KDIGO 2026 guideline emphatically reinforce the necessity of strict management protocols to mitigate ESA-related cardiovascular risk and ensure precise, individualized dosing frameworks (Babitt et al., 2026; Del Vecchio et al., 2014)

The challenge is often compounded by systemic managerial failures. In environments lacking robust standardized practice, ESA dosing is susceptible to inertia, high inter-provider variability, and delayed adjustments (Ingrasciotta et al., 2021). This leads directly to the core problem investigated by this review: when ESA management is left to individual discretion rather than a disciplined protocol, it results in costly over-dosing, wasteful resource utilization, and preventable patient complications (Ingrasciotta et al., 2021; Retat et al., 2024).

The conceptual linkage between hospital management and patient outcomes can be understood through the Donabedian model of healthcare quality and the framework of Clinical Governance. Within this paradigm, institutional structures (e.g., formalized CPGs, AI-supported decision systems) directly standardise clinical processes (e.g., haemoglobin stability and cost minimization). Without standardized managerial oversight, ESA administration is highly vulnerable to clinical inertia and inter-provider variability, inevitably leading to dosing errors and financial leakage.

While previous systematic reviews and meta-analyses has extensively evaluated the pharmacological efficacy of different ESA types and the clinical transition to biosimilars, there remains a critical research gap regarding the operational delivery of these agents. Existing literature lacks a comprehensive synthesis focusing purely on the managerial and structural frameworks, such as multidisciplinary protocolization or nurse-led prescribing models, that govern ESA therapy. Consequently, evaluating these management system is essential to understand how operational discipline serves as the primary mechanism for mitigating the economic and clinical burdens of CKD anemia.

Therefore, this review strategically shifts the focus from the efficacy of the drug itself to the efficacy of the management system overseeing its use (Retat et al., 2024).

By synthesizing evidence on interventions such as pharmacist-led protocols, nurse specialist empowerment, and policy modelling, this study seeks to quantify the direct benefit that formalized hospital management systems bring to both clinical safety and financial sustainability in this high-risk patient group.

2. METHOD

The planning and execution of this Systematic Literature Review (SLR) adhered strictly to established systematic methodology, ensuring validity, transparency, and replicability (Carrera-Rivera et al., 2022). The protocol was designed to rigorously select and synthesize evidence that directly addresses the intersection of clinical practice, management intervention, and economic outcome within ESA therapy.

Search Strategy and Data Sources. The design and reporting of this Systematic Literature Review strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and reproductibility. The search was systematically executed across prominent academic databases, Scopus and PubMed. Scopus was selected as the primary source due to its multidisciplinary nature, ensuring broad coverage of literature at the intersection of hospital administration, health economics, and clinical practice. Google Scholar was subsequently used as a complementary source for grey literature screening and to ensure that highly relevant and up-to-date implementation studies from the industry or conference sectors were not overlooked. The publication window was strictly limited from 2020 through 2025 to ensure a focus on the most current clinical practices, technological advancements (e.g., AI integration), and post-COVID-19 health system reorganizations. A total of twenty-one eligible articles were identified and selected for final synthesis. Key search terms were combined using Boolean operators to ensure comprehensive coverage:

a. Intervention/Agent: *("Erythropoiesis-Stimulating Agents" OR "ESA" OR "Erythropoietin").*
b. Management/Policy: *("Protocol" OR "Guideline" OR "SOP" OR "Management" OR "Policy" OR "Cost-Effectiveness" OR "Efficiency").*
c. Population/Condition: *("Hemodialysis" OR "HD" OR "ESRD" OR "CKD").*

Table 1. Inclusion and exclusion criteria

Criteria	Detail	Rationale
Population (P)	Patients with Anemia of CKD Stage 5 undergoing maintenance Hemodialysis.	Direct relevance to the highest-cost, highest-complication patient group.
Intervention (I)	Implementation of management protocols (e.g., pharmacist-led, nurse specialist-led), institutional policies (e.g., reimbursement, biosimilar uptake), or advanced support systems (e.g., AI/DSS).	Focus on the direct impact of managerial/structural changes on practice.
Comparison (C)	Standard of Care (Physician-led), non-protocolized care, low Hemoglobin TiR, or Hypothetical "No Change" scenarios.	Essential for establishing quantifiable incremental value (Cost-Effectiveness, effectiveness gain).
Outcomes (O)	1) Clinical: Hb level achievement, stability (TiR), transfusion rate. 2) Economic: ESA/Iron utilization, cost-effectiveness, preventable	Direct alignment with the two primary Research Questions (RQ1: Clinical; RQ2: Economic).

	costs, healthcare resource utilization (HCRU).	
Study Design	Intervention Studies, Retrospective Cohort Studies, Policy Analyses, Cost-Effectiveness Analyses, Microsimulation/Modeling Studies.	To gather evidence across the spectrum of policy and clinical implementation.
Exclusion	Case Reports, Editorials, Non-English Publications, Studies focusing only on non-dialysis CKD (PGK 3-4) or Peritoneal Dialysis.	To maintain the focus on the specified high-cost HD population and ensure data interpretability.

Screening and Reviewer Agreement. Following the initial database search, all records were exported to reference management software (Mendeley) for the automated and manual removal of duplicates. The screening procedure was conducted in two phases. First, two independent reviewers screened the titles and abstracts against the predefined PICOC criteria. Second, the full texts of potentially eligible articles were retrieved and independently evaluated. Any discrepancies or disagreements regarding study inclusion or data extraction between the two reviewers were resolved through discussion to reach a consensus, or by adjudication from a third senior reviewer. Data extraction was performed using a standardized, pre-piloted spreadsheet to capture authors, study design, intervention details, and specific clinical/economic outcomes.

Research Questions and PICOC Alignment. The foundation of the analysis rests upon two rigorously formulated Research Questions (RQs), directly derived from the PICOC elements:

a. RQ1 (Clinical Outcomes): How does the implementation of formalized CPGs/SOPs for ESA administration affect Hb achievement/stability (O and P) and the reduction of blood transfusion rates (O) in anemic CKD Stage 5 HD patients?
b. RQ2 (Cost Efficiency): What is the quantifiable cost efficiency and economic value generated by ESA therapy administered under CPGs/SOPs (I) compared to non-protocolized practice (C) within the constraints of hospital management (C and I)?

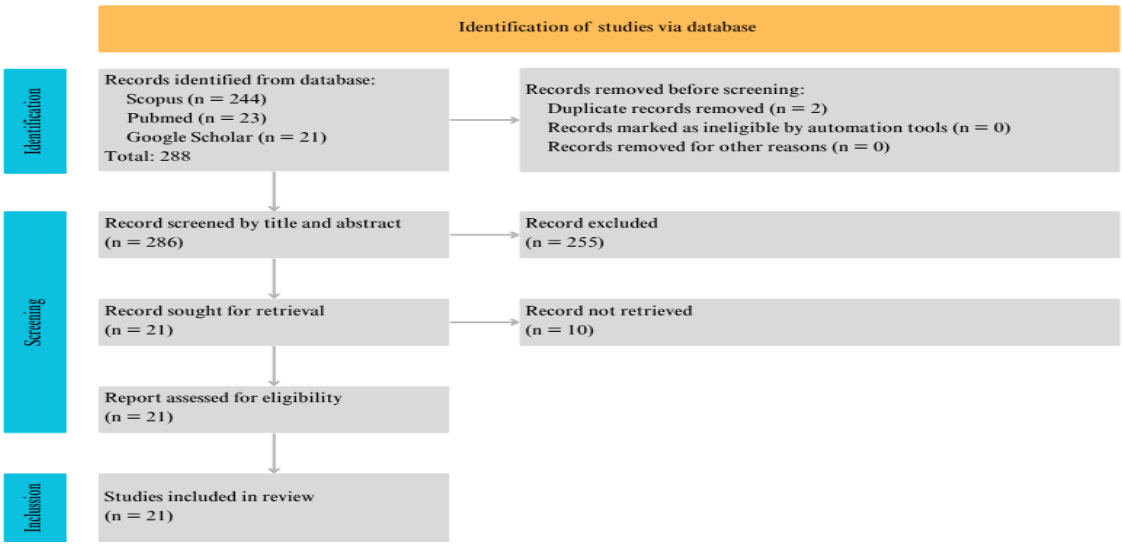

Figure 1. PRISMA Diagram

Risk of Bias and Quality Assessment.

A standardized data extraction form was utilized to ensure all relevant metadata and findings were meticulously captured (Carrera-Rivera et al., 2022). For the purposes of this review, Quality Assessment (QA) focused on methodological rigor and direct relevance of the reported findings to the defined RQs. The primary goal of the QA was to prioritize quantitative outcome measures over purely descriptive accounts. The included studies were critically appraised based on study design, specifically distinguishing between randomized/quasi-experimental studies and observational cohort studies. This critical appraisal was primarily focused on the alignment of the study's design with its conclusions regarding management interventions and economic outcomes, ensuring that the most robust evidence, characterized by a clear intervention (I) and quantifiable outcome (O), received the highest priority in the final narrative synthesis.

To rigorously evaluate the rsik of bias and methodological quality across a diverse set of study design (ranging from randomized intervention to economic modelling and observational cohort), we employed the Mixed Methods Appraisal Tool (MMAT) version 2018. Two independent reviewers critically appraised each included study based on its specific methodological category. Studies were assessed for selection bias, confounding variables, and the integrity of outcome data, ensuring that only robust evidence informed the final synthesis.

3. RESULTS AND DISCUSSION

The twenty-one selected studies encompass a broad range of management interventions across diverse global settings. They include four randomized/quasi-experimental intervention studies (focusing on pharmacist/nurse-led protocols), eight retrospective cohort analyses (quantifying TiR and HCRU), five cost-effectiveness analyses/microsimulation models (assessing economic impact), and four policy/operational analyses. The synthesized results below reflect a robust consensus that formalized management, regardless of the specific model (e.g., human-led vs. AI-supported), consistently delivers superior outcomes compared to discretionary care.

Table 1. Characteristic of Included Study

No.	Article Title	Country Setting	LoE*	QA**	Authors & Year	Study Design	Intervention / Management	Relevance to RQ1 (Clinical)	Relevance to RQ2 (Cost)
1	Health-economic evaluation of an AI-powered decision support system for anemia management in in-center hemodialysis patients	Germany	IV	High	(Gandjour et al., 2025)	Markov Model Simulation (Economic Evaluation)	Use of the Anemia Control Model (ACM), an AI-powered decision support system	Indirect: ACM associated with a 17% reduction in hospitalization and decreased inappropriate ESA use	Direct & Major: ACM dominant (higher QALY and lower cost) vs standard care; reduced ESA cost
2	Direct healthcare costs of chronic kidney disease management in Italy: biosimilar uptake and appropriate ESA use	Italy	III	High	(Ingrasciotta et al., 2021)	Retrospective, Multicenter Cohort (Policy & Cost Analysis)	Regional health policy promoting biosimilar use and preventing inappropriate ESA use	Indirect: 62% inappropriate ESA use (Hb >12 g/dL) may cause adverse clinical outcomes	Direct & Major: Preventable cost €167,641/year; 25% biosimilar uptake saved 8–11% ESA costs
3	Real-world treatment patterns of renal anemia in hemodialysis patients: the RRAHD study	South Korea	III	High	(H. J. Kim et al., 2020)	Multicenter Cohort (Real-world)	DialysisNet EMR-based patient management tool	Direct: 99.3% ESA use, mean Hb 10.5 g/dL; higher Hb variability linked to lower Hb maintenance	Indirect: Focused on ESA dose and transfusion frequency; no direct cost analysis

4	Comparative study of treatment outcomes and mortality among hemodialysis patients by insurance type	South Korea	III	High	(K. M. Kim et al., 2025)	Retrospective Cohort (Policy Analysis)	Fixed-payment system (Medical Aid) vs National Health Insurance (NHI)	Direct: Fixed-payment group achieved lower target Hb; more EPO use but less darbepoetin/CERA	Direct: Fixed-payment policy led to cheaper drug patterns (cost saving) but worse outcomes
5	A nurse prescriber-led protocol for anaemia management in established haemodialysis patients	Ireland	III	High	(George & McCann, 2020)	Retrospective Cohort (Intervention Study)	Nurse prescriber-led protocol vs physician-led approach	Direct: Equally effective in Hb target; reduced IV iron use and improved iron indices	Direct: Lower ESA dose (ns); reduced IV iron implies potential cost savings
6	Impact of an interdisciplinary ESA dosing protocol at an outpatient community hospital hemodialysis unit	USA	III	High	(Dubovetsky et al., 2022)	Retrospective Cohort (Intervention Study)	Pharmacist-directed ESA dosing protocol vs standard care	Direct: Similar Hb control (TTR); no difference in transfusion or CV events	Direct & Major: ESA dose ↓34% (10,064 vs 15,227 units, p=.035); weekly ESA cost ↓$232→$154
7	Prevalence, prescription patterns, and quality of life of anaemia in adults with chronic renal disease	India	IV	Moderate	(Sandeep et al., 2023)	Cross-sectional Observational	ESA prescription patterns (Epoetin, Darbepoetin)	Indirect: Epoetin most prescribed (15.06%); ESA improved QoL and reduced morbidity/mortality	Not relevant: Focused on prescription/QoL, not cost or efficiency

8	Variation in health plan coverage of ESAs for anemia due to CKD	Usa	IV	High	(Margaretos et al., 2021)	Policy Analysis	Health plan coverage for ESA (darbepoetin, epoetin, etc.)	Indirect: 28% plans stricter than FDA label, limiting patient access	Direct: Insurance variation affects both patient access and treatment cost
9	Predicting anemia management in dialysis patients using open-source machine learning libraries	Japan	IV	High	(Inoue et al., 2025)	Intervention Study (ML Experiment)	Machine learning model predicting physician ESA/Iron dose adjustment behavior	Indirect: ML accurately predicts physician behavior, suggesting improved care efficiency	Indirect: Aims to minimize ESA dose and adverse effects, improving cost efficiency
10	Efficacy and safety of a personalized protocol designed to balance Hb levels in hemodialysis patients led by CNS	Israel	II	High	(Israeli et al., 2025)	Prospective Comparative Intervention (Pre–Post Protocol)	Personalized protocol led by Clinical Nurse Specialist vs Nephrologist-led standard care	Direct: CNS-led care equally effective/safe in maintaining Hb, TSAT, URR	Direct: ESA adjustments and physician consults reduced, improving efficiency
11	Cost analysis among CKD patients undergoing haemodialysis in tertiary care hospital	India	IV	Moderate	(Rao et al., 2025)	Cross-sectional Descriptive	Cost analysis of HD care	Not relevant: Cost focus only, no Hb outcome	Direct: HD 47.99% of cost; ESA 10.05%; more HD/week = higher total cost
12	Direct and indirect cost of CKD	Nigeria	IV	Moderate	(Arodiwe et al., 2024)	Descriptive Cross-sectional	Cost of HD treatment	Not relevant: Focused on cost burden only	Direct: HD 86.1% total cost; 88% pay out-of-pocket,

	treatment at the Renal Unit, University of Nigeria Teaching Hospital								high financial burden
13	Cost implication of inpatient CKD care in a tertiary hospital in Southwest Nigeria	Nigeria	IV	Moderate	(Adejumo et al., 2020)	Retrospective Descriptive	Inpatient CKD cost analysis	Not relevant: Focus on inpatient costs only	Direct: Mean inpatient cost $431; major contributors dialysis, ward, pharmacy
14	Cost analysis of CKD patients in Indonesia	Indoneisa	IV	High	(Sunariyanti et al., 2023)	Cross-sectional (Cost Analysis)	Hospital cost across regions (Regional I & III)	Not relevant: Cost components only	Direct & Major: HD is highest cost; regional variation shows efficiency potential
15	Evaluation of SOP in Tabanan Regional Hospital: usage of restricted antimicrobials	Indoneisa	IV	Moderate	(Noviyani et al., 2024)	Qualitative (SOP Evaluation)	Evaluation of antibiotic SOP	Not relevant: Antibiotic SOP, not ESA	Not relevant: Focused on antibiotic costs
16	Impact of Erythropoietin on anemia in ESRD patients on hemodialysis	Iraq	IV	Moderate	(Muhammad-Baqir et al., 2023)	Cross-sectional	EPO-Zeta administration	Direct: Hb ↑ from 8.24±1.77 to 9.57±1.35 g/dL	Not relevant: Focused on clinical/biochemical outcomes only

17	Hb stability impact on healthcare resource utilization and costs among dialysis-dependent ESKD patients	USA	III	High	(Coutinho et al., 2025)	Retrospective Observational (Hb Stability & Cost)	Hemoglobin Time-in-Range (TiR) analysis	Direct & Major: Hb 10–11.5 g/dL, TiR ≥60% → 43–46% fewer transfusions, 19–20% fewer hospitalizations	Direct & Major: Higher TiR reduced total cost by $33,921; transfusion cost ↓$6,201
18	Optimizing anemia management using AI for hemodialysis patients	South Korea	IV	High	(Kang et al., 2024)	Retrospective (AI Experiment)	AI model (GAM) for ESA dosing recommendation	Direct: GAM ESA dosing accuracy 0.78 vs experts; RBC transfusion prediction accuracy 0.99	Indirect: AI optimizes ESA dose, prevents unnecessary transfusions, improving cost efficiency
19	Prevalence of anemia in CKD patients in Japan: data from J-CKD-DB	Japan	IV	High	(Sofue et al., 2020)	Cross-sectional Cohort (Treatment Pattern)	ESA utilization rate analysis	Direct: ESA use low (St.4 7.9%, St.5 22.4%); Hb lower in ESA-treated group	Not relevant: Prevalence/utilization focus, not cost
20	Analysis of SOP implementation for new patient admissions at Siti Halimah Kandangan Hospital	Indoneisa	V	Moderate	(Yusuf & Fauji, 2025)	Qualitative Descriptive (SOP Evaluation)	Implementation of new patient admission SOP	Not relevant: SOP unrelated to anemia/ESA	Not relevant: Focus on operational quality
21	Inside Anemia of CKD: Projecting the Future Burden	China	IV	High	(Retat et al., 2024)	Microsimulation (Economic & Policy Evaluation)	Hypothetical 5% annual reduction in moderate/sever	Direct: Proactive intervention reduced moderate/severe	Direct & Major: 5-year saving ¥3.9B; highlights economic value of

	of Anemia of CKD	e anemia prevalence	anemia from 3.3M→2.7M cases	proactive management

*Level of Evidence (LoE)
** Quality Assessment (QA)
The included studies represent a diverse level of evidence and geographic settings. Based on the MMAT assessment, the majority studies demonstrated moderate to high methodological quality, providing a robust foundation for our synthesis.

Clinical Outcomes: Efficacy and Stability of Hemoglobin (RQ1).

The implementation of formalized management protocols significantly enhanced the predictability and stability of Hb levels, addressing a critical clinical goal that standard, discretionary care often fails to achieve. Equivalence of clinical efficacy across care models. A prominent theme in the contemporary literature is the successful delegation of ESA management responsibilities to non-physician specialists, enabled by clear protocols. This shift demonstrates that optimal outcomes are dependent on process discipline rather than solely physician seniority.

a. Nurse and Pharmacist-Led Models: Multiple comparative studies confirmed that when certified personnel, such as Clinical Nurse Specialists (CNS) or Pharmacists, managed ESA dosing protocols, the resulting clinical outcomes were statistically equivalent to traditional physician-led management. Specifically, these models maintained mean target Hb levels and ensured adherence to core dialysis quality indicators (such as URR and TSAT) with comparable efficacy (Dubovetsky et al., 2022; Israeli et al., 2025).
b. The establishment of a Nurse Prescriber-led Protocol was found to be as effective as a physician's non-protocolized approach in achieving Hb target levels (Ng et al., 2023).
c. Management Efficiency Gains: Beyond clinical equivalence, the adoption of CNS-led protocols explicitly demonstrated an operational efficiency gain by reducing the overall administrative burden on specialist physicians. These protocols led to a quantifiable decrease in the frequency of ESA dose adjustments and the need for nephrologist consultations for routine prescription updates, redirecting specialist time towards complex cases (Israeli et al., 2025).

Hemoglobin Stability (tir) as the Critical Clinical Metric. The most powerful predictor of positive clinical and economic outcomes was found to be Hemoglobin Time-in-Range (TiR), a metric reflecting the stability and consistency of the Hb level, which is a direct reflection of successful, disciplined management (Coutinho et al., 2025).

a. TiR and Complication Reduction: Studies rigorously quantifying patient outcomes based on TiR clearly established its central role: patients maintaining high TiR (≥60% of measurements within the 10.0−11.5 g/dL range) experienced superior outcomes compared to those with low TiR. This stability translated directly into a 19% lower incidence of inpatient hospital visits and a 43% lower incidence rate of costly Red Blood Cell (RBC) transfusions (Coutinho et al., 2025).
b. Technological Reinforcement of TiR: Advanced management interventions validated the use of predictive tools to reinforce TiR: studies demonstrated that sophisticated AI/Machine Learning (ML) models could be developed to accurately predict the optimal ESA dose (0.78 concordance with expert opinion). Crucially, these models achieved 99% accuracy in predicting the urgent need for RBC transfusions ahead of time, effectively giving practitioners a proactive managerial tool to prevent acute anemia events which severely destabilize TiR and incur massive costs (Kang et al., 2024).

Economic Efficiency And Resource Utilization (RQ2)

The economic analysis rigorously demonstrated that systematic management protocols generate massive financial value, primarily through drug utilization optimization and, most importantly, the elimination of costly, preventable complications. Quantifiable drug cost savings through optimization. Structured dosing protocols proved superior to discretionary care in controlling ESA drug expenditure, showing that financial savings are a direct function of improved prescription discipline.

a. Pharmacist-Led Cost Control: The implementation of a pharmacist-directed ESA dosing protocol was empirically linked to a significant reduction in drug utilization. Compared to standard care, the protocolized group required a median weekly ESA dose that was 34% lower (10,064 units vs. 15,227 units). This direct reduction immediately translated into a 34% reduction in drug-associated costs (Dubovetsky et al., 2022). This finding, derived primarily from studies in high-income settings with standardized reporting systems (e.g., North American and European outpatient centers), underscores that even in settings with generally strong adherence, protocolization can yield massive incremental savings. The substantial reduction is likely attributed to eliminating habitual over-dosing prevalent in physician-discretionary models.
b. Conserving Auxiliary Drug Costs: The management imperative extended to auxiliary drugs: the adoption of a Nurse Prescriber-led Protocol led to a statistically significant reduction in intravenous (IV) Iron dosage required by patients, indicating integrated management improved the efficiency of ESA response by adequately managing iron stores, thereby avoiding unnecessarily high dosing schedules (Ng et al., 2023).

The overwhelming cost of preventable management failure

The most significant finding relevant to hospital management's fiduciary responsibility is that the financial burden imposed by management failures (i.e., poor protocol adherence) vastly overshadows the cost of the drug itself.

a. Economic Impact of Inappropriate Use: An observational study highlighted the immense economic cost of deviating from therapeutic boundaries: a massive 62.0% of patients in the observed cohort were documented as receiving inappropriate ESA maintenance therapy (Hb > 12 g/dL), signifying a widespread management failure. The cumulative cost of this failure was quantified, estimating preventable costs from inappropriate ESA use at over €167,641 per year at the investigated institutional level. This cost vastly exceeds the marginal savings typically sought through biosimilar adoption, repositioning the management process itself as the primary cost driver (Ingrasciotta et al., 2021).
b. TiR and HCRU Avoidance: The economic value of achieving high TiR was dramatically quantified: improved Hb stability generated substantial savings by reducing costly HCRU. Patients with high TiR accrued annualized total healthcare costs that were $33,921 lower than those with low TiR. Specifically, this included a verifiable reduction in RBC transfusion costs by $6,201 per patient per year (Coutinho et al., 2025). Since HD costs alone are universally recognized as the single largest expenditure, avoiding secondary costs like transfusions and hospitalization (the costs of clinical instability) is paramount to financial viability (Arodiwe et al., 2024; Rao et al., 2025). The scale of this saving ($33,921 per patient per year), which significantly outweighs the cost of the ESA drug itself, re-emphasizes that the primary financial leverage for hospital management is the prevention of clinical instability (hospitalization and transfusions), not simply negotiating drug procurement (Coutinho et al., 2025). This trend was consistently observed across various countries utilizing different healthcare financing models.

Policy modeling and strategic value

Modeling studies provided a macro-level validation of the cost-effectiveness of management-led, proactive interventions, offering crucial evidence for policy advocacy.

a. Value of Proactive Policy: A sophisticated microsimulation model projected the future burden of anemia and quantified the effect of a hypothetical management intervention (a proactive policy achieving a 5% annual reduction in moderate/severe anemia prevalence). This intervention demonstrated that

proactive management results in a cumulative total direct healthcare cost saving of ¥3.9 Billion over a five-year period, effectively transforming a mounting cost projection into a massive, quantifiable saving (Retat et al., 2024).

b. Impact of Reimbursement Policy: A comparative study examining healthcare financing models (fixed-payment *Medical Aid* vs. *National Health Insurance* systems) highlighted how top-down policy directly influences ESA prescription decisions. The fixed-payment policy incentivized physicians toward lower prescription rates of more expensive, higher-potency ESAs (e.g., Darbepoetin). While fiscally conservative for the payer, this practice correlated with significantly lower achievement of therapeutic goals for the disadvantaged patient group, demonstrating that poorly structured financial policies can compromise clinical quality and that management must design internal protocols to safeguard against such compromises (K. M. Kim et al., 2025).

c. Operational Management: The efficacy of specialized clinical protocols is built upon foundational operational discipline, emphasizing that management must focus on general SOP implementation and control to overcome issues like ineffective service speed and technical constraints (Khan et al., 2024).

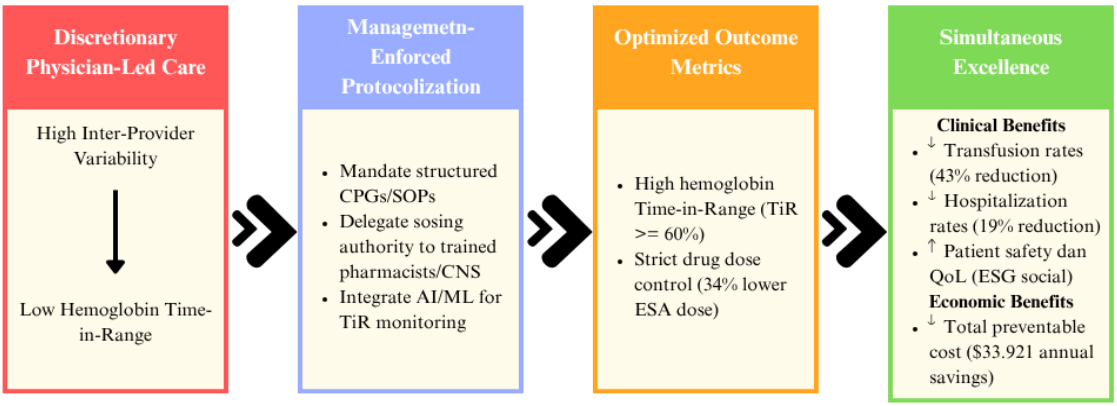

Figure 2. Managerial intervention flow and simultaneous outcome mechanism

DISCUSSION

The synthesis of contemporary evidence mandates a paradigm shift: the challenge of ESA management is fundamentally a challenge of institutional process and management discipline, not merely a deficit of clinical judgment. Hospital management holds the direct, fiduciary, and clinical responsibility to formalize the management process to achieve predictable, efficient, and high-quality patient outcomes.

Reframing Quality: From Discretion to Discipline

The core finding is that optimal outcomes are achieved not solely through physician expertise but through the consistent application of systematic protocols (Dubovetsky et al., 2022; Kang et al., 2024). The economic rationale for adopting non-physician-led protocols is overwhelming: delegating ESA dose adjustments to empowered staff (pharmacists, CNS) not only retains clinical quality but unlocks significant financial savings and operational efficiency (reduced physician consultations) (Israeli et al., 2025). The era of reactive, purely physician-discretionary ESA dosing must yield to one of protocolized precision, where consistency is enforced by management.

The Direct Cost of Non-Adherence

The data re-emphasizes that the greatest financial threat is internal operational leakage. The cost of inappropriate ESA dosing (Hb > 12 g/dL) represents a massive

preventable waste at the micro-level (Ingrasciotta et al., 2021). This leakage directly undermines the hospital's financial stability, serving as empirical proof that poor management discipline is fiscally irresponsible. Management must institute robust audit mechanisms that directly link deviations from the defined CPG to financial reports, establishing accountability for clinical inefficiency (Bhandari et al., 2025).

The Power of Proactive Management

The strategic value of prevention is clearly demonstrated through the success of the Hemoglobin TiR metric. High TiR is the definitive marker of success, yielding multi-faceted benefits: fewer RBC transfusions, fewer hospitalizations, and dramatic total cost savings (Coutinho et al., 2025). Proactive policies that integrate technology (AI/ML) to achieve high TiR provide a roadmap for future management, allowing the system to predict crises (with exceptionally high accuracy for transfusion alerts) rather than react to them, thus moving the institution toward the proven cost savings identified in the long-term microsimulation modelling (Israeli et al., 2025; Retat et al., 2024).

Heterogeneity and Conflicting Findings

While the overarching consensus supports protocolized management, significant heterogeneity exists across the reviewed studies regarding methodological designs, regional healthcare financing, and specific clinical endpoints. For instance, regarding the clinical outcome of blood transfusions, Coutinho et al. (2025) reported a substantial 43% reduction associated with maintaining high Hemoglobin TiR. Conversely, Dubovetsky et al. (202) observed no significant difference in transfusion rates despite successfully reducing the Esa dose by 34% via a pharmacist-led protocol. The conflict likely stems from differences in study populations and primary objectives: Dubovetsky focused on drug dose optimization in an already stable outpatient cohort, whereas Coutinho analyzed broader, long-term resource utilization across a highly variable patient population.

Furthermore, economic outcome exhibit substantial geographic heterogeneity. Evidence from fixed-payment or strict single-payer systems, such as in South Korea (Kim et al., 2025), highlights that overly restrictive reimbursement policies may inadvertently drive cheaper prescription patterns but result in a failure to achieve optimal therapeutic target. This contrasts sharply with models emphasizing proactive, AI-driven management investments, which demonstrate massive long-term cost savings by prioritizind clinical stability over immediate drug cost caps (Retat et al., 20204).

Navigating Implementation Barriers and Change Management

While the economic and clinical mandate for formalized protocols is clear, hospital management must proactively address systemic barriers to change. The most common challenges highlighted in the operational literature include resistance from senior medical staff who may view non-physician-led dosing as infringing on professional autonomy. To mitigate this, management must frame the protocol not as a loss of control, but as an operational efficiency gain that reallocates specialist physician time for complex care (Coutinho et al., 2025; Retat et al., 2024).

Furthermore, the initial investment required for specialized training of pharmacists and nurses, and the integration of new technology (like AI/ML systems) to support TiR monitoring, may present a temporary fiscal hurdle. Management must view these as critical cost-avoidance investments, noting that the cost of non-adherence vastly outweighs the upfront cost of establishing system integrity. Finally, success depends on foundational operational discipline to overcome basic issues like inadequate SOP implementation speed and technical constraints across the facility (Coutinho et al., 2025; Kang et al., 2024). Contemporary guidelines, such as those from the UK Kidney Association (2024) increasingly advocate for multi-professional

workforce plans, recognizing that disciplined SOP execution by specialized staff is paramount (UK Kidney Association, 2026).

The findings of this review highlight a clear managerial imperative within the Environmental, Social, and Governance (ESG) framework. From a Social (S) perspective, maintaining a high Hemoglobin Time-in-Range (TiR) led to substantial clinical improvements, including fewer transfusions and fewer hospitalizations. These outcomes demonstrate that adherence to clinical practice guidelines (CPGs) is not only financially sound but also an ethical responsibility that enhances patient safety, quality of life, and institutional social accountability.

From a Governance (G) standpoint, non-compliance with standardized CPGs results in preventable financial losses annually due to inappropriate dosing. Implementing protocol-based management represents a fundamental governance practice that ensures resource stewardship, transparency, and organizational integrity. By linking multidisciplinary clinical protocols with financial accountability, hospital management can strengthen internal governance systems and promote long-term sustainability within healthcare institutions.

Managerial Mandates for System Integrity

Managerial mandates are essential to ensure the integrity, consistency, and sustainability of the ESA management system within hospital settings. Strong organizational leadership is required not only to develop evidence-based clinical governance but also to foster interdisciplinary collaboration, improve accountability, and optimize resource utilization. These managerial actions should be integrated into hospital policies to minimize unwarranted variation in practice while enhancing patient outcomes and cost-effectiveness.

The first managerial priority is the protocolization of ESA management through the immediate establishment of a formal, multidisciplinary Clinical Practice Guideline (CPG) or Standard Operating Procedure (SOP). The protocol should provide explicit dosing algorithms, standardized monitoring procedures, and clearly define the roles and responsibilities of each professional involved in ESA therapy. In particular, dosage adjustment responsibilities should be delegated to appropriately trained non-physician personnel, such as pharmacists or Clinical Nurse Specialists (CNS), under a structured collaborative care model. Equally important is visible and consistent support from hospital leadership to ensure organizational commitment, overcome professional resistance to role redistribution, and facilitate successful implementation of the protocol across clinical departments (Dubovetsky et al., 2022; Israeli et al., 2025).

The second managerial mandate focuses on strengthening financial accountability by integrating clinical performance with financial oversight. Hospitals should establish a transparent reporting system in which hemoglobin (Hb) stability, measured as Time in Range (TiR), together with the frequency of inappropriate ESA utilization, are monitored as key institutional performance indicators. Routine reporting of these indicators enables administrators to identify preventable inefficiencies, including unnecessary ESA dose escalation and avoidable blood transfusions, both of which contribute substantially to healthcare expenditures. By directly associating adherence to the CPG with financial performance and budget management, hospitals can encourage greater compliance with evidence-based practices while simultaneously improving operational efficiency and resource allocation (Coutinho et al., 2025).

The third managerial priority is sustained investment in education and workforce development. Effective implementation of a sophisticated ESA management protocol depends on the competency of non-physician healthcare professionals who are entrusted with expanded clinical responsibilities. Therefore, hospitals should prioritize comprehensive education, specialized training programs, and competency-based certification for pharmacists, nurses, and other relevant personnel involved in ESA

management. Continuous professional development not only enhances adherence to standardized protocols but also strengthens clinical decision-making, improves patient safety, and reduces unnecessary treatment costs. Such investments should be viewed as strategic initiatives that support long-term improvements in healthcare quality, operational efficiency, and cost avoidance (Israeli et al., 2025; Ng et al., 2023).

4. CONCLUSION

This Systematic Literature Review highlights establishes that the optimal management of ESA therapy in HD patients is a crucial responsibility of hospital administration. The synthesized evidence suggests that the adoption of standardized, technologically-supported, and rigorously enforced CPGs/SOPs represents a highly promising approach associated with simultaneous improvement in clinical outcomes (high Hb stability, low transfusion rates) and fiscal health (cost savings from drug optimization and complication avoidance). However, given the methodological heterogeneity and the observational nature of many included studies, these findings demonstrate strong associations rather than definitive causal effects. to overcome the current literature limitations, further prospective and multicenter studies are fundamentally needed to rigorously validate the long-term clinical and economic efficacy of these management-driven ESA protocols.

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