Transfusion and Iron Supplementation: Key Therapies for Anemia after Acute Gastrointestinal Bleeding

PhD Thesis

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1. Publications

1.1. Scientific metrics (as of 10.09.2025)

Number of **publications related to the subject of the thesis**: Cumulative impact factor of publications related to the thesis: Q1: 3 (D1: 2), Q2: 0, Q3: 0, Q4: 0	**3** **10.700**
Number of **other first author published articles**: Cumulative impact factor of the published articles: Q1: 2 (D1: 1), Q2: 0, Q3: 0, Q4: 0	**2** **10.100**
Number of **total published articles**: Cumulative impact factor of the published articles: Q1: 49, Q2: 3, Q3: 0, Q4: 0	**52** **234.412**
Number of **total citation according to Google Scholar**: Hirsch Index:	**478** **12**
Number of **total citation according MTMT**: Hirsch Index:	**327** **10**

1.2. Publications related to the subject of the thesis

N=**3**, cumulative impact factor=**10.700**

1. **Teutsch, B.**, Veres, D. S., Pálinkás, D., Simon, O. A., Hegyi, P., Erőss, B. (2023). Potential benefits of restrictive transfusion in upper gastrointestinal bleeding : a systematic review and meta-analysis of randomised controlled trials. SCIENTIFIC REPORTS, 13(1). http://doi.org/10.1038/s41598-023-44271-8. Published (**D1, IF: 3.900**).

2. **Teutsch, B.**, Abonyi Tóth, Z., Ferencz, O., … Erőss, B. Hemoglobin decrease predicts untoward outcomes better than severity of anemia. SCIENTIFIC REPORTS. 14(1). http://doi.org/10.1038/s41598-024-82237-6. Published (**D1, IF: 3.900**).

3. **Teutsch, B**., Váncsa, S., Farkas, N., Szakács, Z., Vörhendi, N., Boros, E., … Erőss, B. (2023). Intravenous ferric carboxymaltose versus oral ferrous sulfate replacement in elderly patients after acute non-variceal gastrointestinal bleeding (FIERCE) : protocol of a multicentre, open-label, randomised controlled trial. BMJ OPEN, 13(3). http://doi.org/10.1136/bmjopen-2022-063554. Published (**Q1, IF: 2.900**).

2. Vision

To enhance the clinical management of patients with acute gastrointestinal bleeding (GIB) by developing and promoting evidence-based transfusion and iron supplementation strategies.

3. Mission

The primary aim of our comprehensive research is to identify key triggers that can assist clinicians in optimizing red blood cell (RBC) transfusion strategies after acute GIB, ultimately improving survival rates and reducing adverse events. This aim will be achieved through an extensive literature review and a detailed analysis of prospectively collected registry data.

The secondary aim is to design and implement a randomized controlled trial (RCT) to evaluate the efficacy of iron supplementation in anemic, elderly patients with potential comorbidities after an acute non-variceal GIB (NVUGIB) episode. This trial seeks to prevent complications, enhance quality of life (QoL), and improve healthcare efficiency.

4. Specific goals

- To determine the optimal red blood cell transfusion strategy for patients with upper gastrointestinal bleeding (UGIB).
- To assess the short and long-term impact of restrictive transfusion on mortality, rebleeding and complications.
- To develop evidence-based recommendations for integrating hemoglobin (Hb) change into clinical guidelines improving transfusion and treatment protocols for patients with GIB.
- To evaluate the efficacy and safety of intravenous (IV) and oral iron supplementation in elderly patients following an acute NVUGIB episode.

5. Background

5.1. Gastrointestinal bleeding

Acute GIB is a critical medical emergency that poses substantial economic challenges and demands immediate care, with an in-hospital mortality rate of about 10%.[1-3] In recent decades, improvements in prevention, diagnostic techniques, and treatment strategies have resulted in reduced hospitalization rates and better clinical outcomes.[4,5] Despite these advancements, mortality rates associated with massive bleeding remain twice as high as those linked to non-severe GIB.[6]

5.2. Transfusion

Managing acute blood loss is essential and can be life-saving for individuals with moderate to severe anemia. RBC transfusion is a common component of pre-endoscopic care, which aims to enhance microcirculation and improve tissue oxygenation.[7,8] This has led to growing interest in determining the most appropriate Hb threshold for initiating transfusion.[9-11] Initiating transfusion at a higher threshold (Hb 90–100 g/L) under a liberal strategy may lead to serious complications, such as volume overload. As a result, the potential advantages of a restrictive transfusion approach (Hb 70–80 g/L) have become a key focus of clinical research.[12]

Numerous studies have demonstrated the safety and effectiveness of restrictive RBC transfusion strategies in UGIB. However, RCTs have employed differing thresholds for defining when to begin transfusion, creating variability in treatment standards.[9,13-15] Furthermore, close follow-up after discharge is critical, as adverse outcomes remain prevalent in the months following treatment.[16,17]

In addition to absolute Hb levels, the relative change in Hb (ΔHb%) has proven to be a particularly important factor in transfusion decision-making. Extensive cohort studies in surgical populations indicate that a ΔHb% exceeding 50% is associated with a higher risk of mortality, even when the lowest Hb level (nadirHb) remains above the commonly used transfusion threshold of 70 g/L.[18,19]

5.3. Iron supplementation

Patients with significant gastrointestinal blood loss often develop iron-deficiency anemia (IDA), even if they receive blood transfusions. Post-transfusion evaluation and targeted iron supplementation are essential to replenish iron stores and aid recovery.[20]

Patients with IDA are commonly treated with either one to six IV iron infusions or a three-month regimen of oral iron supplementation. The recommended daily dose for oral iron is 100–200 mg of elemental iron, making it a simple treatment option.[21] However, gastrointestinal side effects are reported by up to 70% of patients, which often leads to poor adherence and compliance.[20] IV iron therapy, on the other hand, requires trained healthcare providers and close supervision. Although IV iron is costlier, it requires fewer doses and causes fewer gastrointestinal side effects compared to oral iron.[22,23] Furthermore, IV iron replenishes iron stores more quickly, usually within three to six weeks, leads to faster QoL improvements, and is particularly effective for patients with poor compliance.[22,24,25]

Current clinical guidelines recommend oral iron as the preferred initial treatment. However, IV iron is recommended in cases of severe bleeding or when adherence to oral therapy is a challenge. Despite these recommendations, there is a lack of specific guidance on the most appropriate approach for elderly patients (over 65 years) who often have multiple comorbidities.[21]

5.4. Objectives and aims

In this thesis, we employed a combination of three clinical research methodologies – a meta-analysis (**1**), a registry analysis (**2**), and a randomized controlled trial protocol (**3**)-, to investigate the role of Hb in the initation of transfusion in acute GIB related-anaemia and to assess the usefullness of IV iron for the prevention of untoward hard clinical endpoints following a GIB episode in elderly patients.

The objectives for each project were defined as follows:

-With the meta-analysis (**1**) we aimed to assess the short and long term efficacy and safety of restrictive transfusion compared to a more liberal modality.

-The registry analysis (**2**) aimed to detect the predictive value of Hb decrease in the transfused patients and the general population for in-hospital mortality and need for urgent intervention.

-With the third study (**3**) we aim to assess the efficacy and safety of IV iron compared to oral iron in elderly patients after acute NVUGIB episode.

6. Potential benefits of restrictive transfusion in upper gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials

6.1. Introduction

Numerous studies have validated the effectiveness and safety of a restrictive RBC transfusion strategy, initiated at Hb levels of 70-80 g/L, compared to a liberal approach set at 90-100 g/L for UGIB. However, RCTs have utilized differing thresholds to determine when to commence the intervention.[9,13-15]

The European Society of Gastrointestinal Endoscopy Guideline advocates for a restrictive transfusion strategy in NVUGIB.[14,26] However, these recommendations are primarily based on two RCTs, each employing different Hb thresholds for restrictive and liberal transfusion strategies.[9,10] A recent Cochrane review analyzed data across various types of hemorrhages and reported a reduction in 30-day mortality among patients experiencing acute blood loss, when a restrictive transfusion strategy was implemented.[27]

The impact of RBC transfusion on short- and long-term outcomes following GIB is still unclear.

6.1.1. Aim of the meta-analysis

The aim of our meta-analysis was compared different transfusion strategies, evaluating the source of bleeding and the length of follow-up separately.

6.2. Materials and methods

We performed our systematic review and meta-analysis following the guidelines of the Cochrane Handbook[28] and PRISMA 2020 checklist.[29] The study protocol was also registered in PROSPERO (identifier CRD42022302923).

6.2.1. Information sources

To ensure the identification of all relevant articles, we conducted an extensive literature search. across four medical databases: MEDLINE (via PubMed), The Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Web of Science, on January 15, 2022.

6.2.2. Inclusion criteria

RCTs were considered eligible for inclusion in the systematic review if they compared restrictive versus liberal transfusion strategies following an acute GIB episode. The definitions for the two transfusion strategies were as follows: (1) RBC transfusions administered below a predefined lower threshold compared to a higher threshold, and (2) RBC supplementation provided in a smaller quantity relative to a larger quantity.

The articles must have reported at least one of the following outcomes: mortality (primary endpoint), rebleeding, ischemic- or thromboembolic events, complications, adverse events related to transfusion, need for intervention and length of hospital stay.

6.2.3. Study selection and data collection

Two independent review authors utilized reference management software (EndNote X9) to facilitate study selection. After removing duplicates, all records were systematically screened—initially by title and abstract, and subsequently by full-text review—following a rigorous protocol. Once the eligible articles were identified, two reviewers independently extracted all pertinent data from them into Excel spreadsheets.

6.2.4. Synthesis methods

The R programming language (R Core Team 2021, v4.1.1) was employed for data analysis. Forest plots were generated to summarize the overall findings from individual studies.

Risk ratios (RRs) were calculated for binary outcomes, while pooled mean differences (MDs) were used for continuous variables, each presented with 95% confidence intervals (CIs). The DerSimonian-Laird method was applied within a random-effects model to estimate the overall effect size.[30] Statistical significance was defined as a p-value less than 0.05. To evaluate heterogeneity, the I^2 statistic was utilized, and the 95% CIs were calculated using the Q-profile method.

When possible, groups were organized according to follow-up duration, and subgroups were formed based on the bleeding source.

6.2.5. Quality assessment and quality of the evidence

The methodological quality of the RCTs was independently evaluated by two reviewers for each outcome using the RoB 2 Tool developed by the Cochrane Collaboration.[31] The quality of evidence for all outcomes was assessed in accordance with the guidelines provided by the GRADE workgroup.[32]

6.3. Results

6.3.1. Search and selection

A total of 3,955 studies were identified through the systematic search. Following the title and abstract screening, 21 articles were considered eligible, which were further narrowed down to seven RCTs after full-text review.

6.3.2. Basic characteristics of the included articles

Except for the multicenter, cluster-randomized feasibility trial by Jairath et al.[9], all the studies were parallel-group, single-center RCTs. Of the seven eligible articles, five[9-11,33,34] focused on UGIB, one[35] specifically targeted variceal UGIB (VUGIB), and one[36] examined NVUGIB patients. Restrictive transfusion thresholds were defined as Hb levels between 70–80 g/L and hematocrit levels of 21%–25±2%, whereas liberal thresholds ranged from 80–100 g/L Hb and 28%–32±2% hematocrit. The amount of the transfused RBC was pre-defined only in one RCT.[10]

6.3.3. Results of the meta-analysis: in-hospital and 30-day mortality

According to the pooled analysis of four RCTs[11,33-35] restrictive transfusion did not lead to an increase in mortality among all included patients or within the UGIB subgroup (Figure 1.1.). Findings from three studies[9-11] indicated a trend toward reduced 30-day mortality, with a 29% risk reduction with restrictive transfusion (Figure 1.2.).

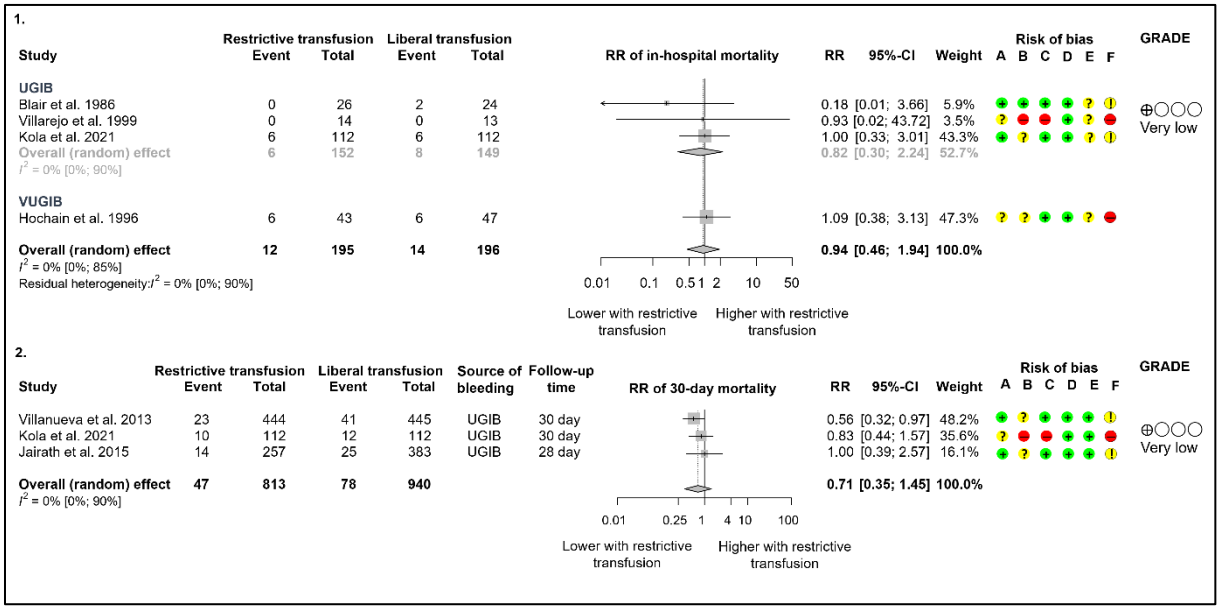

Figure 1. Forest plots from the studies illustrate that restrictive transfusion did not result in higher (**1**) in-hospital mortality or (**2**) 30-day mortality compared to liberal transfusion. **Abbreviations: RR**: risk ratio; **CI**: confidence interval; **UGIB**: upper gastrointestinal bleeding; **VUGIB**: variceal upper gastrointestinal bleeding. **Risk of bias**

legend: (A) Bias arising from the randomization process, (B) Bias due to deviations from intended interventions, (C) Bias due to missing outcome data, (D) Bias in the measurement of the outcome, (E) Bias in the selection of the reported results, (F) Overall bias.

6.3.4. Results of the meta-analysis: in-hospital and follow-up rebleeding

Five studies[9-11,33,35] were included in the analysis of in-hospital rebleeding. The restrictive transfusion approach did not result in a higher risk of rebleeding compared to the liberal strategy (RR: 0.67, CI: 0.30–1.50). Similarly, no significant difference was observed between the intervention and control groups within the UGIB subgroup (RR: 0.60, CI: 0.16–2.32).

Rebleeding within 28 to 45 days post-intervention was evaluated in three RCTs[9,11,36]. Although the results indicated a tendency toward risk reduction in the restrictive transfusion group, the finding was not statistically significant (RR: 0.75, CI: 0.49–1.16).

6.3.5. Results of the meta-analysis: acute kidney injury and length of hospital stay

Acute kidney injury was documented in three studies.[9,10,34] The combined analysis revealed that restrictive transfusion was not inferior to the liberal approach (RR: 0.79, CI: 0.61, 1.03). Additionally, studies with larger sample sizes suggested a trend toward a lower risk of acute kidney injury in patients receiving restrictive transfusions.

Data on the length of hospital stay were reported in three studies.[10,11,34] The analysis indicated no significant difference in the duration of hospital stay, measured in days, between patients who received RBC transfusions at a lower threshold and those treated with a liberal approach (MD: -0.49 days, CI: -1.86, 0.89).

6.3.6. Results of the systematic review: thromboembolic and ischemic events and post-transfusion interventions

Thromboembolic events during hospitalization and the follow-up period were reported in two studies.[9,10] Across all cases, the proportion of participants affected was smaller in the restrictive group compared to the liberal group.

Three RCTs[10,11,9] evaluated the requirement for post-transfusion interventions. In the study by Jairath et al.,[9] restrictive transfusion was linked to a 1% increase in surgical or radiological procedures. However, for all other outcomes, administering RBC transfusion at a lower Hb threshold reduced the need for interventions, particularly for procedures like transjugular intrahepatic portosystemic shunt (TIPS) insertion and balloon tamponade application.

6.3.7. Risk of bias assessment and certainty of the evidence

Variations in baseline characteristics, incomplete details regarding randomization, deviations from intended interventions, and selective reporting of results contributed to a moderate ("some concerns") to high risk of bias across all included RCTs.

The GRADE assessment results of the meta-analysis are presented in **Table 1**.

Table 1. Certainty of Evidence for the Meta-Analysis Results

Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with liberal transfusion	Risk difference with restrictive transfusion
In-hospital mortality	391 (4 RCTs)	⊕◯◯◯ Very low	**RR 0.95** (0.46 to 1.94)	71 per 1,000	**4 fewer per 1,000** (39 fewer to 67 more)
Follow-up mortality	1753 (3 RCTs)	⊕◯◯◯ Very low	**RR 0.71** (0.35 to 1..45)	83 per 1,000	**24 fewer per 1,000** (54 fewer to 37 more)
In-hospital rebleeding	1893 (5 RCTs)	⊕◯◯◯ Very low	**RR 0.67** (0.30 to 1.50)	135 per 1,000	**44 fewer per 1,000** (94 fewer to 67 more)
Follow-up rebleeding	927 (3 RCTs)	⊕◯◯◯ Very low	**RR 0.75** (0.49 to 1.16)	97 per 1,000	**24 fewer per 1,000** (49 fewer to 16 more)
Acute kidney injury	1504 (3 RCTs)	⊕◯◯◯ Very low	**RR 0.79** (0.61 to 1.03)	137 per 1,000	**29 fewer per 1,000** (53 fewer to 4 more)
Length of hospital stay	1140 (3 RCTs)	⊕◯◯◯ Very low	-	-	MD **0.49 days lower** (1.86 lower to 0.89 higher)

Abbreviations: CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **RCT**: randomized controlled trial

6.4. Discussion

Our meta-analysis aimed to investigate the effectiveness and safety of restrictive versus liberal transfusion following acute GIB. Although the restrictive arms exhibited fewer unfavorable outcomes, including in-hospital mortality, 30-day mortality, in-hospital rebleeding, 28 to 42-day rebleeding, and acute kidney injury, the differences between the groups were not statistically significant. Similarly, no variation in the length of hospital stay was observed between the two transfusion strategies. Findings from individual studies suggested that restrictive transfusion was associated with lower rates of ischemic events, thromboembolic complications, and adverse events.

Our meta-analysis has the notable strength of providing a thorough overview of various transfusion strategies, incorporating data from over 2,000 patients. We showed that restrictive transfusion did not lead to an increased risk of adverse outcomes, whether measured during hospitalization or at extended follow-up periods.However, a significant limitation lies in the variability of transfusion threshold definitions across the included studies. Furthermore, only two studies[10,11] conducted sample size estimations, which may explain the lack of statistically significant results. Additionally, several outcomes were associated with moderate to high risk of bias. The most frequent reason for downgrading the evidence was the absence of blinding in the included studies, introducing potential performance and detection bias. Blinding in RCTs of this type is inherently challenging, but one possible strategy to address this issue could involve masking outcome assessors and data analysts to treatment allocations.

6.4.1. Implications for research

In future RCTs and cohort studies, extended follow-up of all patients post-discharge is essential. The variation in the number of variceal and peptic ulcer bleeders across the included studies makes generalizing the results difficult. Therefore, upcoming RCTs should investigate these populations separately, as transfusion practices may have differing impacts on their outcomes. Patients with prior ischemic and thromboembolic events were largely excluded from the analyzed trials, leaving the benefits of a restrictive transfusion policy uncertain for these individuals. Future studies should address this gap while also examining Hb thresholds for transfusion in both restrictive and liberal protocols. Notably, across the included studies, participants in the liberal arm generally received more blood, and prior research has highlighted a dose-dependent relationship between the number of RBC units transfused and adverse outcomes. In line with transfusion guidelines, we recommend initiating treatment with a single

RBC unit in cases of controlled bleeding and non-severe conditions, with subsequent adjustments based on the patient's response.[37]

6.4.2. Implications for practice

In practical scenarios, RBC supplementation should be conducted under ideal conditions, ensuring close monitoring of the patient's haemodynamic status and laboratory indicators to minimize transfusion-related complications. Adopting a restrictive transfusion policy in routine practice is crucial, as it not only reduces post-discharge mortality but also lowers hospital expenses compared to a liberal transfusion approach. Over recent years, particularly during the COVID-19 pandemic, there has been a worldwide RBC shortage.[38,39] Data from the Australian National Blood List indicated that in 2022, the cost of one RBC unit was approximately A$357. According to our findings, participants in the restrictive group used 1.35 fewer RBC units, potentially reducing costs by A$482 per participant with this approach. Furthermore, liberal transfusion strategies are associated with a higher rate of complications, which demands additional human and financial resources.

6.4.3. Conclusion

In summary, restrictive transfusion, when compared to the liberal approach, does not seem to result in a higher incidence of major clinical endpoints. However, these findings should be approached with caution due to the substantial uncertainty surrounding the results.

7. Hemoglobin decrease predicts untoward outcomes better than severity of anemia – registry analysis

7.1. Introduction

Current guidelines for GIB recommend maintaining Hb levels above 70 g/L in most patients and 80 g/L for those with cardiovascular conditions.[14,26] However, the ability of individuals to tolerate anemia differs greatly. A significant drop in Hb from a normal baseline to the transfusion threshold, without proper physiological adaptation, can increase the likelihood of adverse outcomes.[40-42]

Large-scale cohort studies in surgical patients have shown that the relative drop in Hb levels (ΔHb%) from baseline may be more important than the nadirHb as a predictor. These findings revealed that when ΔHb% exceeds 50%, the risk of mortality rises, even if the nadirHb remains above the transfusion threshold of 70 g/L.[18,19]

The use of Hb change as a tool for guiding transfusion decisions, as well as their ability to predict in-hospital mortality related to bleeding and the necessity for urgent intervention, remains unexplored in GIB. Nonetheless, it is vital to consider individual variations in nadirHb and ΔHb%, as these elements greatly affect a patient's capacity to tolerate bleeding.

7.1.1. Aim of the registry analysis

The primary aims of our study were: (1) to establish the absolute and relative thresholds for significant Hb changes, and (2) to examine the impact of nadirHb levels and the associated ΔHb% on the outcomes of GIB.

7.2. Materials and methods

Our cohort analysis follows the recommendations outlined in the STROBE guideline.[43] Data collection was conducted in compliance with the principles of the Declaration of Helsinki.

7.2.1. Data sources

The study utilized data from the Hungarian Gastrointestinal Bleeding Registry (ethical approval number: 24433-5/2019/EÜIG).[44] Data were gathered both prospectively and retrospectively from two Hungarian tertiary care hospitals: the University of Pécs Medical School in Pécs and the Fejér County Szent György University Teaching Hospital in Székesfehérvár, during the period from November 1, 2019, to August 31, 2022.

7.2.2. Participants

All adult patients who exhibited clear signs of GIB—including melena, hematochezia, hematemesis, blood detected in a nasogastric tube, or active bleeding identified during endoscopy—were considered eligible for inclusion in the Registry. Information was gathered on a daily basis during their hospital stay and recorded in electronic case report forms.[44]

7.2.3. Outcomes

Following recent guidance on outcome evaluation in GIB-related clinical research, we identified a composite endpoint as the primary outcome. This composite included in-hospital bleeding-related mortality and the necessity for urgent interventions, such as repeat endoscopy due to signs of rebleeding, surgical procedures, or trans-arterial embolization.[17] Furthermore, in-hospital bleeding-related mortality and the requirement for urgent interventions were examined individually as secondary outcomes.

7.2.4. Variables

NadirHb:

Initially, we identified participants who had a documented lowest Hb level (nadirHb) during their hospitalization. For the composite endpoint, the Hb measurement taken prior to the urgent intervention was included, as it indicated the first outcome experienced by the participant.

Hb change:

To assess the potential impact of nadirHb changes on outcome rates, we analyzed delta Hb (ΔHb) as a predictor for reaching the endpoint. Only cases with at least two Hb results—one at admission and one during hospitalization—were considered eligible for analysis. ΔHb was calculated as the difference between the admission Hb value (first Hb) and the nadirHb. The relative reduction in Hb (ΔHb%) was determined using the formula: ΔHb% = [(firstHb – nadirHb) / firstHb] * 100. Furthermore, the hourly rate of decrease for both ΔHb and ΔHb% was also examined.

NadirHb and ΔHb:

Participants may exhibit varying tolerance to blood loss, even when their nadirHb levels remain above the recommended transfusion threshold. To explore this, we conducted an analysis focusing on Hb reduction relative to the nadirHb achieved. Participants were categorized into four groups based on their nadirHb levels (>50-≤60, >60-≤70, >70-≤80, >80-≤90 g/L) and further divided into four subgroups according to the ΔHb% decrease as follows: 0-≤10%, >10-≤20%, >20-≤30%, and >30-≤40%. Individuals who received RBC transfusions were analyzed separately.

7.2.5. Statistical analysis

The analyses were carried out using R version 4.3.1, incorporating the pROC 1.18.5 and emmeans 1.10.2 packages.

To define thresholds for ΔHb and ΔHb%, we determined cut-off values along with their sensitivity and specificity. The area under the curve (AUC) with 95% CIs was evaluated as follows: ≥0.9 was categorized as excellent, 0.8–0.9 as considerable, 0.7–0.8 as fair, 0.6–0.7 as poor, and 0.5–0.6 as failure.[45]

For the second analysis, we used binomial logistic regression to estimate the probability of events. The explanatory variables included nadirHb and ΔHb%, both treated as continuous variables, as well as their interaction term. Probabilities were estimated at 16 specific points corresponding to the midpoints of the four nadirHb and ΔHb% groups. Subgroup comparisons were conducted using Tukey's post-hoc test, with statistical significance defined as $p < 0.05$.

Additionally, for group comparisons, we calculated odds ratios (ORs) with 95% CIs, standard errors, and Z ratios.

7.3. Results

7.3.1. Participants

During the data collection period, 1021 cases were recorded in the Registry. Of these, ΔHb values were available for 652 cases for analysis of the composite endpoint, while data on the need for urgent intervention were accessible for 619 cases.

7.3.2. Baseline characteristics

The baseline characteristics of the included population can be found in **Table 2.**

Table 2. Baseline characteristics of the population investigated

	ΔHb decrease	Total
Number of participants	**619**	**1021**
Mean age (SD)	**68.50 (13.98)**	**69.46 (13.56)**
Male n (%)	**385 (62.20)**	**611 (59.84)**
Comorbidities		
Vascular disease n (%)	**180 (29.08)**	**298 (29.19)**
Thromboembolic disease n (%)	**72 (11.63)**	**117 (11.46)**
Ischemic heart disease n (%)	**106 (17.12)**	**187 (18.32)**
Regular medication		
Antiplatelet drugs n (%)	**171 (27.63)**	**293 (28.70)**
Anticoagulant drugs n (%)	**189 (20.53)**	**321 (31.44)**
Bleeding severity		
Mean pre-endoscopy Rockall Score (SD)	**3.87 (1.44)**	**4.12 (1.47)**
Mean Glasgow Blatchford Score (SD)	**7.89 (4.55)**	**10.70 (4.01)**
Transfusion during hospitalization		
Fresh frozen plasma transfusion n (%)	**51 (8.24)**	**118 (11.56)**
Thrombocyte transfusion n (%)	**20 (3.27)**	**35 (3.43)**
Coagulation factor concentrate replacement n (%)	**72 (11.63)**	**127 (12.44)**
Laboratory parameters		
Mean admission Hb g/L (SD)	**107.15 (26.03)**	**95.89 (30.95)**
Mean ΔHb decrease g/L (SD)	**21.58 (14.18)**	**21.58 (14.18)**
Mean nadirHb g/L (SD)	**84.88 (23.20)**	**79.42 (24.49)**
In-hospital outcomes		
Need for surgery n (%)	**17 (2.75)**	**32 (3.13)**
Need for trans-arterial embolization n (%)	**2 (0.32)**	**4 (0.39)**
Need for intensive care unit admission n (%)	**44 (7.11)**	**90 (8.81)**
Need for repeat endoscopy n (%)	**49 (7.92)**	**101 (9.89)**
Rebleeding n (%)	**29 (4.68)**	**54 (5.29)**
Bleeding-related mortality n (%)	**16 (2.58)**	**33 (3.23)**
All-cause mortality n (%)	**55 (8.89)**	**108 (10.58)**
Composite endpoint	**76 (12.28)**	**154 (15.08)**
Mean length of hospital stay (SD)	**7.77 (4.98)**	**7.83 (5.17)**

Abbreviations: SD: standard deviation; **n**: number of participants; **Hb**: hemoglobin.

7.3.3. Results of the registry-analysis: the predictive value of ΔHb and ΔHb%

We examined whether ΔHb and ΔHb% could predict the outcomes of interest among all patients included in the study. The analysis showed that both absolute and relative decreases in Hb, as well as their hourly decrease rates, had high specificity in distinguishing patients who did not

experience the composite endpoint. Despite this, the overall diagnostic accuracy of these measures was low or inadequate across the entire cohort. (**Figure 2**).

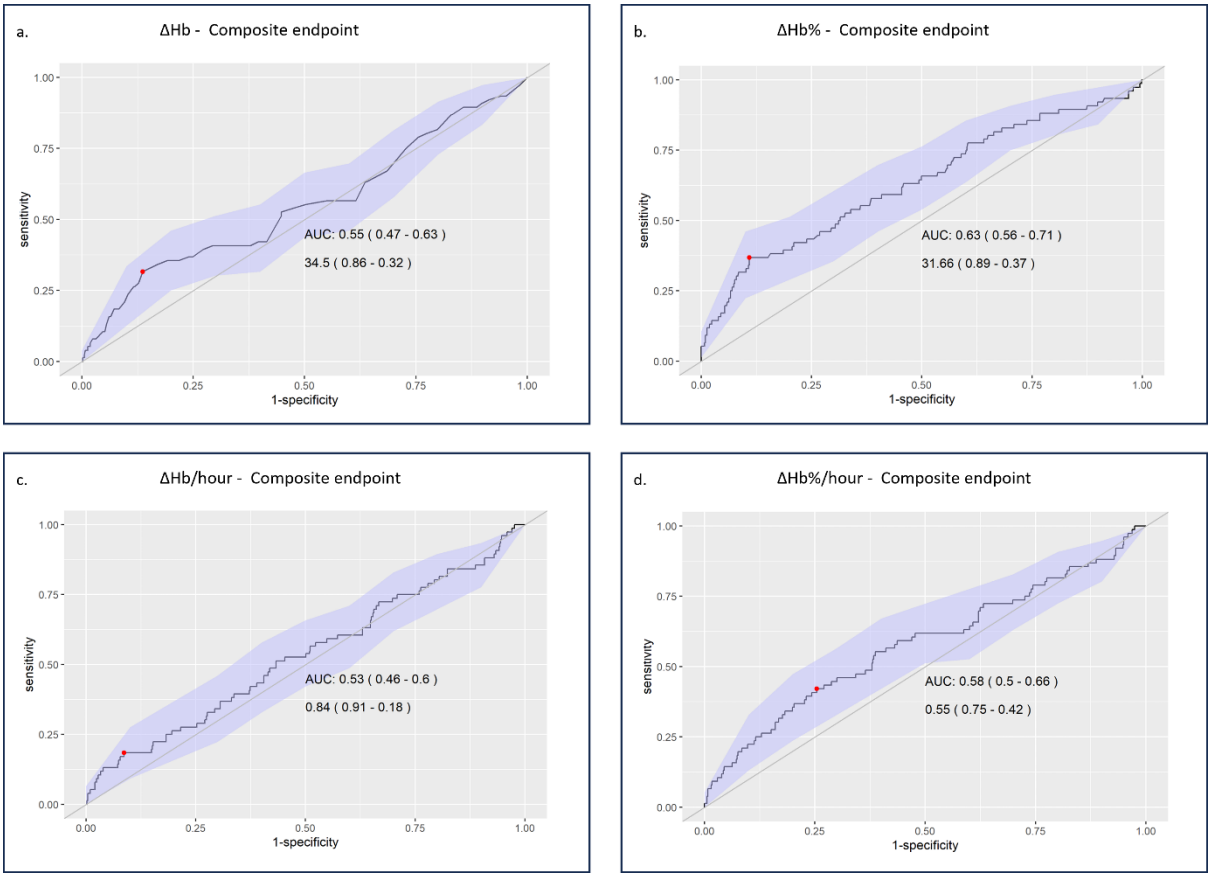

Figure 2. Prediction of the composite endpoint based on ΔHb (a), ΔHb% (b), ΔHb/hour (c), and ΔHb%/hour (d) is illustrated. Each figure displays the area under the curve (**AUC**) with 95% confidence intervals in the first row and the hemoglobin cut-off values, along with their associated specificity and sensitivity, in the second row.

When evaluated separately for bleeding-related mortality and the need for urgent intervention, prediction models using ΔHb and ΔHb% decreases produced similar results.

7.3.4. Results of the registry-analysis: the combined assessment of nadirHb and ΔHb%

Composite endpoint

When participants were grouped based on ΔHb% and nadirHb levels, we found that an increase in ΔHb% was associated with a greater likelihood of reaching the composite endpoint across all participants. While the probability of the outcome doubled, the increase was not statistically significant when comparing the 0–10% ΔHb% subgroups in the nadirHb ranges of 80–90 g/L and 50–60 g/L (8% vs. 16%; OR: 2.18, CI: 0.70–6.75; p=0.581). In contrast, participants in the 30–40% ΔHb% subgroup within the same nadirHb categories exhibited 5.4 times higher odds

of reaching the composite endpoint (10% vs. 36%; OR: 5.40, CI: 1.52–19.15; p<0.001) (**Figure 3a**).

Among the RBC-transfused population in the 0–10% ΔHb% subgroup, the likelihood of reaching the composite outcome was consistent across all nadirHb categories (13% vs. 13% vs. 13% vs. 14%). For participants with a 30–40% Hb decrease, larger differences were observed between nadirHb groups compared to those with a nadirHb of 80–90 g/L, but these differences were not statistically significant (10% vs. 17%; OR: 1.74, CI: 0.97–3.13; p=0.090; 10% vs. 26%; OR: 3.03, CI: 0.94–9.77; p=0.090; 10% vs. 38%; OR: 5.26, CI: 0.91–30.56; p=0.090) (**Figure 3b**).

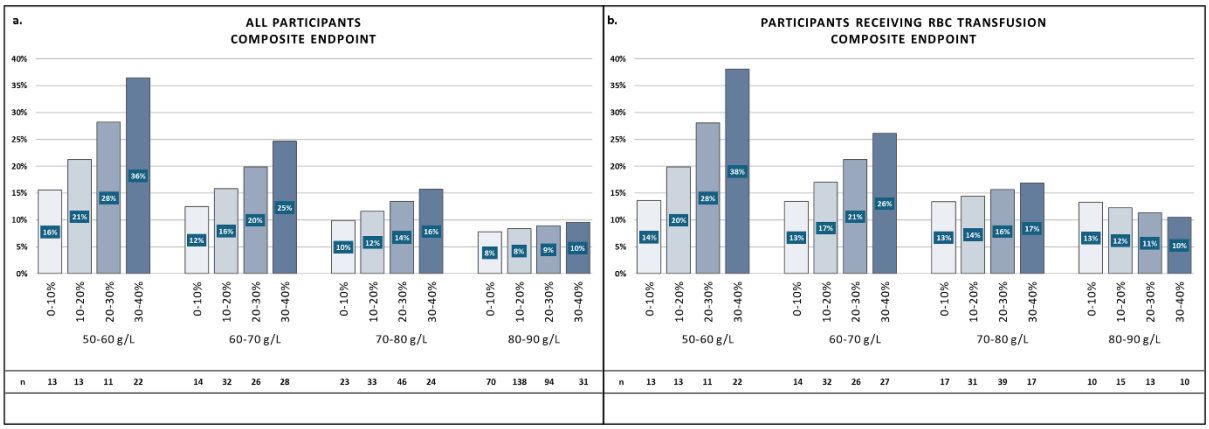

Figure 3. The bar chart illustrates the rate of the composite endpoint (expressed as a percentage) across four nadirHb groups (50–60, 60–70, 70–80, and 80–90 g/L) and four ΔHb% subgroups (0–10, 10–20, 20–30, and 30–40%) for two populations: all participants (a.) and those receiving red blood cell (**RBC**) transfusions (b.). The sample sizes for each subgroup are displayed below their corresponding bars.

Bleeding-related mortality

Bleeding-related mortality probabilities ranged from 1% to 4% in all subgroups with nadirHb levels between 60–90 g/L. A ΔHb% reduction of 30–40% leading to a nadirHb of 60–70 g/L resulted in a comparable outcome rate to a 0–10% reduction reaching a nadirHb of 50–60 g/L (4% vs. 4%; p=1.00). Additionally, in the 50–60 g/L nadirHb group, a 30–40% decrease was linked to twice the odds of the outcome compared to the 0–10% decrease group (8% vs. 4%; OR: 2.05, CI: 1.04–4.05; p=0.028) (**Figure 4a**). Similar trends were observed among participants who received RBC transfusions (**Figure 4b**).

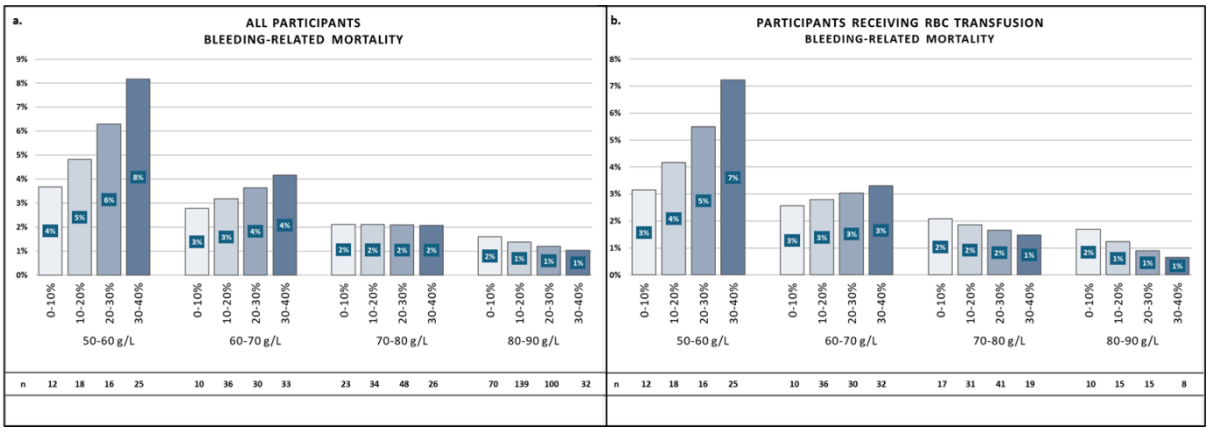

Figure 4. The bar chart illustrates the rate of bleeding-related mortality (expressed as a percentage) across four nadirHb groups (50–60, 60–70, 70–80, and 80–90 g/L) and four ΔHb% subgroups (0–10, 10–20, 20–30, and 30–40%) for two populations: all participants (a.) and those receiving red blood cell (**RBC**) transfusions (b.). The sample sizes for each subgroup are displayed below their corresponding bars.

Need for urgent intervention

Participants with a 30–40% Hb reduction reaching a nadirHb of 80–90 g/L were predicted to have an outcome rate comparable to those with a 0–10% reduction in the 60–70 g/L nadirHb group (**Figure 5.a**). Among transfused individuals, 14% of those experiencing a 30–40% Hb reduction to a nadirHb of 80–90 g/L were likely to require urgent intervention. Similar probabilities were observed for patients with a 0–10% reduction to nadirHb levels of 50–60 g/L and 60–70 g/L (14% vs. 16%; p=1.00; 14% vs. 13%; p=1.00) (**Figure 5.b)**.

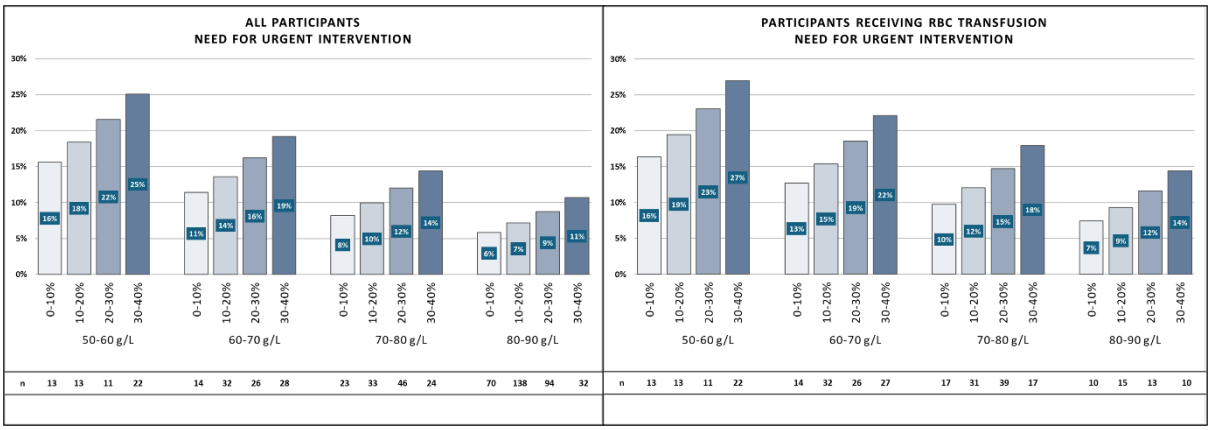

Figure 5. The bar chart illustrates the rate of urgent interventions (expressed as a percentage) across four nadirHb groups (50–60, 60–70, 70–80, and 80–90 g/L) and four ΔHb% subgroups (0–10, 10–20, 20–30, and 30–40%) for two populations: all participants (a.) and those receiving red blood cell (**RBC**) transfusions (b.). The sample sizes for each subgroup are displayed below their corresponding bars.

7.4. Discussion

Several surgical studies have explored the relationship between changes in Hb levels and hard clinical outcomes.[18,19,46-48] However, to the best of our knowledge, this is the first study to examine this association in the context of acute GIB. Our results showed that while ΔHb% demonstrated high specificity, neither ΔHb nor ΔHb% was able to accurately predict the outcome of interest. Nonetheless, our second analysis supported the hypothesis that greater blood loss increases the likelihood of bleeding-related in-hospital mortality or the need for urgent intervention, even when nadirHb levels exceed 70 g/L.

In this study, we analyzed a large cohort of participants encompassing all bleeding sources. However, follow-up data were not included in the Registry, preventing us from assessing the recommended 30-day follow-up for NVUGIB and the 42-day follow-up for VUGIB.[17] Due to the limited number of participants reaching the endpoints, we were unable to create subgroups for evaluating ΔHb cut-off values. Future studies should focus on defining specific cut-offs for major comorbidities (e.g., ischemic heart disease) and different bleeding sources (e.g., variceal bleeding). Additionally, prospective data collection was not feasible during the COVID-19 pandemic, leading to the unavailability of transfusion initiation times for all cases. However, by using the nadirHb measured before the outcome of interest, we minimized the inclusion of Hb levels potentially affected by secondary blood loss (e.g., rebleeding or surgical procedures).

7.4.1. Implications for research

Integrating ΔHb% as an additional parameter in future GIB risk scoring systems could improve the efficiency of resource allocation. If ΔHb% data is accessible, it might be more effective than relying exclusively on Hb levels. Nevertheless, future research should focus on thoroughly examining the causal link between clinical outcomes, ΔHb%, and nadirHb in randomized settings. This could lead to the development of more precise and broadly applicable transfusion guidelines.

7.4.2. Implications for practice

Our registry analysis emphasizes the need for a more tailored approach to risk evaluation. Patients with significant blood loss might gain from earlier interventions; therefore, those with elevated ΔHb% levels should be monitored more attentively, even if their nadirHb remains above 70 g/L.

7.4.3. Conclusion

In conclusion, this study highlights ΔHb% as an important predictor of adverse outcomes. Our results suggest that ΔHb% offers greater predictive value than nadirHb alone, providing a better basis for determining the timing and need for RBC transfusions. Further research is needed to confirm these findings in larger cohorts, followed by randomized trials, to assess the potential of ΔHb% in improving transfusion strategies for GIB management.

8. Intravenous ferric carboxymaltose versus oral ferrous sulfate replacement in elderly patients after acute non-variceal gastrointestinal bleeding (FIERCE): protocol of a multicentre, open-label, randomized controlled trial

8.1. Introduction

Anemia in older adults greatly increases the likelihood of complications. A large prospective cohort study, which included participants with moderately severe anemia and an average age of approximately 60 years, found a threefold rise in 30-day hospital readmission rates compared to those without anemia.[49]

To date, only two RCTs have evaluated the efficacy of IV iron compared to oral iron supplementation after acute GIB.[24,50] The findings from these RCTs suggest that IV iron is effective in rapidly restoring iron stores. However, both trials excluded patients with severe anemia or major comorbid conditions. In the open-label RCT by Ferrer-Barcelo et al., participants were treated with six weeks of oral ferrous sulfate (FS). Notably, 40% of the patients in the oral iron group failed to achieve normal Hb levels by the end of the study.

In the Bager et al. study, normal Hb levels were achieved even with reduced doses of oral iron (200 mg/day for three months) and IV iron (1000 mg). However, the slower rate of Hb improvement with oral iron increases the risk of anemia-related complications in elderly patients. A multicenter retrospective study reported that among patients with Hb levels between 70–100 g/L, 22.6% were readmitted to the hospital, and 4.6% died within one month of discharge.[16] Elderly patients with severe anemia are at even greater risk of readmission and mortality if iron stores are not replenished quickly.

Existing RCTs fail to address this significant clinical issue. We propose that IV iron is more effective and safer than oral iron across all the outcomes assessed in this study.

8.1.1. Aim of the RCT

The primary aim of our trial (1) is to examine the effects of IV iron supplementation compared to oral iron replacement on mortality, anemia-related emergency visits, and hospital readmissions in elderly patients with acute NVUGIB. The secondary objective (2) focuses on evaluating the impact of ferric carboxymaltose (FCM) and FS on patients' QoL and physical health. Furthermore, we aim to compare (3) the side effects of these two treatments and assess (4) their efficiency in restoring iron levels and increasing Hb concentrations.

8.2. Methods

The study protocol was developed by the Steering Committee (SC) and the International Trial Advisory Board (ITAB) members in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.[51] The Hungarian Scientific and Research Ethics Committee of the Medical Research Council has approved the protocol (approval number: 46395-5/2021/EÜIG). During the study we will adhere to the principles outlined in the Declaration of Helsinki.

The trial will be funded by the Institute for Translational Medicine, University of Pécs, Pécs, Hungary. The sponsors will not have access to the randomization code or the database generated throughout the trial.

8.2.1. Trial design and setting

The FIERCE study will be conducted as a multicenter, parallel-group, open-label RCT with a superiority design.

Initially, the trial will be implemented at two academic hospitals: the Division of Gastroenterology, First Department of Medicine, University of Pécs, Pécs, Hungary and Fejér County Szent György University Teaching Hospital, Székesfehérvár, Hungary. Additional hospitals with internal medicine departments equipped with endoscopic imaging capabilities will be invited to participate.

8.2.2. Population

Inclusion criteria:

(1) Age ≥ 65 years. (2) Endoscopically proven acute NVUGIB source. (3) At least 48 hours since the endoscopic diagnosis and/or treatment. (4) Hemodynamically stable. (5) Patient discharge is planned. (6) Hb level <100 g/L on the day of randomization. (7) At least 24 hours

since the last transfusion with no further transfusion required.(8) Signed informed consent and patient information leaflet provided.

Exclusion criteria:

(1) Known hypersensitivity to iron products (mild side effects excluded). (2) History of iron overload. (3) Pregnancy or breastfeeding. (4) History of iron malabsorption.(5) Chronic end-stage diseases. (6) Active malignant disease or malignancies under treatment that impact anemia. (7) Liver cirrhosis with varices at high risk of bleeding. (8) Gastrointestinal malignancies associated with a high risk of bleeding. (9) High likelihood of poor compliance or lack of a fixed residence. (10) Eastern Cooperative Oncology Group (ECOG) Performance Status >2. (11) Myelo- or lymphoproliferative disorders. (12) Anemia not caused by iron deficiency. (13) Primary coagulation disorders. (14) Planned transfer of the patient to another facility after discharge.

8.2.3. Intervention

The interventions will start immediately following randomization. Participants in Group A will receive a single IV dose of 1000 mg FCM on the day of randomization. In Group B, oral iron supplementation will consist of one 200 mg FS tablet taken daily for three months.

8.2.4. Endpoints

Primary outcome

The primary outcome will be a composite measure that includes all-cause mortality, unplanned emergency visits related to anemia, and anemia-associated unplanned hospital admissions, assessed within three months of participant enrollment in the trial.

Secondary outcomes

At 1 and 3 months after enrollment, the assessment will include the absolute values and causes of: (1) all-cause mortality; (2) anemia-associated unplanned emergency visits; and (3) anemia-associated unplanned hospital readmission.

At 1 and 3 months (±7 days) after treatment, the following outcomes will be evaluated: (4) changes in QoL; (5) changes in gait speed relative to baseline; (6) differences in Six-Minute Walk Test (6MWT) performance from baseline; (7) variations in handgrip strength compared to baseline; (8) Hb level normalization (>120 g/L for women and ≥130 g/L for men) (9) absolute changes in hematological and biochemical parameters, including hematocrit, serum iron, serum transferrin, transferrin saturation, soluble transferrin receptor (sTfR) concentration, ferritin,

reticulocyte count, red blood cell count, total iron-binding capacity (TIBC), erythropoietin, C-reactive protein (CRP), phosphate, and hepcidin levels; (10) treatment discontinuation due to adverse events; (11) adherence to the oral treatment; (12) cost-effectiveness of the treatment.

8.2.5. Baseline and follow-up assessments

Baseline and follow-up assessments will be carried out at each study site at enrollment and again at 1 and 3 months (±7 days) after enrollment (see **Figure 6**). Participants' medical histories, treatment details for the acute NVUGIB episode, and transfusion requirements will be recorded. Furthermore, physical examinations, evaluations of participants' health status, QoL assessments, functional tests, and laboratory analyses will be conducted at baseline and during each follow-up visit.

	STUDY PERIOD				
	Enrollment	Allocation	Post-allocation		Close-out
TIMEPOINT**	*hospitalization period*	*day of planned discharge*	*day of planned discharge*	*1st month*	*3rd month*
ENROLLMENT:					
Eligibility screen	X				
Physical examination	X		X	X	X
Endoscopy	X				
Laboratory tests	X		X	X	X
BP, HR measurement	X		X	X	X
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
IV ferric carboxymaltose			X		
Oral iron sulphate			◆—	—	—◆
ASSESSMENTS:					
Questionnaire A			X		
Questionnaire B				X	X
Questionnaire C			X	X	X

Figure 6. Participant timeline. **Abbreviations: BP**: blood pressure; **HR**: heart rate; **IV**: intravenous.

8.2.6. Randomization

Participants will be randomized on the day they are scheduled for hospital discharge. The Independent Data Management Board (IDMB) will assign participants to either Group A (IV FCM) or Group B (oral FS) using a 1:1 allocation ratio, generated through a random sequence with variable block sizes ranging from 2 to 6. The randomization will be stratified by the participating study centers and the requirement for a transfusion during the same hospitalization prior to trial enrollment. The allocation sequence will be securely managed through the use of sealed envelopes.

8.2.7. Blinding

The FIERCE trial will be designed as an open-label RCT. Blinding the physicians administering the treatments would compromise the trial's feasibility, as it would necessitate additional staff to monitor patients following IV administration. Additionally, stool discoloration caused by oral iron makes it impractical to blind participants in the control group. Data analysts responsible for evaluating primary and secondary outcomes will remain blinded to the intervention groups.

8.2.8. Data collection and management

Participants will be assigned unique identification numbers in consecutive order. Data will be collected continuously using standardized forms (Questionnaire A, B, C). Personal information and identification numbers of participants will only be accessible to the research team directly involved in the study and will be securely stored separately from other data. De-identified data will be entered into Electronic Case Report Forms (eCRF) after collection. The eCRF data will then be validated in a four-step process coordinated by the IDMB.

8.2.9. Safety and adverse events

Patients who exhibit less than a 10 g/L increase in Hb levels at the one-month follow-up visit will receive a rescue iron infusion of 1000 mg FCM, regardless of their study group.

Participants undergoing IV iron infusion will be monitored during the procedure and for 30 minutes afterward to address any potential allergic reactions.[14] If hypersensitivity, intolerance, or paravenous leakage occurs, the infusion will be halted immediately.[14] Phosphate levels will be measured throughout the follow-up period. For patients with phosphate levels below 1.5 mg/dL and experiencing increased fatigue, IV phosphate infusions will be administered. Gastrointestinal side effects are most commonly associated with oral iron administration.[52]

8.2.10. Statistical analysis

Statistical analysis will be performed using the R programming language (R Core Team, 2019, Vienna, Austria).

The t-test or Mann-Whitney test will be used to analyze continuous variables, while dichotomous outcomes will be evaluated using the Chi-squared test or Fisher's exact test. Kaplan-Meier survival analysis and Cox regression are also planned. Statistical significance will be set at a p-value of less than 0.05.

8.3. Discussion

The FIERCE trial seeks to address a critical gap in the management of anemia in elderly, potentially multimorbid patients following acute NVUGIB. The current literature highlights the limitations of oral iron supplementation due to its gastrointestinal side effects, delayed Hb normalization, and low adherence rates. Although IV iron has shown promise in rapidly replenishing iron stores, no previous RCTs compared its efficacy and safety to oral iron in older adults.

If the hypothesis is confirmed, the results could be included in GIB guidelines favoring IV iron therapy in elderly patients with significant anemia, ensuring longer survival, reduced healthcare utilization and improved QoL.

9. Summary of novel findings

Potential benefits of restrictive transfusion in upper gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials

- The results of our meta-analysis showed that restrictive transfusion did not increase the risk of adverse outcomes during hospitalization or extended follow-up periods.
- Restrictive transfusion could also results potential cost savings by reducing the number of RBC units used, with fewer associated complications.
- Future research should focus on extended follow-up, addressing population-specific impacts (e.g., variceal vs. peptic ulcer bleeders), and exploring the dose-dependent relationship of RBC transfusions.

Hemoglobin decrease predicts untoward outcomes better than severity of anemia

- The results of our registry analysis demonstrated that a higher ΔHb% was associated with an elevated probability of bleeding-related mortality and the need for urgent intervention, even when nadirHb levels remain above 70 g/L.
- Current GIB risk scores, such as the Glasgow-Blatchford and Rockall, do not adequately account for ΔHb%. Incorporating ΔHb% into future scoring systems may enhance predictive accuracy and resource allocation.
- Future cohort studies and RCTs should further investigate the role of ΔHb% since it may be a more informative measure than nadirHb for guiding transfusion timing and improving transfusion protocols.

Intravenous ferric carboxymaltose versus oral ferrous sulfate replacement in elderly patients after acute non-variceal gastrointestinal bleeding (FIERCE): protocol of a multicentre, open-label, randomised controlled trial

- This RCT aims to address a critical gap by evaluating the effectiveness and safety of IV iron compared to oral iron supplementation in older adults.
- In addition to key clinical endpoints such as mortality, anemia-related emergency visits, and hospital readmissions, the study will assess the impact on quality of life and the effectiveness of iron store restoration.

- The FIERCE trial is poised to provide the first evidence specific to elderly patients with anemia following an acute NVUGIB episode, potentially paving the way for reduced healthcare costs in the future.

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11. List of conference presentations

11.1. Conference presentations related to the subject of the thesis

1. ESGE Days 2023, Dublin - Restrictive transfusion decreases mortality in acute upper gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials – ePoster
2. MGT 65. Nagygyűlés 2023, Siófok - Az anaemia és dinamikájának hatása a GIV kimeneteleire – oral presentation
3. MGT 65. Nagygyűlés 2023, Siófok - Restrictive transfusion is non-inferior to liberal transfusion in upper gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials – poster presentation
4. UEG Week 2023, Copenhagen - RESTRICTIVE TRANSFUSION IS NON-INFERIOR TO LIBERAL TRANSFUSION IN UPPER GASTROINTESTINAL BLEEDING: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS – poster presentation
5. UEG Week 2023, Copenhagen - OPTIMAL THRESHOLD FOR RESTRICTIVE TRANSFUSION AFTER ACUTE GASTROINTESTINAL BLEEDING: INSIGHTS FROM THE HUNGARIAN GASTROINTESTINAL BLEEDING REGISTRY – poster presentation
6. ESGE Days 2024, Berlin - A HAEMOGLOBIN LEVEL OF 61-70 g/L SEEMS AN OPTIMAL THRESHOLD FOR RED BLOOD CELL TRANSFUSION AFTER ACUTE GASTROINTESTINAL BLEEDING: a cohort analysis from the Hungarian Gastrointestinal Bleeding Registry – poster presentation

11.2. Other conference presentations

1. 55th EPC meeting 2023, Alpbach - Psychological interventions improve mental health in inflammatory digestive system diseases: a systematic review and meta-analysis – poster
2. 56th EPC meeting 2024, Santiago de Compostela - Utilizing deep learning models to forecast acute pancreatitis severity – poster presentation
3. ECR 2025, Vienna - Incidence and management of splanchnic vein thrombosis in pancreatic cancer – ePoster