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Ph.D. értekezések

3322.

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HEMODYNAMIC INSTABILITY AND REFEEDING IN PATIENTS WITH GASTROINTESTINAL BLEEDING

Ph.D. Thesis

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Budapest

2025

“Change is the only constant”

Heraclitus

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1 LIST OF ABBREVIATIONS

AASLD	American association for the study of liver diseases
ACG	American college of gastroenterology
APC	Argon plasma coagulation
AVB	Acute variceal bleeding
BP	Blood pressure
CDB	Colonic diverticular bleeding
CENTRAL	Cochrane central register of controlled trials
CI	Confidence interval
DN	Delayed nutrition
EN	Early nutrition
ESGE	European society of gastrointestinal endoscopy
EVBL	Esophageal variceal band ligation
GEVB	Gastroesophageal variceal bleeding
GIB	Gastrointestinal bleeding
GRADE	Grading of recommendations, assessment, development, and evaluations
GVB	Gastric variceal bleeding
HI	Hemodynamic instability
HRS	High-risk stigmata
LOHS	Length of hospital stay
MD	Mean difference
MELD	Model for end-stage liver disease
MWT	Mallory-Weiss tear
NVUGIB	Non-variceal upper gastrointestinal bleeding
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PUB	Peptic ulcer bleeding
RCT	Randomized clinical trial
REDCap	Research electronic data capture
ROB	Risk of bias
RR	Risk ratio
SD	Standard deviation
UGIB	Upper gastrointestinal bleeding
VUGIB	Variceal upper gastrointestinal bleeding

2 STUDENT PROFILE

2.1 Vision, mission, and specific goals

My vision is to improve the care and outcomes of patients with gastrointestinal bleeding through evidence-based, guideline-driven approaches. My mission is to establish the clinical importance of hemodynamic instability, explore how the patient's hemodynamic status influences clinical decision-making, and assess the impact of early refeeding on clinical outcomes. My specific goals are to investigate the proportion of hemodynamic instability in gastrointestinal bleeding and how this affects the timing of endoscopy, as well as to compare the safety and efficacy of early versus delayed refeeding strategies following hemostasis of upper gastrointestinal bleeding.

2.2 Scientometrics

Number of all publications:	16
Cumulative IF:	107.1
Average IF/publication:	6.69
Ranking (SCImago):	D1: (9), Q1: (7)
Number of publications related to the subject of the thesis:	3
Cumulative IF:	33.3
Average IF/publication:	11.1
Ranking (Sci Mago):	D1: (2), Q1: (1)
Number of citations on Google Scholar:	52
Number of citations on MTMT (independent):	25
H-index:	4

The detailed bibliography of the student can be found on pages 74-79

2.3 Future plans

My future plan is to complete my residency training in the field of gastroenterology and interventional endoscopy. I will continue to advance my scientific career by supervising junior PhD students and clinical research methodology supervisors, while also initiating new research projects, including my ongoing international surveys on the pre-endoscopic assessment and management of acute upper gastrointestinal bleeding.

I am also committed to continuing my postgraduate medical education at Harvard Medical School, and to teaching and mentoring medical students as they develop their careers. In parallel, I plan to develop a randomized clinical trial protocol to investigate the impact of early versus delayed refeeding, stratified by bleeding source (variceal and non-variceal) and severity of bleeding, in order to identify which patient subgroups benefit most from each refeeding strategy.

3 SUMMARY OF THE THESIS

This thesis summarizes three distinct and clinically relevant investigations in the field of gastrointestinal bleeding (GIB). The first project is a comprehensive systematic review and meta-analysis that examined the proportion of hemodynamic instability (HI) and shock across various sources of GIB. Including 220 studies and over six million patients, the analysis revealed that one in four patients with GIB develops HI or shock on admission or during hospitalization, with proportions varying by bleeding source: 22% in non-variceal upper GIB, 25% in variceal upper GIB, and 12% in colonic diverticular bleeding. These findings highlight the critical need for early identification and proactive management of hemodynamic instability to prevent adverse outcomes.

In our second project, we conducted an international survey targeting clinicians treating upper GIB, including gastroenterologists, surgeons, and emergency medicine physicians. The 33-question survey assessed participants' demographics, clinical practice settings, definitions of HI, pre-endoscopic assessment, and how the patient's hemodynamic status influences the timing of endoscopy. In total, 533 clinicians completed the survey. We found that the more hemodynamically unstable a patient is, the earlier clinicians tend to perform endoscopy. Physicians with more experience, those working in university-based hospitals, and those treating higher patient volumes were more likely to favor earlier endoscopy, especially in unstable patients. Notably, we also observed a low level of adherence to current international guideline recommendations among respondents.

The third project focused on the timing of nutritional refeeding after upper GIB hemostasis. Through a meta-analysis of 10 randomized controlled trials involving 1051 patients, this study demonstrated that early nutrition (within 24 hours) is safe and does not increase the risk of rebleeding or mortality compared to delayed nutrition in both variceal and non-variceal bleeding sources. Furthermore, early feeding was associated with a significant reduction in hospital length of stay. Together, these studies provide evidence to support guideline-based improvements in the management of HI and nutritional refeeding following GIB.

4 GRAPHICAL ABSTRACT

4.1 Study 1

Investigating The Proportion of Hemodynamic Instability and Shock in Patients with Gastrointestinal Bleeding
A Systematic Review and Meta-analysis

Clinical Question Framework	
Condition	Hemodynamic instability and/or shock
Context	Gastrointestinal bleeding
Population	Adult patients >18 years

Number of articles screened	11,859
Embase	8,129
PubMed	3,134
CENTRAL	326

Bleeding source	N of studies	N of patients	Proportion	95% CI
Gastrointestinal bleeding	18	6414375	0.25	0.17-0.36
Upper gastrointestinal bleeding	43	3621670	0.20	0.15-0.27
Non-variceal upper gastrointestinal bleeding	25	3379357	0.22	0.14-0.31
Peptic ulcer bleeding	66	56882	0.25	0.21-0.30
Variceal upper gastrointestinal bleeding	34	100446	0.25	0.19-0.32
Lower gastrointestinal bleeding	17	3350511	0.27	0.13-0.49
Colonic diverticular bleeding	8	1517	0.12	0.06-0.22

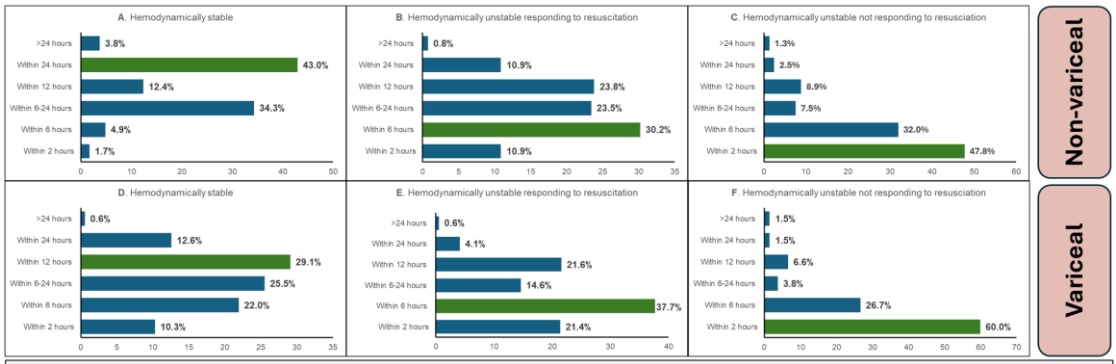
Obeidat M. et al., 2023, World Journal of Gastroenterology; DOI: https://dx.doi.org/10.3748/wjg.v29.i28.4466

4.2 Study 2

Hemodynamic Status as a Determinant Factor of Optimal Endoscopy Timing in Upper Gastrointestinal Bleeding
Results from an International Survey of 533 Clinicians

Main section of the questionnaire	N
Demographics and Clinical Practice	9
Definition of Hemodynamic Instability	1
Pre-endoscopic Assessment	17
Optimal Time for Endoscopy	6
Total questions	33

FACTORS INVESTIGATED	
Hemodynamic Instability	Stable, unstable responding, unstable not responding
Bleeding Source	Variceal and non-variceal bleeding
Years of Clinical Practice	Still in training | < 5 | 5-10 | 11-15 | 16-20 | > 20 years
Annual Patient Volume	< 100 | 100-200 | > 200 patients
Type of Hospital	Community | University | Private



In total, 533 clinicians completed the survey (50 countries). We fount a consistent trend: the more hemodynamically unstable the patients are, the earlier physicians tend to perform endoscopy for upper GIB. More experienced physicians working in university-based hospitals, and managing high patient volumes, favor earlier endoscopy, particularly in hemodynamically unstable patients. Poor adherence to guideline recommendations was observed.

Obeidat M. et al., 2025, *Gastroenterology*

4.3 Study 3

Early versus Delayed Nutrition after Upper Gastrointestinal Bleeding Hemostasis
A Systematic Review and Meta-analysis of Randomized Clinical Trials

Articles screened	1712
Embase	904
PubMed	211
CENTRAL	340
Scopus	101
Web of Science	165

RCTs included = 10
Variceal bleeding = 5
Peptic ulcer bleeding = 5
Patients in total = 1051

Outcomes investigated	Early Nutrition (n = 527)	RR with 95% CI	Delayed Nutrition (n = 524)
Early rebleeding (7-days)	24/465	1.04 (0.66-1.63)	21/458
Late rebleeding (30-42 days)	25/347	1.16 (0.63-2.13)	22/346
Early mortality (7-days)	3/274	1.20 (0.85-1.71)	2/269
Late mortality (30-42 days)	17/335	0.61 (0.35-1.06)	29/332
New-onset bacterial infection	8/128	0.48 (0.08-3.05)	16/123
New-onset ascites	12/128	0.64 (0.34-1.20)	18/123
Outcomes investigated		**MD with 95% CI**	
Length of hospital stay (days)	289	-1.22 (-2.43 to -0.01)	281
Blood transfusion (units)	292	0.00 (-0.04 to 0.05)	286

Early nutrition (within 24 hours) following upper gastrointestinal bleeding is safe, does not increase the risk of complications compared to delayed nutrition (> 24 hours), and is associated with a reduced length of hospital stay.

Obeidat M. et al., 2024, Scientific Reports; DOI: 10.1038/s41598-024-61543-z

5 INTRODUCTION

5.1 Overview of hemodynamic instability in gastrointestinal bleeding

The annual incidence of gastrointestinal bleeding (GIB) is 100 per 100,000 population, with an estimated mortality between 2-10%, primarily due to complications related to the admission state and individual patient factors (1, 2). It is associated with significant morbidity and health care costs (3, 4). The mortality rate of upper GIB (UGIB) has not considerably decreased over the past decades, despite the improvement in the diagnosis and endoscopic treatment (5).

Several studies showed that hemodynamic instability (HI) and shock in GIB are highly associated with unfavorable outcomes; they can lead to higher mortality, rebleeding, prehospital transfusion, and endoscopic sedation complications (6-8). Furthermore, the hospital mortality of bleeding with shock can be 10 times higher than without shock (9).

5.2 Overview of refeeding after upper gastrointestinal bleeding

The optimal time of refeeding after UGIB endoscopic hemostasis is still debated. Early nutrition (EN) has been suggested to improve outcomes by reducing the risk of infections (10) and maintaining gut mucosal integrity. On the other hand, delayed nutrition (DN) has been considered to minimize the risk of rebleeding and other complications arising from introducing food or nutrients too soon after an episode of bleeding (11, 12). However, it can also lead to malnutrition and delayed recovery.

The optimal time to start feeding remains a controversial topic, and the nutrition strategy should be based on endoscopic findings in patients with UGIB (11). Individual patient factors, such as severity of bleeding (e.g., Forrest classification and varices grade), comorbidities, and risk of complications, should also be considered when making clinical decisions. In this context, it is essential to weigh up the potential benefits and risks of early versus delayed refeeding.

6 OBJECTIVES

6.1 Study 1

At the time of our systematic search, there were no published systematic reviews assessing the proportion of HI or shock in GIB. There are large variations in the proportions of these outcomes. Some studies in variceal (VUGIB) and non-variceal bleeding (NVUGIB) resulted in proportions of 10% or lower (13-16), whereas others exceeded 60% (17-19). Therefore, we aimed to highlight the importance of recognizing those patients by quantifying the pooled proportions based on the bleeding source. Additionally, we did a subgroup analysis based on the assessment time of these outcomes (on admission or during hospital stay). Furthermore, we aimed to collect all the available definitions of HI reported in the included studies (20).

6.2 Study 2

This international online survey aimed to investigate how physician characteristics (years of clinical practice, hospital type, and annual UGIB patient number) influence the preferred time of endoscopy in UGIB patients with different hemodynamic conditions (stable, unstable responding, and unstable not responding to hemodynamic resuscitation). We hypothesized that significant variability exists in clinical decision-making based on these factors.

6.3 Study 3

Some studies showed that EN could be beneficial in reducing complications in patients with UGIB (21-23); however, others favored DN (12, 24). A previous meta-analysis by Zhang et al. (25) set out to investigate this clinical question, but included only five studies. In contrast, we evaluated a broader spectrum of outcomes and analyzed the early and late rebleeding and mortality separately. In addition, we included five more trials. Therefore, we meta-analyzed randomized controlled trials (RCTs) to assess the efficacy and safety of EN compared to DN and grouped them by source of bleeding (26).

7 METHODS

In case of our first and third studies, both systematic reviews and meta-analyses were conducted following the recommendations of the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines (27, 28). The study protocols were registered on PROSPERO (CRD42021283258; CRD42022372306) in advance, and we fully adhered to them (29). Regarding our international survey study, it was conducted following the recommendations of the Checklist for Reporting Of Survey Studies (CROSS) guideline (30).

7.1 Study 1

7.1.1 Eligibility criteria

We applied the CoCoPop (condition, context, and population) framework to establish the eligibility criteria (31). The condition of interest was HI and/or shock in the context of GIB. The study population included adult patients (>18 years). All available definitions of HI and shock were accepted and systematically collected.

RCTs, cohorts, and case-control studies were included. Cross-sectional studies were included only if the hemodynamic parameters were assessed on admission. We included studies only if the primary cause of hospital admission was GIB and excluded articles that assessed our investigated outcomes after specific interventions. Articles that could not be found were sought for retrieval by contacting the journals and the authors. In the case of studies with overlapping populations, we kept the ones with larger sample sizes.

7.1.2 Information sources

Our systematic search was conducted in three main databases: MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from the inception to 14th October 2021. No language or other restrictions were applied.

7.1.3 Search strategy

Our search key contained two main concepts: all types of bleeding sources and hemodynamic instability or shock. This was our full search key: (gastrointestinal haemorrhage OR gastrointestinal hemorrhage OR gastrointestinal bleed* OR GI bleed* OR GIB OR UGIB OR LGIB OR ((nonvariceal OR non variceal OR variceal OR varix OR ulcer) AND bleeding)) AND ((shock) OR ((hemodynamic* OR haemodynamic*) AND (instability OR unstable OR compromised))).

7.1.4 Screening and selection

All identified articles were imported into a reference management software (EndNote version 20.1). Duplicate records were removed based on overlapping publication year, authors, and title. Screening and selection were conducted independently by two reviewers (M.O. and E.T.), initially by title and abstract, followed by full-text evaluation. Inter-reviewer agreement was assessed using Cohen's kappa coefficient (κ) at both screening levels. Any disagreements were resolved through discussion with the corresponding author (B.E.) when necessary.

7.1.5 Data extraction

Relevant data from the eligible studies were extracted independently by two authors (M.O. and A.R.). Discrepancies were resolved in consultation with the corresponding author (B.E.). All extracted data were recorded in a standardized Excel spreadsheet (Office 365, Microsoft, USA). The following variables were collected: first author, year of publication, geographical location, study period and design, number of centers, patient demographics, source of bleeding, total number of GIB patients and those who developed HI or shock, definitions of outcomes, and timing of outcome detection (on admission or during hospital stay).

7.1.6 Risk of bias assessment and quality of evidence

Two independent authors (M.O. and E.T.) performed the risk of bias assessment using the 'Joanna Briggs Institute Prevalence Critical Appraisal Tool' (31). A third reviewer

resolved potential disagreements (A.R.). The tool contains nine items regarding the target population and study settings. Each item was rated as 'yes', 'no', 'unclear', or 'not applicable' according to information provided in each study, with a maximum score of nine points. The higher the score, the lower the risk of bias.

We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence of our results (32), and the GRADEpro tool (software) was used. Study design, risk of bias, inconsistency, indirectness, and imprecision were the determining factors.

7.1.7 Statistical synthesis

We used forest plots to summarize the findings of the studies and show the pooled result. Pooled event rates were calculated with 95% confidence intervals (CIs). The random-effect model was anticipated as applied in all analyses, as considerable between-study heterogeneity. The random intercept logistic regression model method was used for the pooling method as recommended by Schwarzer et al. (33). To estimate the heterogeneity variance measure τ^2, the maximum likelihood method was used. For the outcomes where the study number was at least five, a Hartung-Knapp adjustment was used (34, 35). If the number of studies was less than five, we applied the adjustment if it was more conservative than without the adjustment. Statistical heterogeneity was assessed by Higgins and Thompson's I^2 (36).

Egger's test with Peter's modification and funnel plots were applied to assess and visualize publication bias when at least 10 studies were included in the analysis (37). A P value <0.1 was considered indicative of potential publication bias. In addition, we conducted an influential sensitivity analysis using the leave-one-out method to evaluate whether any single study had a substantial impact on the overall proportional rate or heterogeneity.

A subgroup analysis was performed based on the timing of assessment of HI or shock (on admission vs. during hospitalization). Studies without clear information on the timing of assessment were classified as during hospitalization. Differences between subgroups were evaluated using the Cochrane Q test (38). We did not compute pooled effects or heterogeneity estimates for subgroups with fewer than three studies. Prediction intervals were calculated for the main outcomes to estimate the probability that future studies would yield similar results in comparable settings (39). All statistical analyses were conducted in R using the *meta* package.

7.2 Study 2

7.2.1 Study design

This cross-sectional international online survey included two phases of prospective data collection. The distribution was conducted between April 2023 and November 2023.

7.2.2 Study population

The target population consisted of physicians who actively managed patients with acute UGIB, including gastroenterologists, surgeons, anesthesiologists, emergency department physicians, and intensivists.

7.2.3 Survey development and content

Content validity was established following an independent review of the survey, which included 12 international experts. A pilot phase was then performed by a group of 20 physicians, including the co-authors, whose insights contributed to the final version of the survey.

The survey consisted of four domains, totaling 33 questions. The first domain concerned demographics and clinical experience of physicians; the second domain focused on how clinicians define HI, the third domain covered pre-endoscopic assessment and management, and the fourth addressed the timing of endoscopy for UGIB patients based on their hemodynamic status (stable, unstable responding to resuscitation, and unstable

not responding to resuscitation). In this study, we focused on the first, second, and fourth domains related to the optimal timing of endoscopy.

7.2.4 Data management

Survey data were collected and managed using Research Electronic Data Capture (REDCap), an electronic data capture hosted at Semmelweis University (40, 41). Only complete survey responses were included; incomplete ones were excluded. All participant data were de-identified to ensure confidentiality.

7.2.5 Survey distribution

The survey was first distributed at the ESGE Days endoscopy conference in Dublin, Ireland, in April 2023; the QR code of our survey was projected during the conference. Additionally, invitations were sent via email to national and international gastrointestinal societies to solicit their endorsement of our survey. We also distributed the survey during the United European Gastroenterology (UEG) week in Copenhagen, Denmark, in October 2023. Following this, the study period closed in November 2023, and analyses were conducted.

The survey was officially endorsed by the Hungarian Society of Gastroenterology, the French Society of Gastroenterology, the French Society of Endoscopy, the Spanish Society of Gastrointestinal Endoscopy, the Romanian Society of Gastroenterology, the Czech Gastroenterology Society, the Inter-American Society of Digestive Endoscopy, and the Association of Scientific-Medical Societies of Chile. It was also distributed in *Endoaula,* a virtual endoscopy academy with over 2,000 endoscopists from Spain and Latin America, with the assistance of Joaquín Rodríguez Sánchez. Additionally, the survey link was shared on X and LinkedIn, and co-authors distributed it within their professional networks.

7.2.6 Statistical analysis

The primary analysis involved a descriptive assessment of individual survey response items across the four domains. Descriptive statistics were reported as proportions for categorical data (number of cases and percentages) (40, 41). The secondary analysis examined differences in survey responses based on the number of years of clinical experience.

To assess heterogeneity in endoscopy timing preferences across clinician experience levels, categorical data were analyzed using Pearson's Chi-square tests (42). The null hypothesis assumed no association between clinician experience and endoscopy timing preferences, indicating uniform practice patterns. Group differences were considered statistically significant if the p-value was less than 0.05.

We used multinomial logistic regression to predict the probability of selecting the timing of endoscopy, using R software (v4.3.1) and the *nnet* package (v7.3- 19) (43). Three explanatory variables were selected based on variable importance determined by random forests: years in practice (still in training, <5 years, 5–10 years, 11–15 years, 16–20 years, and >20 years), hospital type (community-based, university-based, or private), and annual UGIB patient volume (<100, 100–200, or >200 patients). Physicians who were unaware of their patient volume were excluded. The probability of selecting each endoscopy timing (within 2, 6, 12, 24, 6-24, and >24 hours of patient presentation) was estimated across three different hemodynamic statuses for both variceal (VUGIB) and non-variceal (NVUGIB) bleeding sources. Statistical significance was defined as p <0.05.

7.3 Study 3

7.3.1 Eligibility criteria

We applied the PICO (patients, intervention, comparison, outcome) framework to establish our eligibility criteria; patients were upper gastrointestinal bleeders, including VUGIB and NVUGIB sources, and the intervention was EN compared to DN. Our primary outcomes were early (within 7 days) and late (within 30-42 days) rebleeding and mortality, whereas the length of hospital stay (LOHS), bacterial infection, transfusion

requirement, new-onset ascites, and hepatic encephalopathy were our secondary endpoints. Any definition for EN and DN was accepted as specified by the included studies. Only RCTs were included in our analysis.

7.3.2 Information sources

Our systematic search was conducted in five main databases: Embase, MEDLINE (via PubMed), Cochrane Library, Scopus, and Web of Science, from inception to 10th November 2022, and we updated the search on the 27th of August 2023. No language or other restrictions were applied. In addition, a backward and forward citation search was performed using a reference-checking tool to identify all potential references that met our eligibility criteria.

7.3.3 Search strategy

Our search key included three domains. The first domain focused on the refeeding time, whereas the second domain included sources of GIB. The third domain focused on the concept of randomization. This was our full searchkey used: (((oral or enteral or early or immediate or delayed or late) and (feeding OR nutrition OR refeeding)) OR enteral nutrition OR enteric feeding) AND (gastrointestinal haemorrhage OR gastrointestinal hemorrhage OR gastrointestinal bleed* OR GI bleed* OR GIB OR UGIB OR ((nonvariceal OR non variceal OR non-variceal OR variceal OR varix OR ulcer) AND bleeding)) AND random*.

7.3.4 Screening and selection

The resulting articles were imported into a reference management program (EndNote 20.1). Duplicate articles with overlapping publication years, authors, and titles were removed. Screening and selection were performed by two independent reviewers (M.O. and D.E.F.), first by title and abstract, and then by full text. Cohen's kappa coefficient was calculated at both levels of selection to measure the inter-reviewer reliability. In case of any disagreement, consensus was reached after discussion with the corresponding author (B.E.).

7.3.5 Data extraction

Relevant data from the included studies were independently extracted by two authors (M.O. and D.E.F.), and disagreements were resolved through consultation with the corresponding author (B.E.). All data were manually collected and entered into an Excel spreadsheet (Office 365; Microsoft, Redmond, WA, USA) for subsequent analysis.

7.3.6 Data items

The following data were extracted: first author, year of publication, study population, geographic location, study design and period, basic demographics (sex and age), source of bleeding, and bleeding severity scores, including Forrest classification for peptic ulcer bleeding (PUB). Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, and size of esophageal varices were also extracted. In addition, we extracted the definition of the outcomes of interest and the definition of the interventions in terms of timing and type of diet used.

7.3.7 Risk of bias assessment and quality of evidence

The methodological quality of each trial was independently assessed by two authors (M.O. and D.E.F.) using the revised Cochrane risk-of-bias tool (ROB 2) (44). Disagreements were resolved by a third reviewer (B.T.). The following domains were evaluated: bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Risk-of-bias plots were generated using the RobVis (Risk-Of-Bias VISualization) tool (45).

To assess the quality of evidence for our results, we followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (32), and used the GRADEpro Guideline Development Tool (software) to produce the summary tables of findings. The determinants were study design, risk of bias, inconsistency, indirectness, and imprecision.

7.3.8 Statistical synthesis

A minimum of three studies was required to perform a meta-analysis. Given the anticipated between-study heterogeneity, random-effects models were applied to pool effect sizes. All statistical analyses were conducted in R (R Core Team, 2019; Vienna, Austria).

Risk ratios (RRs) with 95% CIs were used as the effect measure for dichotomous outcomes, while mean differences (MDs) were used for continuous outcomes. To calculate study-specific and pooled RRs, we extracted the total number of patients and the number of patients with the event of interest in each group. Results were reported as the risk of an event in the EN group compared with the DN group. For pooled MDs, we extracted the mean and standard deviation (SD) from each study. Two studies by Jatin et al. (23) and Gong et al. (24) reported the LOHS using median and SD; therefore, we performed the analysis without them, and included them in a separate analysis assuming a symmetrical distribution where the mean was equal to the median (as the other study reported using mean and SD, we assumed that this was acceptable). The MD was expressed as the mean of the EN group minus the mean of the DN group.

The pooled RR was calculated using the Mantel-Haenszel method (46, 47). The exact Mantel-Haenszel method (without continuity correction) was used to handle zero cell counts as recommended (48). The inverse variance weighting method was used to calculate the pooled MD. We used a Hartung-Knapp adjustment for CIs (34, 35). To estimate the heterogeneity variance measure (τ^2) for RR calculation, the Paule-Mandel method (49) was used. For the MD calculation, the restricted maximum-likelihood estimator was used with the Q profile method for CI. Prediction interval calculations were based on the t-distribution.

Results were considered statistically significant if the 95% CI did not include the null value. Meta-analysis findings were summarized in forest plots. For studies with zero cell counts, a continuity correction of 0.5 was applied to calculate RRs with 95% CIs (used

only for forest plots). Where appropriate (i.e., sufficient number of studies and acceptable heterogeneity), prediction intervals were also reported. Heterogeneity was assessed using Higgins and Thompson's I^2 statistic in addition to τ^2 (36).

For subgroup analyses, we applied a fixed-effects "plural" (mixed-effects) model, assuming different τ^2 values across subgroups. Differences between subgroups were assessed using Cochran's Q test, with statistical significance set at $P < 0.05$. The subgroup analysis by source of bleeding was pre-specified before data collection. Publication bias in small studies was evaluated by visual inspection of funnel plots and by statistical testing using Harbord's test for RRs (50) and Egger's test for MDs (51). A P value < 0.10 was considered indicative of potential small-study effects, while recognizing the limited power of these tests with fewer than 10 studies. Potential outliers were examined using influence measures and plots as recommended by Harrer et al. (52).

All statistical analyses were performed with *R* (v4.1.2) using the *meta* (53) (v6.1.0) package for basic meta-analysis calculations and plots, and the *dmetar* (54) (v0.0.9000) package for additional influential analysis.

8 RESULTS

8.1 Study 1

8.1.1 Systematic search, selection, study characteristics

Altogether, 11,589 studies were identified. Of them, 9,192 records remained for title and abstract selection after duplicate removal. In total, 466 studies were assessed for full-text eligibility, of which 246 were excluded. Altogether, 220 studies were included. Details of search and selection are illustrated in the PRISMA 2020 flow chart (Figure 1).

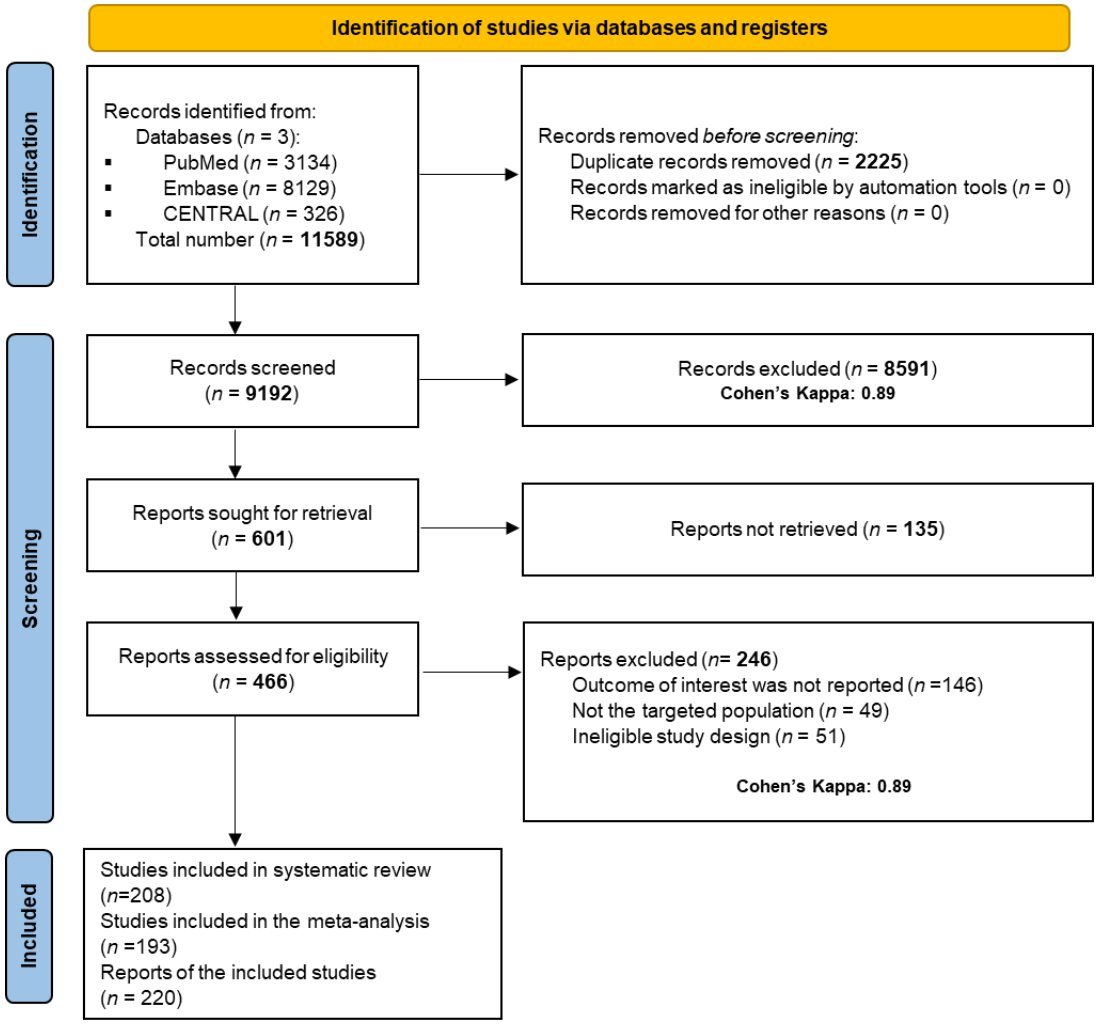


Figure 1. PRISMA flowchart of the article selection process of study 1

Most of the included studies were cohort studies; additionally, we identified 28 RCTs, 6 case–control studies, and 4 cross-sectional studies. Geographically, 80 records originated from Asia, 66 from Europe, 25 from North America, and 13 from Africa. Altogether, the analysis included more than six million patients. The largest study contributed 6,411,838 patients with various bleeding sources, based on a 12-year national dataset from the United States (9).

8.1.2 Main outcomes

We included all studies with unspecified bleeding sources. HI was assessed on admission and during hospital stay with pooled event rates of 0.29 (CI: 0.12 – 0.56) and 0.34 (CI: 0.11 – 0.68), respectively. Shock on admission was 0.27 (CI: 0.08 – 0.60), whereas during hospital stay it was 0.15 (CI: 0.05 – 0.36). One in four patients with GIB developed HI or shock; 0.25 (CI: 0.17 – 0.36). (Figure 2)

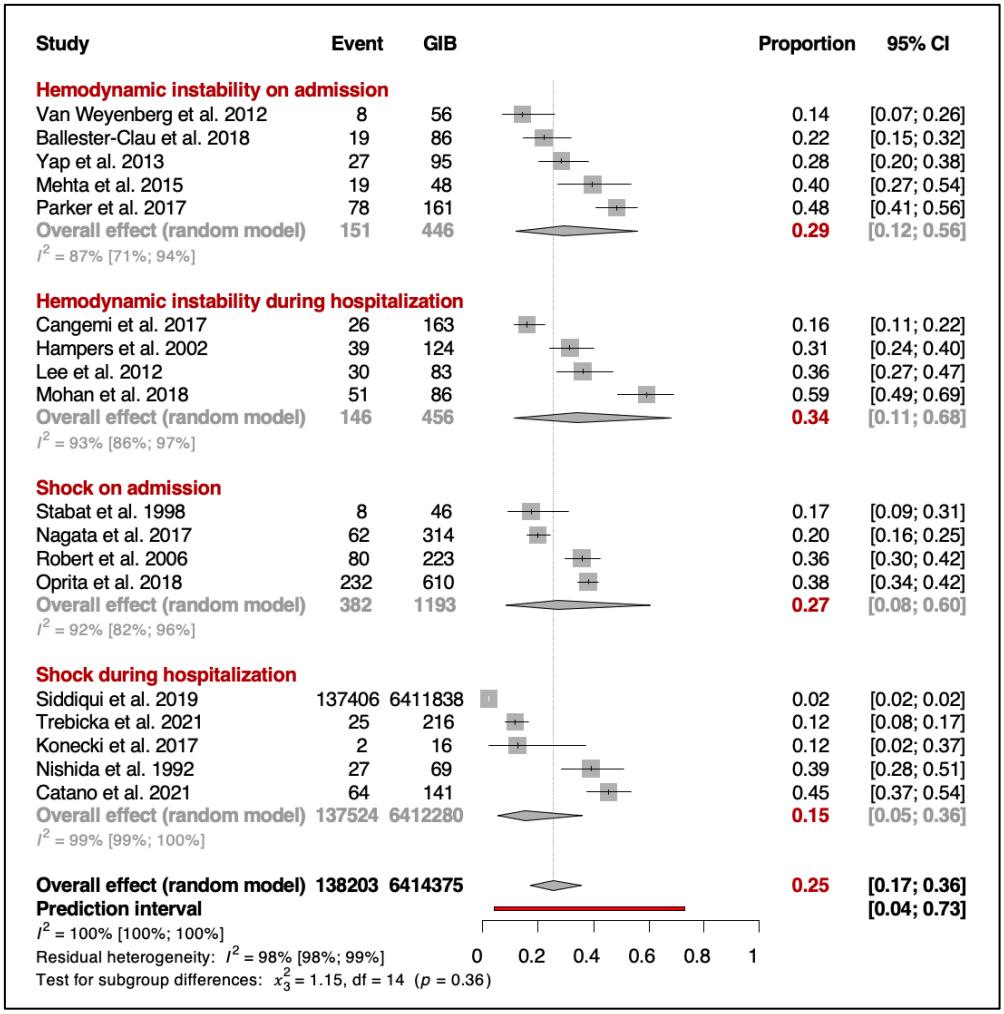


Figure 2. Forest plot demonstrates the proportion rates for hemodynamic instability and shock in unspecified gastrointestinal bleeding sources. GIB: Gastrointestinal bleeding, CI: Confidence interval

In the case of NVUGIB, more than three million patients were included in the analysis. The proportion of HI on admission was 0.21 (CI: 0.12 – 0.36). Moreover, shock on

admission was the highest at 0.36 (CI: 0.21 – 0.53), with a noticeable difference from those who developed shock during hospitalization, with a rate of 0.07 (CI: 0.02 – 0.18). Altogether, 0.22 (CI: 0.14 – 0.31) of non-variceal bleeders developed shock or HI on admission or during the hospital stay. (Figure 3)

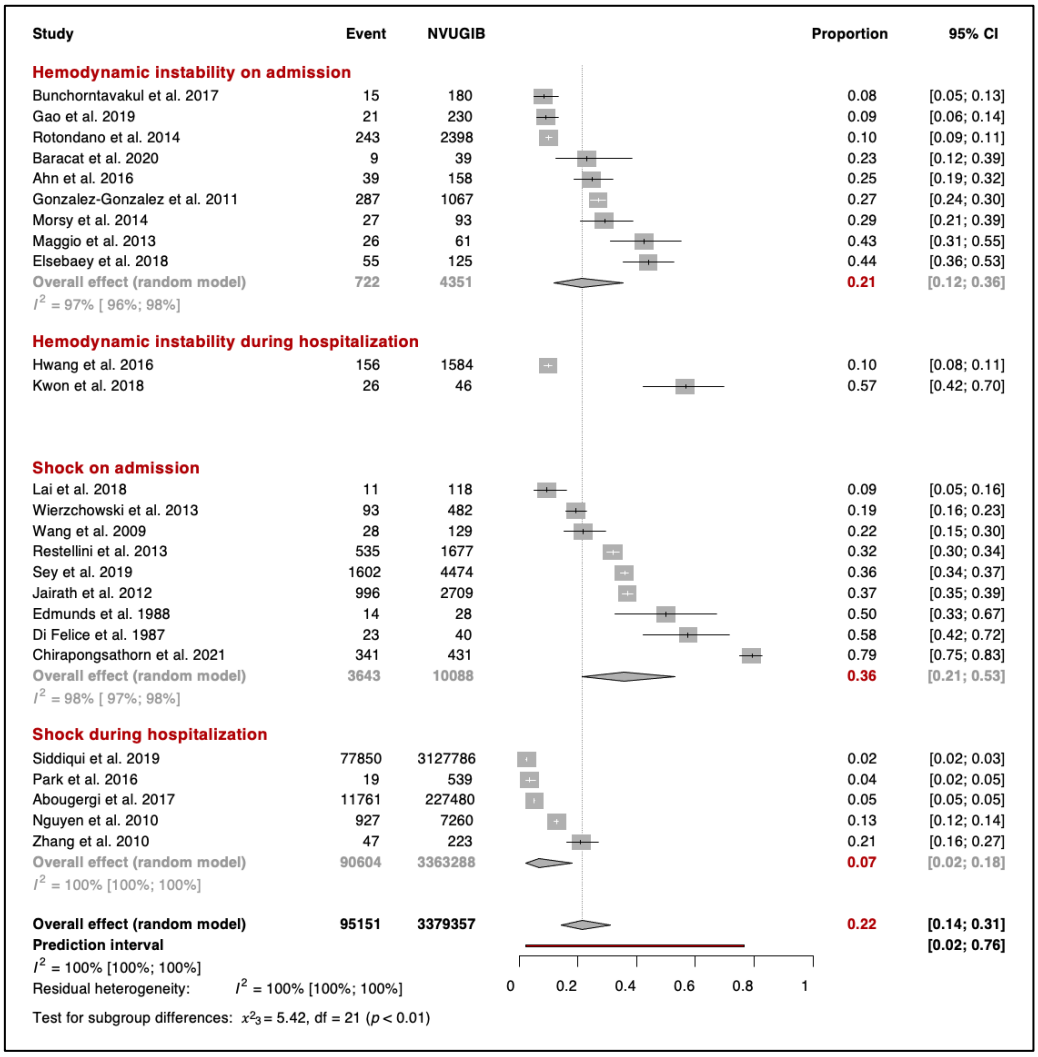


Figure 3. Forest plot demonstrates the proportion rates for hemodynamic instability and shock in non-variceal bleeding. NVUGIB: Non-variceal upper gastrointestinal bleeding, CI: Confidence interval

The rate of patients with VUGIB who presented with HI on admission was 0.38 (CI: 0.12 – 0.73). The shock rate on admission was 0.26 (CI: 0.18 – 0.36), whereas it was 0.18 (CI: 0.10 – 0.30) during the hospital stay. In total, one in four patients with VUGIB developed shock or HI at presentation or during hospital stay, 0.25 (CI: 0.19 – 0.32). (Figure 4)

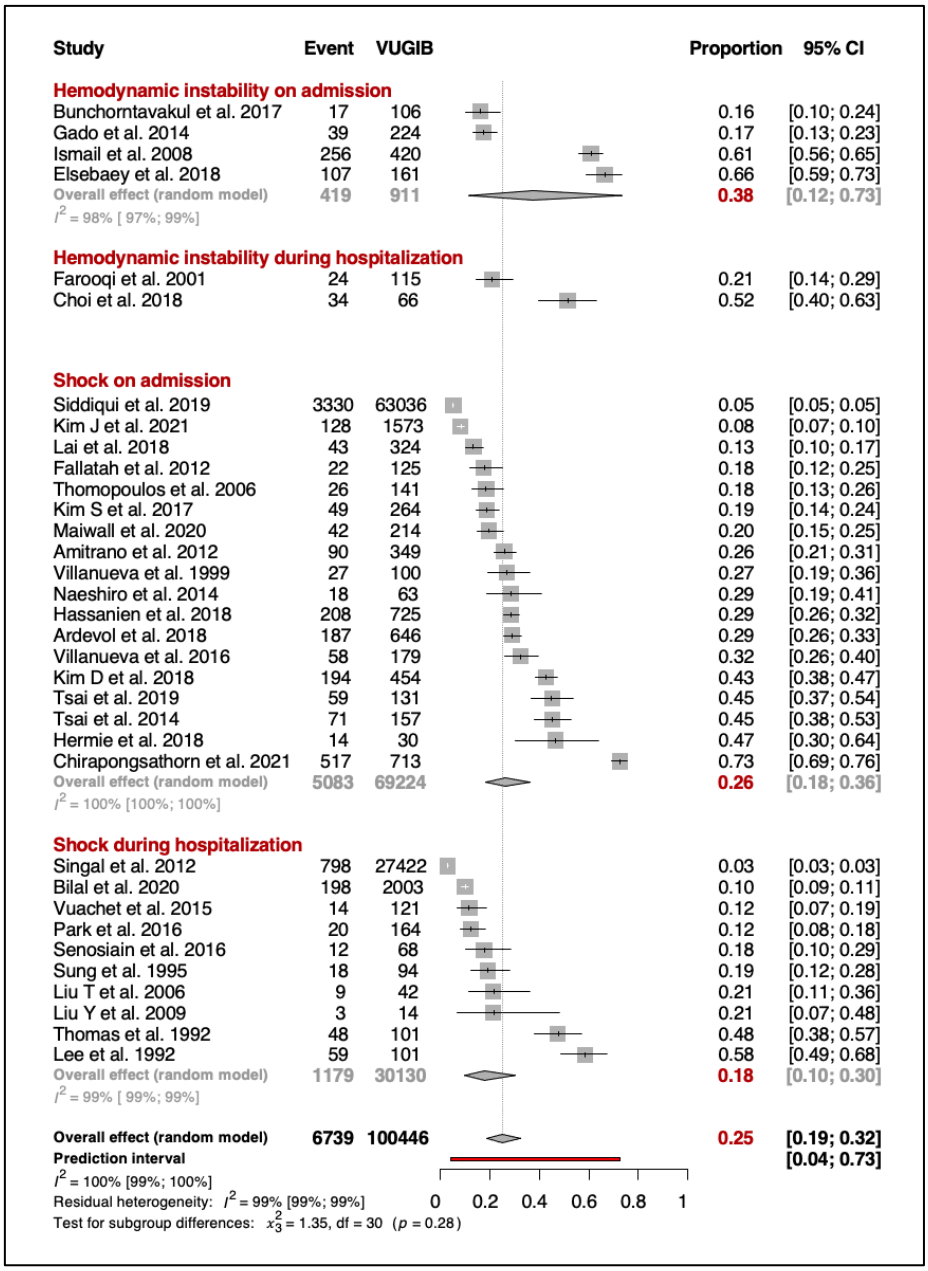


Figure 4. Forest plot demonstrates the proportion rates for hemodynamic instability and shock in variceal bleeding. VUGIB: Variceal upper gastrointestinal bleeding, CI: Confidence interval

Thirteen studies evaluated HI in the lower GIB population: three studies on admission with a rate of 0.14 (CI: 0.01 – 0.81), and 10 studies during hospitalization with a rate of 0.49 (CI: 0.27 – 0.71). The study by Lv et al. (55), which involved patients with life-threatening bleeding, resulted in the highest pooled event rate of shock, with a rate of 0.68

(CI: 0.50 – 0.82). In total, of the general lower GIB population, 0.27 (CI: 0.13 – 0-49) developed shock or HI. (Figure 5)

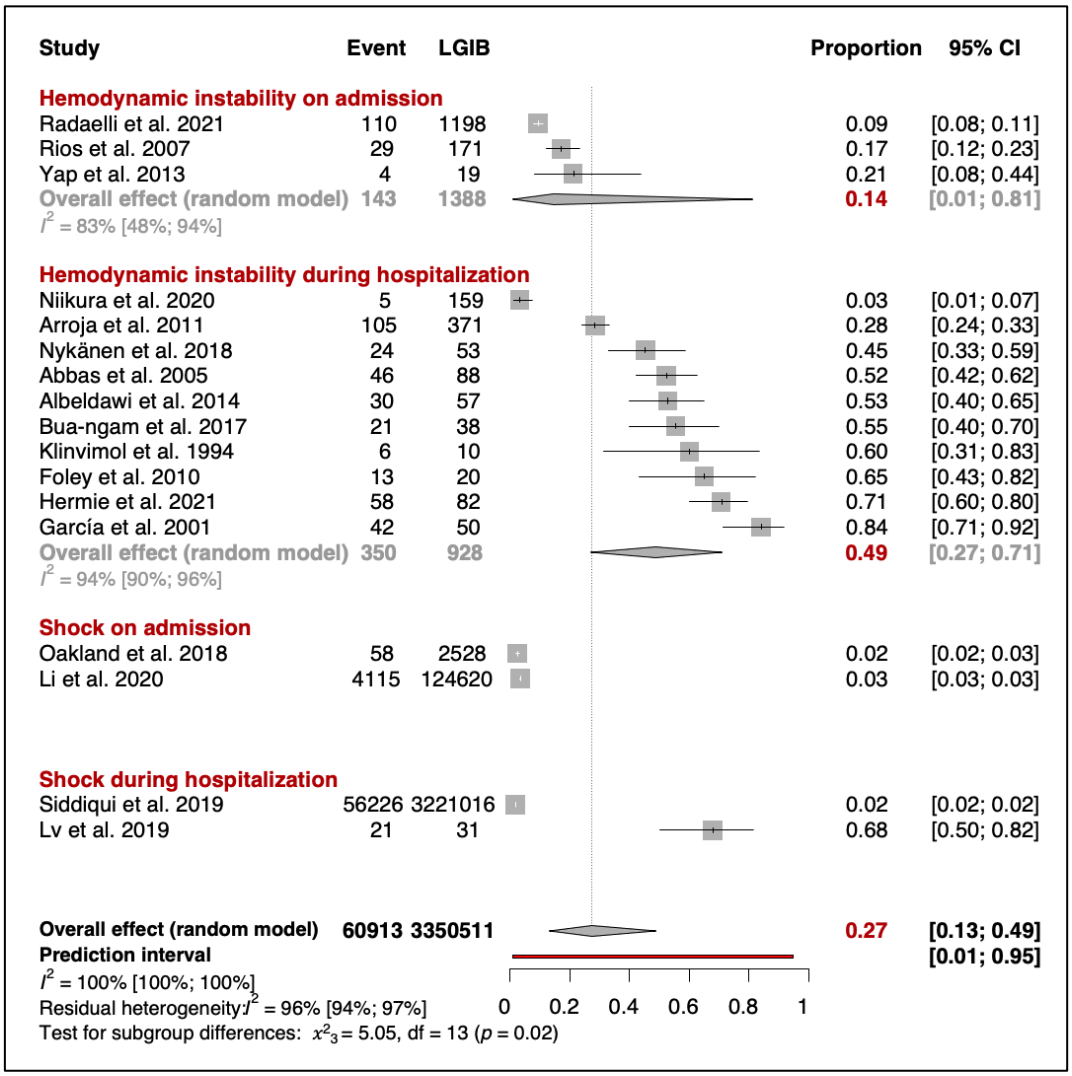


Figure 5. Forest plot demonstrates the proportion rates for hemodynamic instability and shock in lower gastrointestinal bleeding. LGIB: Lower gastrointestinal bleeding, CI: Confidence interval

8.1.3 Other outcomes

PUB was the most reported source of bleeding among the included studies. Sixty-seven studies were involved. On admission, 0.22 (CI: 0.09 – 0.44) of the patients were hemodynamically unstable, whereas during the hospital stay, it was 0.41 (CI: 0.12 – 0.78). The rate of shock on admission was 0.25 (CI: 0.19 – 0.32), whereas 0.24 (CI: 0.17 – 0.33)

developed shock during hospitalization. Overall, one in four PUB patients was affected by HI or shock on admission or during hospital stay; 0.25 (CI: 0.21 – 0.30).

Some studies included patients with UGIB; however, they did not specify the source of bleeding. All the studies that reported HI were assessed on admission, with a rate of 0.33 (CI: 0.21 – 0.48). Seventeen studies were included in the shock on admission subgroup with a rate of 0.15 (CI: 0.09 – 0.25), whereas 18 studies evaluated shock during hospitalization with a rate of 0.20 (CI: 0.12 – 0.32). In total, one in five patients with UGIB developed shock or HI; 0.20 (CI: 0.15 – 0.27).

Six studies evaluated shock on admission in colonic diverticular bleeding (CDB) with a rate of 0.12 (CI: 0.05 – 0.26). Only two studies reported HI, that of Gilshtein et al.(56) reported a rate of 0.05 (CI: 0.02 – 0.11), and Ichiba et al.(57) a rate of 0.21 (CI: 0.17 – 0.26). As an overall effect, the proportion of shock and HI in CDB was 0.12 (CI: 0.06 – 0.22).

Regarding the risk of bias assessment, most of the studies received a score of 6 or higher, indicating a moderate to low risk of bias. Only 10 studies were rated with a score of less than six. Serious heterogeneity (with more than 80%) was observed in all our analyses. The large number of included studies with heterogeneous populations regarding age and sex could explain this. The definitions of HI and shock in the studies were not the same, resulting in considerable heterogeneity, too.

8.2 Study 2

8.2.1 Demographics and clinical practice

A total of 533 physicians completed our survey out of 868 contacted (61.4%). The majority of responses were from Europe, 355 (66.6%), followed by Latin America, 101 (18.9%), and Asia, 44 (8.2%). Most respondents specialized in gastroenterology, 446 (83.7%), while others worked in surgery, 43 (8.1%), or emergency

medicine/ICU/anesthesiology, 34 (6.4%). Over half of the physicians, 291 (54.6%), practiced in university hospitals, with more than 100 UGIB patients hospitalized annually, 361 (67.7%). Regarding clinical experience, 297 (55.7%) reported less than 10 years, 114 (21.4%) 11-20 years, and 122 (22.9%) more than 20 years. (Table 1)

Table 1. Demographics and clinical practice of survey respondents

Practice location (n = 533)	**N (%)**
Europe	355 (66.6)
Latin America	101 (18.9)
Asia	44 (8.2)
North America	16 (3)
Africa	13 (2.4)
Australia	4 (0.75)
Medical specialty (n = 533)	
Gastroenterology	446 (83.7)
Intensive Care Unit	7 (1.3)
Surgery (performing GI endoscopy)	43 (8.1)
Emergency Medicine	23 (4.3)
Anesthesiology	4 (0.8)
Other	10 (1.9)
Type of practice (n = 533)	
University hospital	291 (54.6)
Private hospital	92 (17.3)
Community-based hospital	150 (28.1)
Years in practice (n = 533)	
Currently in training	82 (15.4)
< 5 years	129 (24.2)
5-10 years	86 (16.1)
11-15 years	74 (13.9)
16-20 years	40 (7.5)
> 20 years	122 (22.9)

Yearly UGIB patients (n = 533)	
< 100	148 (27.8)
100 - 200	153 (28.7)
> 200	208 (39.0)
Not sure	24 (4.5)

N: number of responders, UGIB: upper gastrointestinal bleeding, GI: gastrointestinal

The majority of clinicians, 443 (83.1%), had 24-hour emergency endoscopy (including weekends) available. Emergency interventional radiology was only available to 295 (55.3%) of respondents. Nearly all clinicians, 516 (96.8%), had access to surgical support when needed. Most of them, 378 (70.9%), followed a clinical care pathway or protocol for the initial assessment of UGIB, yet 155 (29.1%) did not. Risk stratification scores were used only by 322 (60.4%) of respondents, and the Glasgow-Blatchford Score (GBS) was the most commonly used (72.7%). These findings highlight variability in resource availability and adherence to acute UGIB assessment protocols. (Table 2)

Table 2. Location of clinical practice for UGIB management.

Question (n = 533)	N (%)
24-hour emergency endoscopy (including weekends)	
Yes	443 (83.1)
No	90 (16.9)
Interventional radiology (emergency on-call)	
Yes	295 (55.3)
No	238 (44.7)
Surgery (if needed)	
Yes	516 (96.8)
No	17 (3.2)
Local clinical care pathway/protocol used for initial assessment	
Yes	378 (70.9)
No	155 (29.1)

The use of risk stratification scores	
Yes	322 (60.4)
No	211 (39.6)

N: number of responders, UGIB: upper gastrointestinal bleeding.

8.2.2 Definition of hemodynamic instability

We proposed six different definitions of HI, based on the literature (20). While the most commonly chosen definition (systolic blood pressure <100 mmHg and heart rate >100 bpm or syncope, or orthostatic hypotension, or signs of organ hypoperfusion) was selected by 345 (64.7%) of respondents, the remaining 188 (35.3%) used more limited criteria. These included definitions based solely on systolic blood pressure <100 mmHg or heart rate >100 bpm, 62 (11.6%), or a combination of both, 72 (13.5%). This variability highlights the lack of consensus in defining HI, which may affect clinical decision-making and risk stratification. (Table 3)

Table 3. Definitions of hemodynamic instability among survey respondents

Definition	N (%)
Systolic BP <100 mmHg and HR >100 bpm or syncope or orthostatic hypotension or signs of organ hypoperfusion	345 (64.7)
Systolic BP <100 mmHg and HR >100 bpm	72 (13.5)
Systolic BP <100 mmHg or HR >100 bpm	62 (11.6)
Shock index >1 (calculated by dividing the HR by Systolic BP)	30 (5.6)
Systolic BP <100 mmHg only	12 (2.3)
HR >100 bpm only	5 (0.9)
Other	7 (1.3)

8.2.3 Optimal time of endoscopy

8.2.3.1 Non-variceal upper gastrointestinal bleeding

The majority, 229 (43%), preferred endoscopy within 24 hours for hemodynamically stable NVUGIB. Clinicians with <15 years of experience most commonly selected this timing, whereas those with >15 years of experience more frequently chose the 6-24 hour window. The type of hospital and years of clinical practice did not significantly impact the model, whereas the annual patient number did. Physicians from hospitals treating >200 UGIB patients/year most frequently selected endoscopy within 24 hours, with all other timing options being significantly less common ($P < 0.0001$). However, for physicians in hospitals treating <100 patients/year, the probability of choosing endoscopy within 6 hours was significantly higher ($P = 0.0048$).

For hemodynamically unstable NVUGIB patients responding to resuscitation, the results were more evenly distributed. Most physicians, 161 (30.2%), preferred endoscopy within 6 hours, followed by 127 (23.8%) within 12 hours and 125 (23.5%) within 6-24 hours. Experienced physicians preferred earlier endoscopy, while junior ones favored the 6–24 hour window. The annual number of patients and the type of hospital did not significantly affect the model. However, years of clinical experience did. Performing endoscopy within the 2-, 6-, and 12-hour timeframes was significantly preferred among most experienced physicians with >20 years of clinical experience ($P = 0.028$, $P < 0.0001$, and $P = 0.040$, respectively). In contrast, physicians with 5-10 years of experience were significantly less likely to choose endoscopy within 2 hours ($P = 0.032$). This was more pronounced among physicians with <5 years of experience, who were significantly less likely to select endoscopy within 2 hours and 6 hours ($P = 0.002$ and $P = 0.039$, respectively).

For hemodynamically unstable NVUGIB patients not responding to resuscitation, nearly half, 254 (47.8%), preferred endoscopy within 2 hours, followed by 170 (32%) within 6 hours, with a significant preference for earlier intervention among more experienced physicians. Endoscopy within 2 hours was the predominant choice, with preference increasing in high-volume centers and among senior physicians. All timings were

significantly less frequent than within 2 hours, except within 6 hours of patient presentation.(Figures 6-8)

8.2.3.2 Variceal upper gastrointestinal bleeding

Responses were more evenly distributed for hemodynamically stable VUGIB, with the majority, 155 (29.1%), preferring endoscopy within 12 hours, 136 (25.5%) within 6-24 hours, and 117 (22%) within 6 hours. Despite hemodynamic stability, some physicians, 55 (10.3%), chose endoscopy within 2 hours. All three variables (years of experience, hospital type, and annual UGIB cases) significantly affected the model. Physicians at university hospitals and those treating >200 cases/year were more likely to recommend endoscopy within 12 hours. Private and community-based physicians showed greater variability, favoring longer waiting times.

For hemodynamically unstable VUGIB patients responding to resuscitation, most physicians, 201 (37.7%), preferred endoscopy within 6 hours, followed by 115 (21.6%) and 114 (21.4%) who preferred endoscopy within 12 and 2 hours, respectively. There was a notable shift toward earlier intervention among more senior physicians. The number of patients treated annually and hospital type significantly influenced timing, but not years of clinical experience. University-based physicians with >200 patients/year preferred endoscopy within 6 hours, whereas those in private and community hospitals preferred it within 6-12 hours.

Regarding hemodynamically unstable VUGIB patients not responding to resuscitation, the majority, 319 (60.0%), preferred endoscopy within 2 hours, followed by 142 (26.7%) within 6 hours, with the preference for this time frame increasing with years of experience. Endoscopy within 2 hours, followed by within 6 hours, was the most commonly preferred, regardless of annual patient volume, hospital type, or years of clinical practice. This preference was particularly strong among experienced physicians and those in high-volume centers, while younger doctors and those in community settings showed more significant variability in their choices. (Figures 6-8)

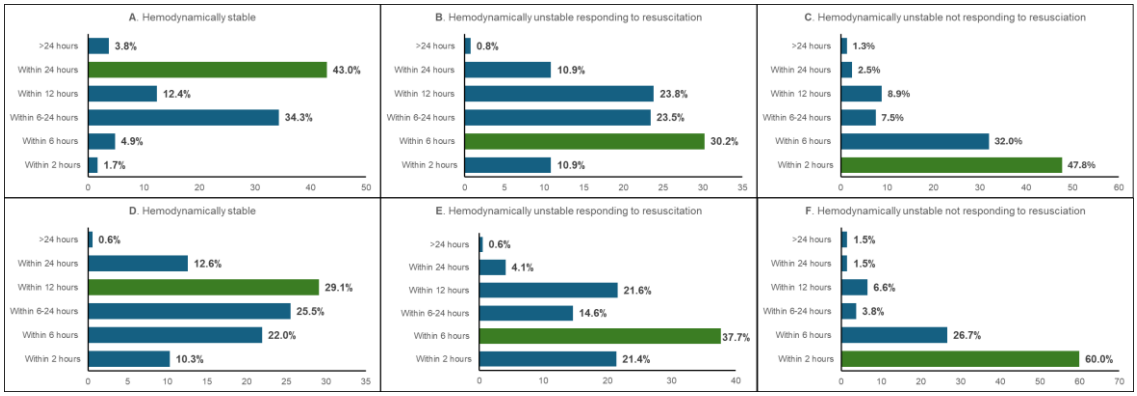


Figure 6. Survey responses on the preferred endoscopy timing for upper gastrointestinal bleeding based on patients' hemodynamic status. **A, D**: Hemodynamically stable; **B, E**: Hemodynamically unstable responding to resuscitation; **C, F**: Hemodynamically unstable not responding to resuscitation.

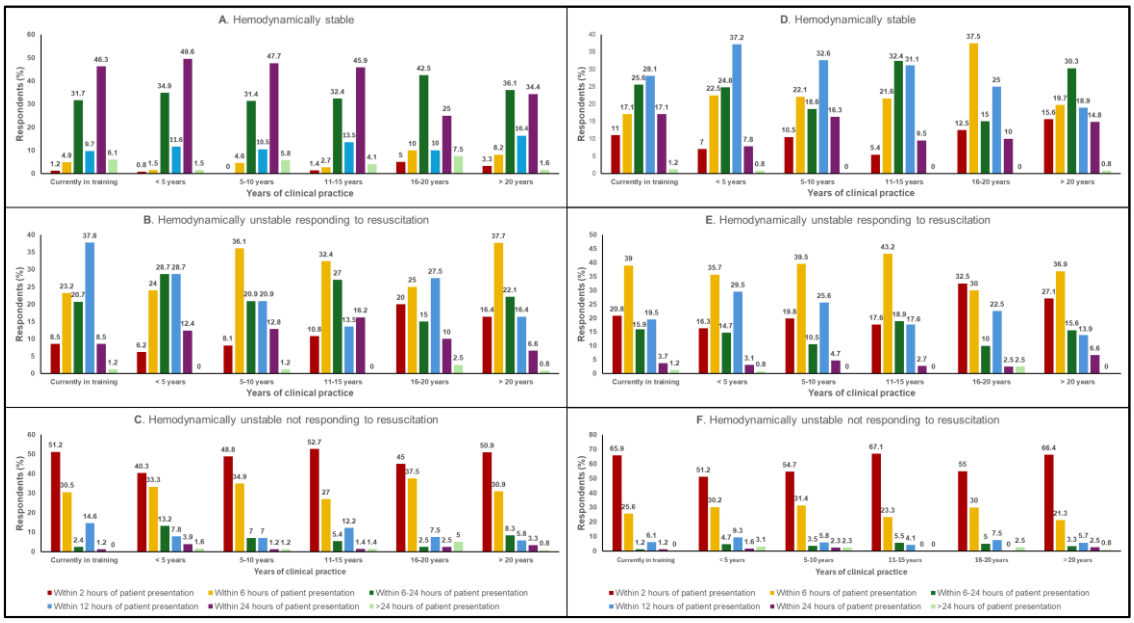


Figure 7. Survey responses on the preferred endoscopy timing for upper gastrointestinal bleeding based on patients' hemodynamic status and the respondents' years of clinical experience. **A, D**: Hemodynamically stable; **B, E**: Hemodynamically unstable responding to resuscitation; **C, F**: Hemodynamically unstable not responding to resuscitation.

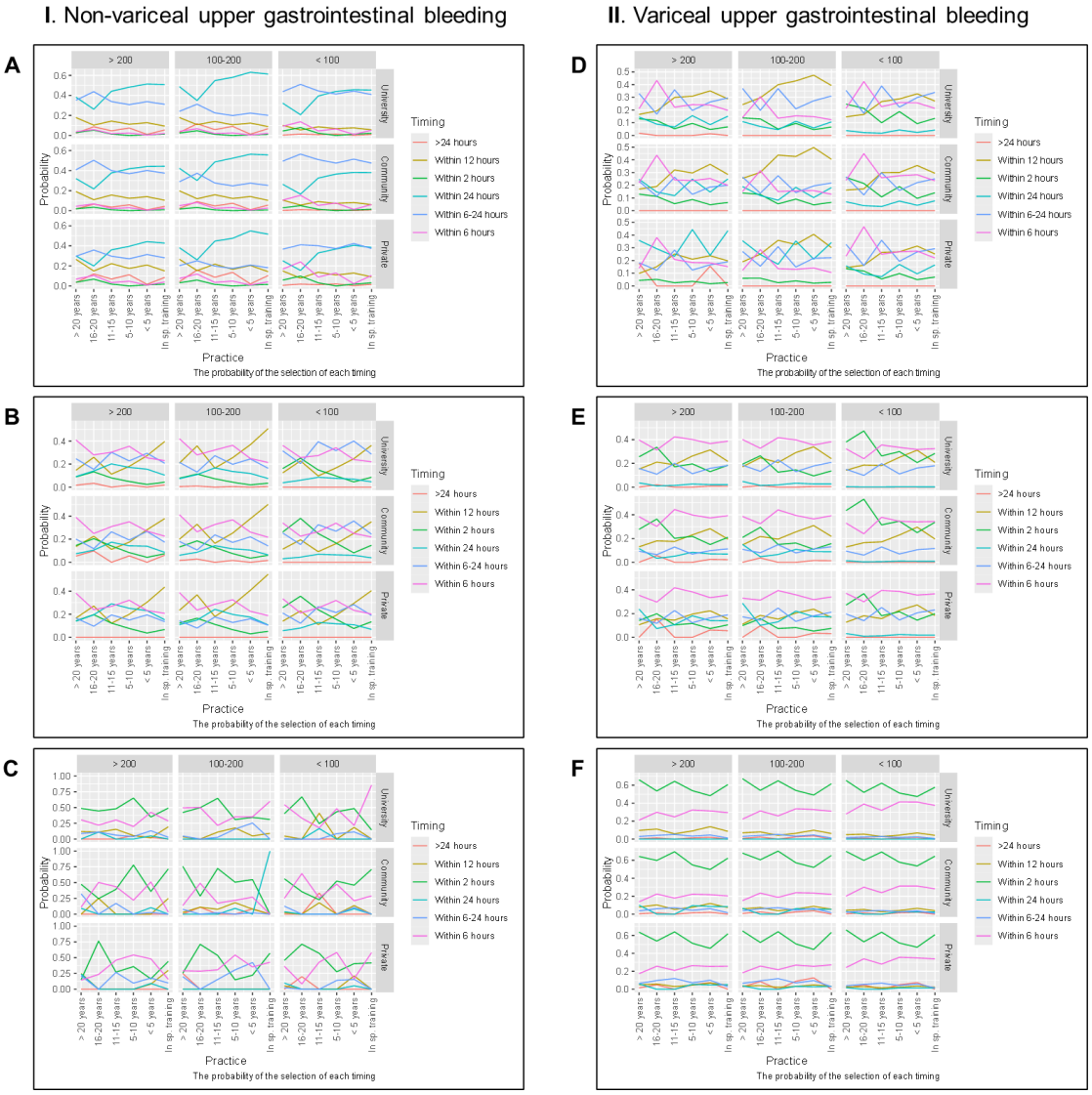


Figure 8. Multivariate analysis of the probability of choosing the preferred endoscopy timing based on years of clinical experience (in specialty training, <5 years, 5-10 years, 11-15 years, 16-20 years, >20 years), type of hospital (university, community, private), and the annual number of upper gastrointestinal bleeding patients (>100, 100-200, >200). **I.** Non-variceal upper gastrointestinal bleeding; **II.** Variceal upper gastrointestinal bleeding; **A, D:** hemodynamically stable; **B, E:** hemodynamically unstable responding to resuscitation; **C, F:** hemodynamically unstable not responding to resuscitation.

8.3 Study 3

8.3.1 Systematic search, selection, study characteristics

Altogether, 1,712 records were identified across the five databases. After removing duplicates, 1,196 records remained for title and abstract screening. Fifteen studies were assessed for full-text eligibility, of which six were excluded (58-63). Five of the excluded studies were duplicates published under different titles (58, 60-63), and one had an ineligible study design (59). Additionally, 391 records were identified through citation chasing; of these, only one study met the eligibility criteria and was included for data extraction (64). Further details of the search and study selection process are provided in the PRISMA flowchart. (Figure 9)

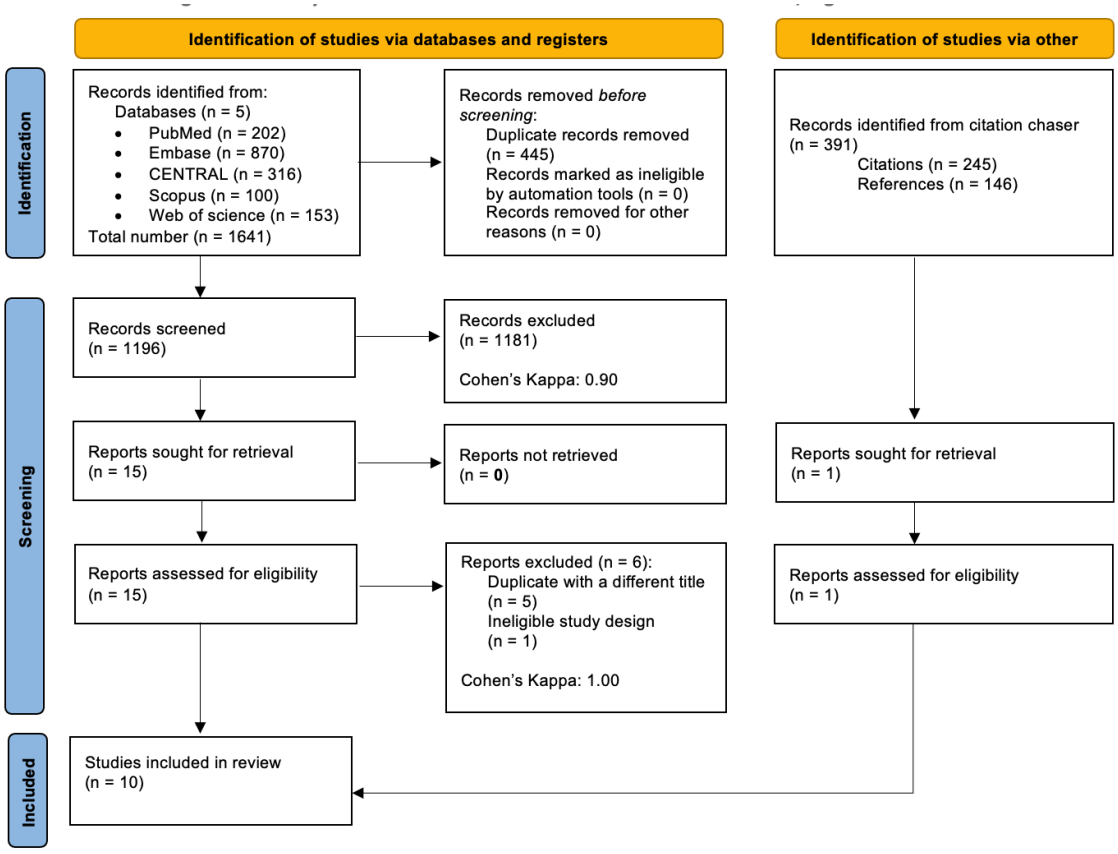


Figure 9. PRISMA flowchart of the article selection process of study 3

Our study consisted of 10 RCTs with a total of 1,051 patients (10, 12, 21-24, 64-67). One of these studies was published as a conference abstract (67). Five of the 10 studies focused

on patients with NVUGIB, mainly PUB (21, 24, 65-67), whereas the other five focused on patients with VUGIB (10, 12, 22, 23, 64). The studies were conducted across different geographical regions: five in Asia, three in Europe, one in Africa, and one in North America. Further details on the trials and their baseline characteristics are provided in Tables 4–5.

Table 4. Basic characteristics of included studies with variceal upper gastrointestinal bleeding

Study (year)	Study site	N of patients (female%)	Age (years), mean±SD	Child-Pugh Score (A/B/C) (Mean score±SD)	Size of the Esophageal Varices (F1/F2/F3) (MELD Score±SD)	Time of feeding	
						Early Nutrition	Delayed Nutrition
Sidhu et al. 2019 (10)	India	EN: 52 (11.5)	EN: 51.48±11.2	EN: 12/36/4 (9.1±1.2)	EN: 0/40/12 (14.6±8.2)	Liquid diet after 1h, regular diet after 4h	Liquid diet after 4h, soft diet after 48h, regular diet after 72h
		DN: 49 (22.4)	DN: 47.21±12.6	DN: 9/34/6 (8.6±1.5)	DN: 0/38/11 (13.8±6.6)		
Goda et al. 2018 (64)	Egypt	EN: 45 (20)	EN: 57.56±8.7	EN: 9/25/11	EN: 4/14/27	4h after endoscopic intervention	

		DN: 45 (28.8)	DN: 56.96±8.8	DN: 10/24/11	DN: 3/13/29		48h after endoscopic management
Gin-Ho Lo et al. 2015 (22)	Taiwan	EN: 36 (13.8)	EN: 47.5±12.6	EN: 10/14/12 (7.6±1.8)	EN: 6/22/8 (12.4±3.7)	4h after endoscopic intervention	48h after endoscopic intervention
		DN: 34 (17.6)	DN: 53.2±11.8	DN: 11/17/6 (8.2±2.2)	DN: 5/22/7 (13.3±4.2)		
Ledinghen et al. 1997 (12)	France	EN: 12 (33.3)	EN: 59±11.8	EN: 1/5/6 (10.1±2.7)	EN: 1/9/2	Within 24 hours	After 72 hours
		DN: 10 (10)	DN: 52.3±10	DN: 1/4/5 (10.4±2.7)	DN: 0/8/2		
Jatin et al. 2022 (23)	India	EN: 40	EN: 39.4±12.3	EN: 0/33/7 (8,7±1.3)	EN: NA (13±3.4)	Liquid diet after 1 h for 6 h with soft diet	Only liquid diet for 48h, then solid diet was started
		DN: 40	DN: 42.6±10.5	DN: 0/28/10 (8.8±1.6)	DN: NA (14.1±4.5)		

EN, early nutrition; DN, delayed nutrition; SD, standard deviation; MELD: Model for End-Stage Liver Disease; NA, not available

Table 5. Basic characteristics of included studies with non-variceal upper gastrointestinal bleeding

Study (year)	Study site	N of patients (female%)	Age (years), mean±SD	Forrest classification Ia/Ib/IIa/IIb/III	Time of feeding	
					Early Nutrition	Delayed Nutrition
Gong et al. 2020 (24)	Korea	EN: 103 (14.6)	EN: 61.2±17	EN: 14/36/50/3/0	24h after successful hemostasis	48h after successful hemostasis
		DN: 106 (21.7)	DN: 61.6±15.9	DN: 17/36/49/4/0		
Khoshbaten et al. 2013 (21)	Iran	EN: 50 (38)	EN: 56.6±17.8	EN: 0/0/43/7/0	6-12 hours after endoscopic treatment	72 hours after endoscopic treatment
		DN: 50 (36)	DN: 58.7±18.1	DN: 0/0/46/4/0		
Laine et al. 1992 (65)	US	EN: 130	NA	NA	Immediate	After 36 hours
		DN: 128	NA	NA		

Ledinghen et al. 1998 (66)	France	EN: 12	EN: 75 (33-91) [a]	EN: 0/4/2/6/0	Within 24 hours	After 72 hours
		DN: 14	DN; 69 (46-92) [a]	DN: 0/7/3/4/0		
Hepworth et al. 1995[b] (67)	UK	EN: 47	NA	NA	Normal diet and milk after hemostasis	After 24 hours
		DN: 48	NA	NA		

a. Median and range

b. Conference abstract

EN, early nutrition; DN, delayed nutrition; SD, standard deviation; NA, not available; US, United States; UK, United Kingdom

8.3.2 Main outcomes

We analyzed eight trials (10, 12, 21-24, 64, 65) that reported rebleeding within seven days, involving 923 patients (465 in the EN group and 458 in the DN group). In the VUGIB subgroup, our analysis showed no significant difference between the two groups (RR: 1.48, CI: 0.38 - 5.71); similarly, in the PUB subgroup (RR: 0.95, CI: 0.54 - 1.68). Overall, EN did not significantly or relevantly increase the risk of early rebleeding compared to DN (RR: 1.04, CI: 0.66 - 1.63, p=0.845, I^2 = 0%, CI: 0% - 68%). (Figure 10)

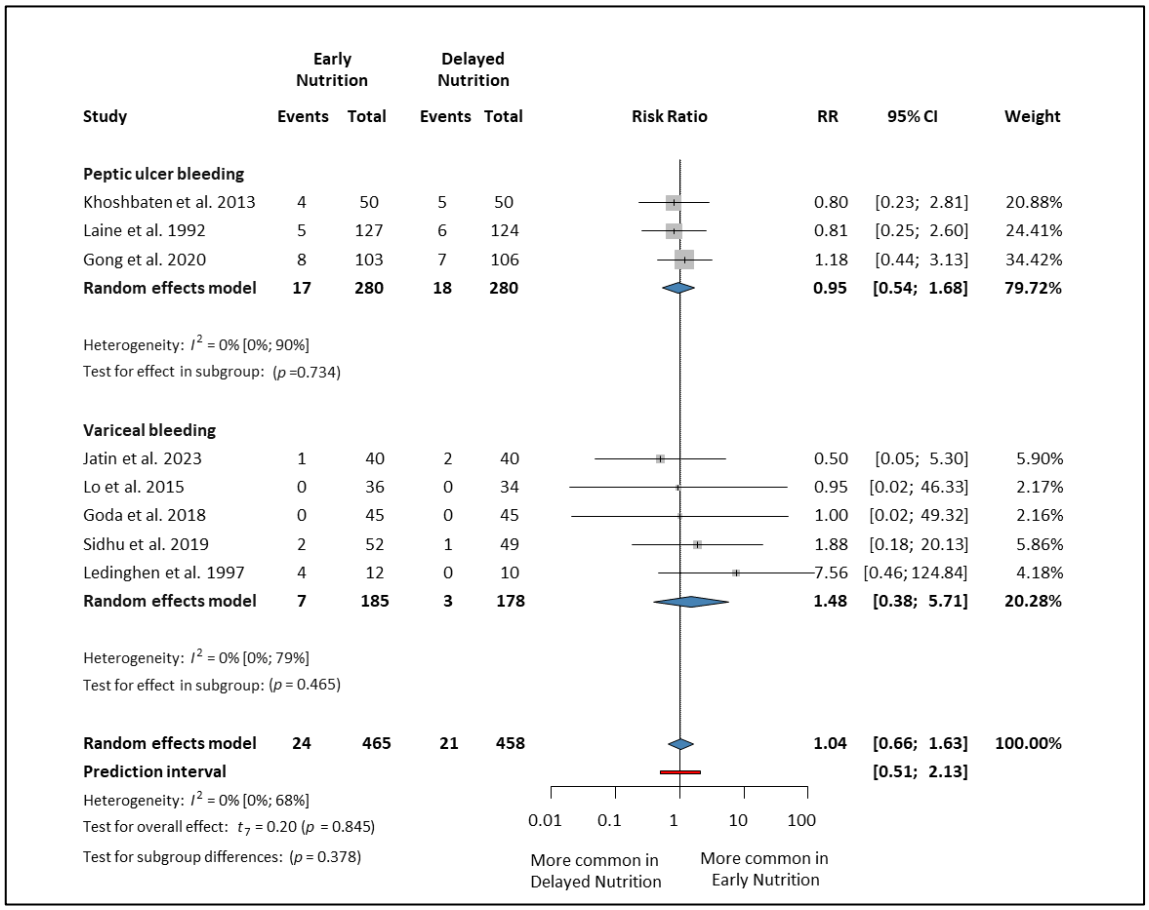


Figure 10. Forest plot demonstrating the effect of early versus delayed nutrition on early rebleeding (within 7 days) after upper gastrointestinal bleeding. RR, risk ratio; CI, confidence interval

Another analysis included eight studies (10, 12, 22-24, 64, 66, 67) that reported rebleeding within 30, 35, or 42 days, involving 693 patients (347 in the EN group and 346 in the DN group). The results were not statistically significant for either subgroup,

including PUB (RR: 1.14, CI: 0.16 - 7.98) and VUGIB (RR: 1.13, CI: 0.40 - 3.17). Overall, EN did not increase the risk of late rebleeding compared to DN (RR: 1.16, CI: 0.63 - 2.13, $p = 0.58$, $I^2 = 0\%$, CI: 0% - 68%). (Figure 11)

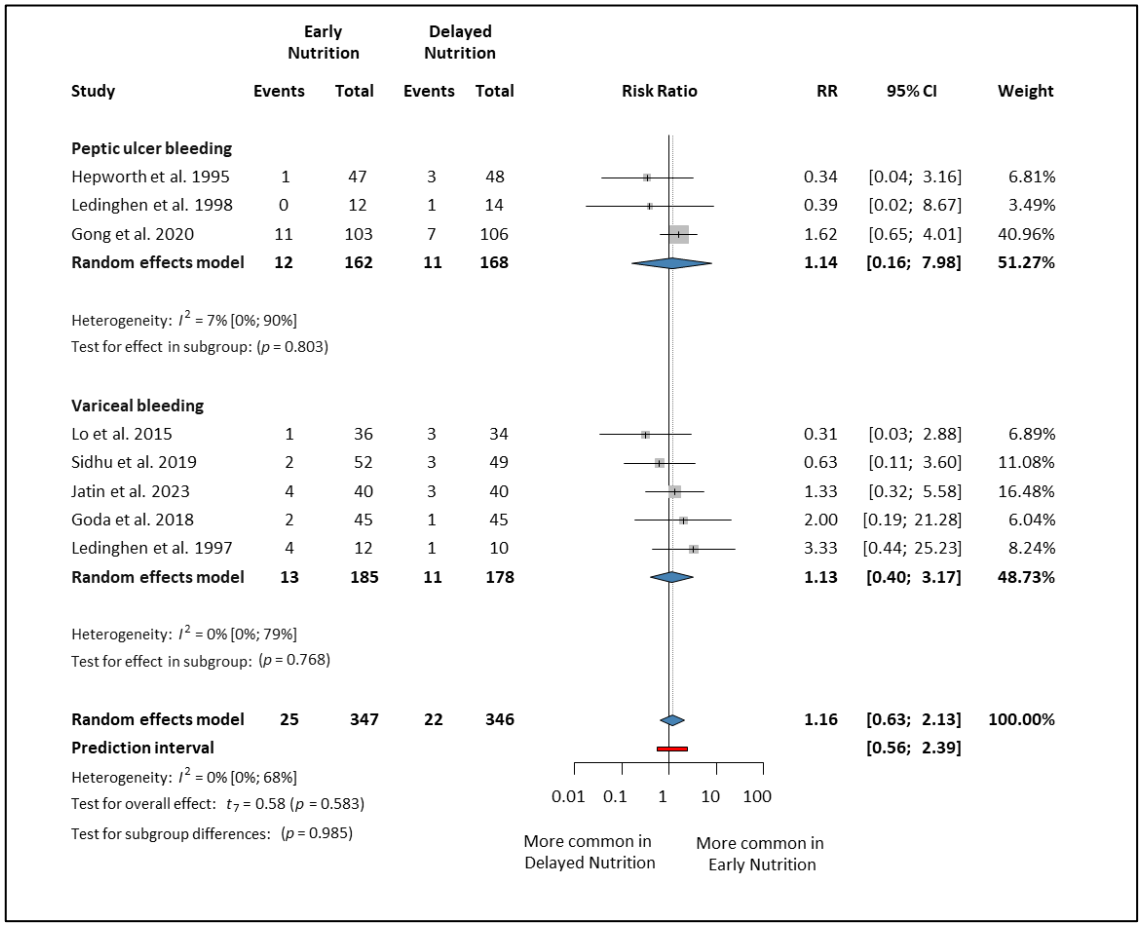


Figure 11. Forest plot demonstrating the effect of early versus delayed nutrition on late rebleeding (within 30-42 days) after upper gastrointestinal bleeding. RR, risk ratio; CI, confidence interval

Only five studies were included (12, 21, 23, 64, 65) that reported mortality within seven days, with a total of 543 patients (234 in the EN group and 229 in the DN group). There were no statistically significant differences between the studies in the PUB and VUGIB subgroups (RR: 0.98, CI: 0.85 - 1.14, and RR: 1.36, CI: 0.63 – 2.93, respectively). The

overall effect was not statistically significant between the two groups (RR: 1.20, CI: 0.85 - 1.71, p=0.214, I^2 = 0%, CI: 0% - 79%). (Figure 12)

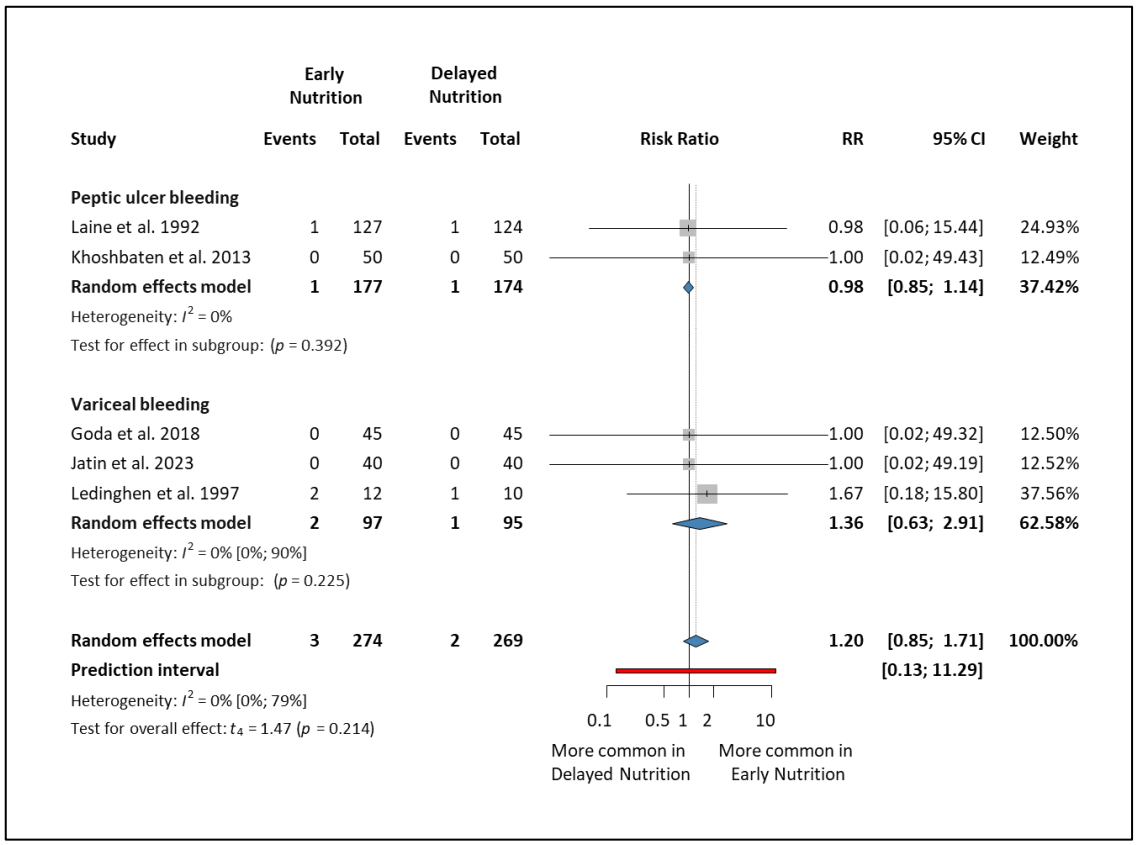


Figure 12. Forest plot demonstrating the effect of early versus delayed nutrition on early mortality (within 7 days) after upper gastrointestinal bleeding. RR, risk ratio; CI, confidence interval

The analysis included seven studies (10, 12, 22-24, 64, 67) that reported mortality within 30, 35, or 42 days. Altogether, 667 patients were involved (335 in the EN group and 332 in the DN group). There was no statistical difference in either subgroup; in the PUB subgroup (RR: 0.51, CI: 0.03 - 7.83) and the VUGIB subgroup (RR: 0.73, CI: 0.26 - 2.02). Overall, there was no statistically significant difference between the two groups; however, the results were clinically relevant with a tendency towards the EN group (RR: 0.61, CI: 0.35 - 1.06, p=0.072, I^2 = 0%, CI: 0% - 71%). (Figure 13)

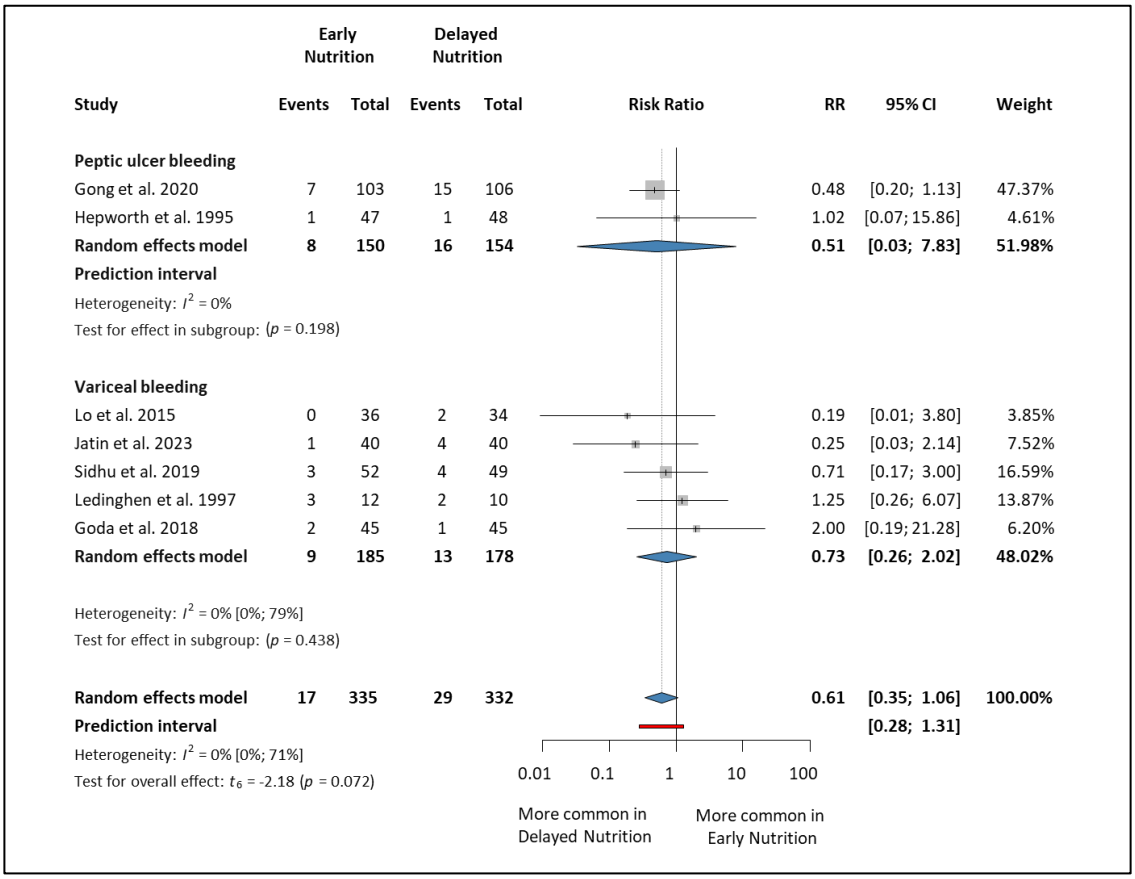


Figure 13. Forest plot demonstrating the effect of early versus delayed nutrition on late mortality (within 30-42 days) after upper gastrointestinal bleeding. RR, risk ratio; CI, confidence interval

8.3.3 Other outcomes

Regarding the LOHS outcome, we included six studies (10, 12, 21, 22, 65, 66) involving 570 patients (289 in the EN group and 281 in the DN group). In the PUB subgroup, there was no statistically significant difference between the two groups (MD: - 1.34 days, CI: - 5.01 to 2.33), whereas in the VUGIB subgroup, EN significantly decreased LOHS (MD: - 1.54 days, CI: - 2.67 to - 0.41). Overall, EN reduced the LOHS compared to DN (MD: -1.22 days, CI: - 2.43 to - 0.01, p=0.049, I^2 = 94%, CI: 90% - 97%). (Figure 14)

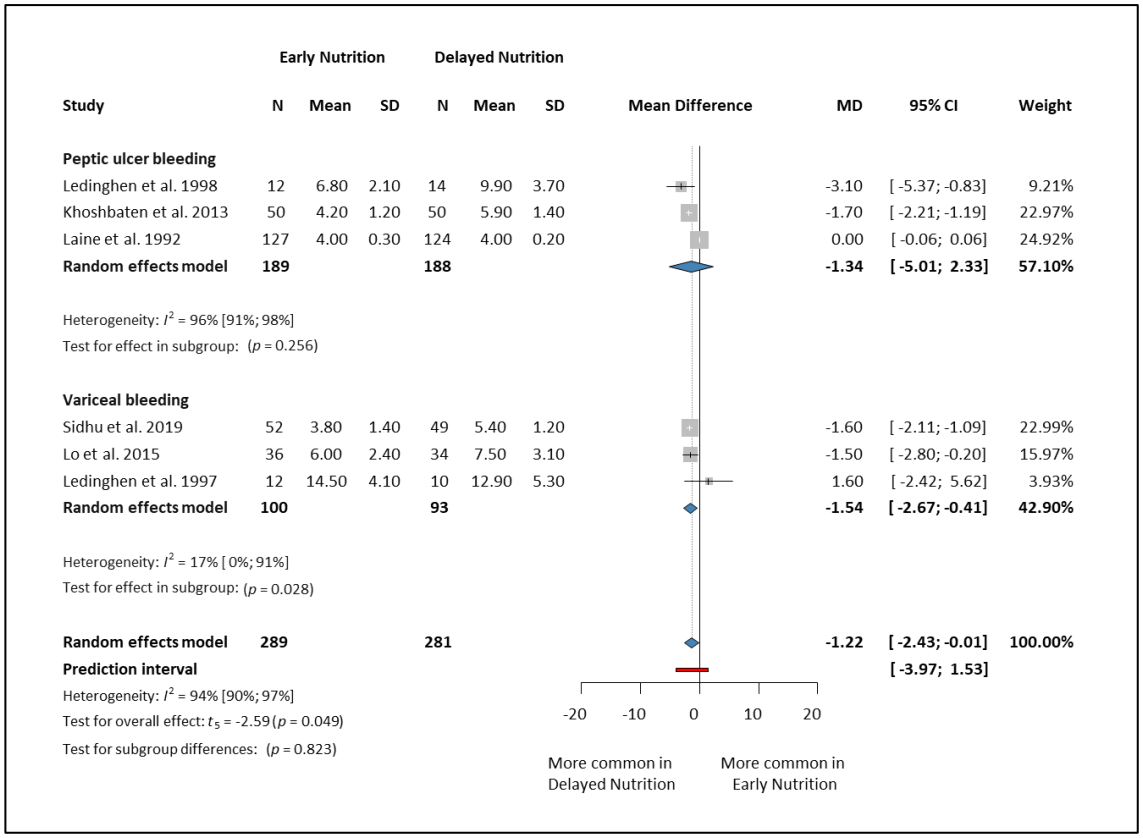


Figure 14. Forest plot demonstrating the effect of early versus delayed nutrition on the length of hospital stay after upper gastrointestinal bleeding. N, number of patients in each arm; SD, standard deviation; MD, mean difference; CI, confidence interval

Seven studies (10, 12, 21, 22, 24, 65, 66) reported transfusion requirement as an outcome; however, we could analyze only four studies (292 in the EN group and 286 in the DN group) (10, 24, 65, 66) due to heterogeneous definitions of this outcome among the included studies. Overall, there was no statistically significant difference between the two groups (MD: 0.00, CI: - 0.04 to 0.05, p=0.980, I^2 = 0%, CI: 0% - 85%). (Figure 15A)

Three studies reported on new-onset ascites (10, 22, 23). Overall, there was a tendency that ascites was more common in the DN group; however, it was not statistically significant (RR: 0.64, CI: 0.34 – 1.20, p=0.094, I^2 = 0%, CI = 0% - 90%). (Figure 15B). In addition, two studies (10, 23) reported on new-onset hepatic encephalopathy. (RR:

1.03, CI: 0.50 - 2.11 and RR: 0.75, CI: 0.18 - 3.14, respectively). We were not able to draw a statistical inference based on only two studies.

Only three studies (10, 22, 23) reported new-onset bacterial infections, including 251 patients (128 in the EN group and 123 in the DN group). Overall, there was no statistically significant difference between the two groups (RR: 0.48, CI: 0.08 - 3.05, p=0.229, I^2 = 0%, CI = 0% - 90%). (Figure 15C)

In the included articles, the domains of the randomization process and selection of reported results were judged as raising some concerns. Deviations from intended interventions and missing outcome data were associated with the lowest risk of bias. Outcome measurement bias was rated high for LOHS. The quality of evidence was low or very low for all our outcomes.

Across all outcomes, statistical heterogeneity was negligible, with values of 0% or <10%, except for LOHS, which showed high heterogeneity. This discrepancy may be explained by differences in bleeding severity among patients, which influenced hospitalization needs. Regarding publication bias, given the limited diagnostic accuracy of tests with fewer than 10 studies and the fact that none of our analyses met this threshold, we did not perform this assessment.

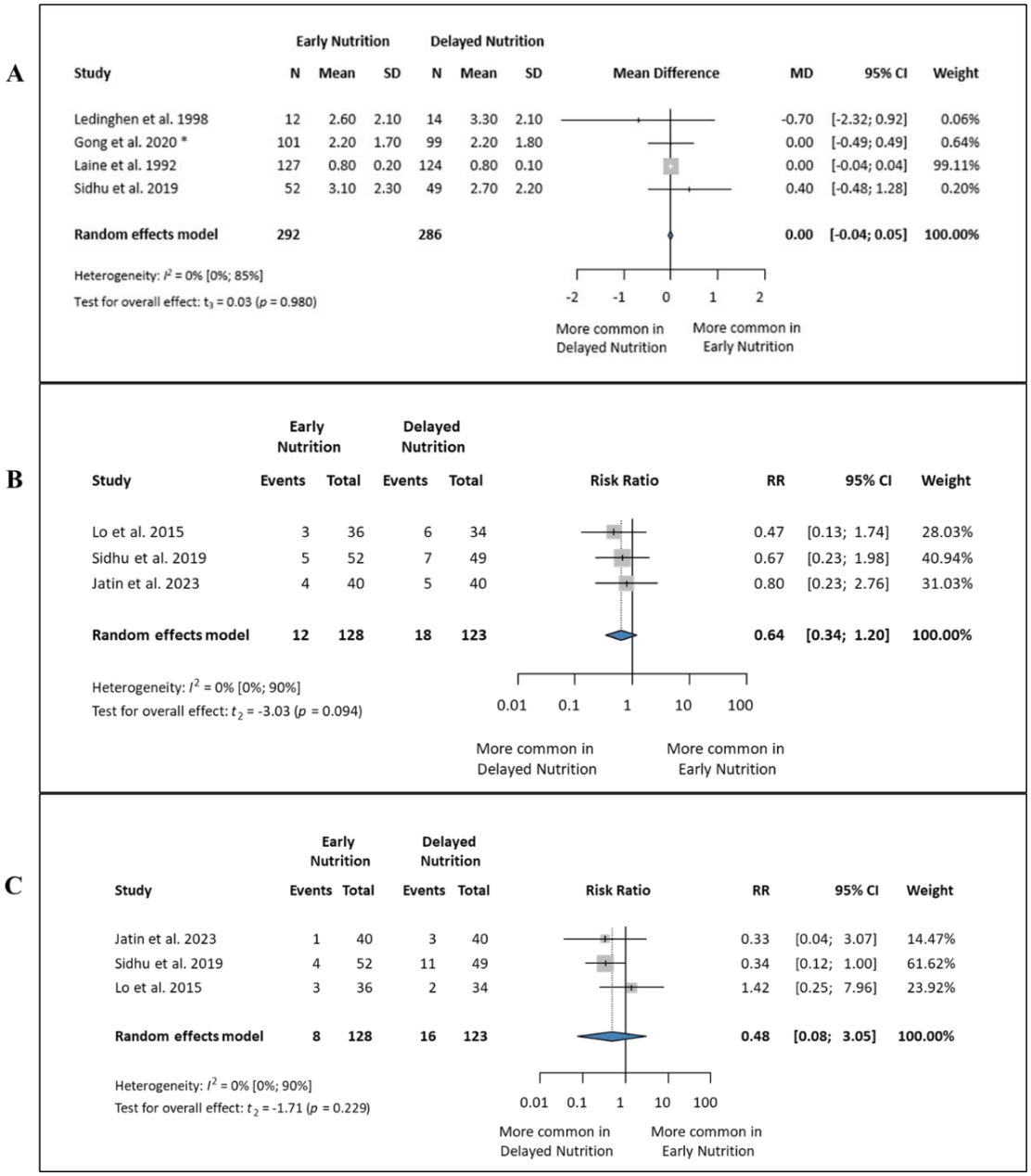


Figure 15. Forest plot demonstrating the effect of early versus delayed nutrition on: **(A)** blood transfusion requirement, **(B)** newly onset ascites, **(C)** newly onset bacterial infection. SD, standard deviation; MD, mean difference; RR, risk ratio; CI, confidence interval

9 DISCUSSION

9.1 Summary of findings

Our first study found that HI and shock are common complications and presentations of GIB. Either shock or HI affects one in every four patients; even the lowest proportion, one in eight colonic diverticular bleeders, is still a significant portion of patients.

VUGIB resulted in the highest HI on admission, with a rate of 38% among various bleeding sources. In contrast, the highest HI rates during hospitalization were observed in PUB (41%) and LGIB (49%). The rate of shock on admission was generally the highest among different NVUGIB sources (36%), whereas PUB specifically led to the highest rate of shock during hospitalization (24%).

Our results about unspecified GIB sources, NVUGIB, and PUB showed higher rates of HI during hospitalization than on admission and higher rates of shock on admission than during hospitalization. In contrast, VUGIB showed higher rates of HI and shock on admission than during hospitalization. Lower GIB, on the other hand, showed higher rates of these outcomes during hospitalization than on admission.

Blood loss leads to HI, characterized by a decrease in systolic blood pressure (BP) and an increase in heart rate (HR). Eventually, it can lead to a more severe state of shock, which is caused by a rapid reduction of intravascular blood volume, resulting in decreased hemoglobin levels, thereby decreasing the oxygen delivery capacity of the heart. HI is not just a sign; it is the starting point of a chain of events leading to hypoxemia and hypoperfusion. If it is not appropriately treated as soon as possible, it will lead to multiple organ failures. Therefore, health care providers must emphasize continuous monitoring and efficient stabilization for those patients (68).

Our second study highlights significant variability in the timing of endoscopy for acute UGIB based on hemodynamic status, years of clinical experience, hospital type, and

annual UGIB patient volume. We found that more experienced physicians and those working in high-volume or university hospitals were more likely to recommend earlier endoscopy, particularly in hemodynamically unstable patients. This suggests that exposure to a higher number of UGIB cases and institutional protocols may influence decision-making. While most respondents adhered to current guideline recommendations, nearly one-third (155, 29.1%) reported not following a standardized clinical care pathway or protocol, emphasizing the need for greater consistency in clinical practice.

The observed variation in endoscopy timing preferences could be due to multiple factors, including differences in training, institutional policies, the time of day at which the patient presented, and available local resources. Physicians in training or with fewer years of experience were more likely to delay endoscopy, possibly due to concerns about patient stability, availability of senior support, or a more conservative approach to risk management. Interestingly, younger doctors demonstrated greater adherence to guideline recommendations, likely because they are more familiar with current guidelines than their more experienced counterparts who had been in practice for over 20 years. Additionally, hospital infrastructure plays a crucial role, as centers with 24-hour emergency endoscopy services are more likely to offer timely interventions. As our results showed, 16.9% of the practice locations lacked 24-emergency endoscopy services (including weekends).

Our third study found no significant difference in early and late rebleeding and mortality between EN and DN after UGIB hemostasis; however, these findings are clinically relevant. The results showed that EN could significantly decrease LOHS compared to DN. In addition, there was no difference between the two groups in terms of blood transfusion requirement and bacterial infection.

Despite the advances in intensive care technologies and improvements in the endoscopic treatment of GIB, it remains a life-threatening emergency with considerable mortality (1). Our study revealed a late mortality ratio of 6.89% (46 out of 667 cases), indicating an important concern; we reached a similar conclusion in terms of late rebleeding, with a ratio of 6.78% (47 out of 693 cases).

The precise definitions of both interventions (early and delayed nutrition) played an essential role in determining the timing, dietary type, procedure, and requirements, particularly because there were variations in how these interventions were defined across the included studies.

9.2 Comparisons with other international publications

Regarding our first study, possible predictors were observed that resulted in higher rates of our investigated outcomes. We observed some outliers in different sources of bleeding; in VUGIB, ICU admission (69-71), elderly population (17), and severe uncontrolled bleeding (72) were possible predictors for higher rates of shock and HI. In NVUGIB, elderly patients >60 years (17) and those who underwent embolization (73) accounted for the highest rate of HI on admission and during hospitalization, respectively. As for UGIB in general, the study by Chirapongsathorn et al.(18) included VUGIB and NVUGIB, where they defined shock as a mean arterial pressure lower than 50 mmHg, which results in a very high rate of shock (75%).

Lower GIB is three times less common than UGIB and has not been the focus of much attention yet. Mortality rises to 20-40% in the case of massive lower GIB complicated by unstable hemodynamics (74). Super-selective patients who underwent arterial embolization (75), angiography (76), or were diagnosed with acute severe bleeding (77) showed higher rates of the investigated outcomes.

Regarding the second study, current guidelines, such as those from the ESGE (78, 79), Baveno VII (80), ACG (81), and the American Association for the Study of Liver Disease (AASLD) (82), recommend endoscopy for suspected variceal UGIB within 12 hours and for non-variceal UGIB within 24 hours. Although our findings generally align with these recommendations for hemodynamically stable patients, the survey revealed a subset of

clinicians who preferred earlier or later endoscopic intervention based on the patient's hemodynamic status, suggesting a gap between guidelines and real-world practice.

An RCT by Lau et al. (2020) demonstrated that endoscopy in high-risk patients (GBS ≥12) with acute UGIB within 6 hours did not reduce 30-day mortality, rebleeding, or ICU admission, compared to endoscopy performed between 6 and 24 hours (83). However, unstable patients who did not respond to initial resuscitation were excluded, as well as those unable to provide informed consent, such as intubated patients. In other studies, delaying endoscopy beyond 24 hours was associated with an increase in in-hospital mortality, as well as longer ED and length of hospital stays (84). These data highlight the need for structured protocols to guide decision-making and improve adherence to best practices.

Several systematic reviews and meta-analyses have examined the impact of early versus delayed endoscopy in UGIB. A meta-analysis of RCTs by Merola et al. (2021) (85) found no significant advantage of performing very early endoscopy (<12 hours) over early endoscopy (>12 – 48h) in terms of risk of rebleeding, mortality, ICU admission, blood transfusion, need for surgery, or length of hospital stay. However, the need for endoscopic hemostasis was significantly higher in patients who underwent very early endoscopy (RR: 1.23, CI: 1.06 - 1.42). Another meta-analysis by Bai et al. (2021) on VUGIB showed that endoscopy within 12 hours may improve overall survival but did not significantly reduce the risk of rebleeding (86). Our study contributes to this ongoing debate by providing real-world insights into how clinicians make decisions on endoscopy timing, suggesting that clinical experience, institutional policies, and annual patient numbers likely influence practice patterns. Future meta-analyses incorporating individual patient data may help refine timing recommendations for different risk groups.

Regarding our third study, according to the current literature, patients at a high risk of rebleeding should be advised to fast and remain hospitalized for a minimum of 48-72 hours after endoscopic treatment. Within this timeframe, most high-risk lesions will transition into low-risk lesions, and most rebleeding events will occur (87). Therefore,

prolonged fasting can be justified. Furthermore, a retrospective study (88) showed that delaying refeeding in patients with low-risk lesions who should have been fed promptly is not advisable, and early refeeding is recommended for NVUGIB patients. According to a recent review (89), the timing of initiating feeding after the diagnosis of UGIB should be determined by considering patient-specific risk factors associated with the underlying disease. For low-risk patients, it is advisable to resume feeding without delay following endoscopy, as these bleeds are often self-limited and rarely require intervention. However, for higher-risk lesions (Forrest Ia-IIb), the available data on the safety of early refeeding are inconclusive (89). This was also a challenge in our analysis, as different studies included patients with varying severities. For example, Gong et al. (24) included FIa-FIb bleeders, whereas Khoshbaten et al. (21) did not.

Enteral nutrition has the potential to provide several benefits. These include the delivery of local nutrition directly to the gastric tissue, stimulating mucus glands and epithelial cells to support the maintenance of the protective mucus barrier, and promoting increased blood flow to the splanchnic region, which can aid ulcer healing (87). In addition, a prospective study (90) aimed to compare the early and late postoperative oral feeding of gastric cancer patients undergoing surgery for the recovery of gastrointestinal function. It was found that initiating early oral feeding in patients with gastric cancer facilitates the recovery of postoperative gastrointestinal function without increasing the rate of associated complications or adverse events. Another meta-analysis (91) concluded that, in comparison to traditional oral feeding, early refeeding after upper gastrointestinal surgery could shorten the LOHS and time of first exhaust without increasing postoperative complications, while also reducing the risk of pneumonia.

Several reviews (92-94) suggest that enteral nutrition may protect against stress ulceration. Numerous studies in basic science indicate that enteral nutrition can enhance mucosal blood flow and reverse the production of inflammatory mediators (94). In addition, the results of a meta-analysis (95) indicated that stress ulcer prophylaxis with a histamine-2 receptor blocker may not be necessary for patients receiving enteral nutrition. They found that prophylactic use of a histamine-2 receptor blocker for stress ulcer

prevention resulted in a decreased risk of GIB with an odds ratio (OR) of 0.47 (CI: 0.29 - 0.76; p<0.002). However, this treatment effect was observed only in patients who did not receive enteral nutrition. Among patients who were fed enterally, stress ulcer prophylaxis did not have a significant impact on the risk of GIB (OR: 1.26; CI: 0.43 - 3.7).

In contrast to the meta-analysis by Zhang et al. (25), our study extended their research by including five more clinical trials and examining a broader range of outcomes. Furthermore, we conducted a subgroup analysis based on the source of bleeding, which allowed for more accurate and specific data in our investigation. Their findings also suggested that EN administered within 24 hours did not show a higher risk of rebleeding and mortality compared to DN for patients with UGIB. However, EN was associated with a reduction in the LOHS.

9.3 Strengths

9.3.1 Study 1

This is the first comprehensive overview to assess the proportion of patients affected by HI and shock in GIB and specify it according to the bleeding source. Our study included many studies with a large sample size. Additionally, subgroup analysis, which was based on the time of assessment, whether on admission or during hospital stay, provided a more precise overview. This study also gives an insight into some of the possible predictors that result in higher rates of our investigated outcomes.

9.3.2 Study 2

A major strength of our study is its international scope, representing diverse healthcare settings. In addition, we had a high number of survey responses (n = 533), enhancing our findings' reliability and generalizability. However, more than 60% of respondents practice in Europe. Additionally, the use of structured methodology and robust statistical analysis contributed to valuable insights into this field.

9.3.3 Study 3

Regarding the strengths of our analysis, we strictly adhered to our protocol, which was registered beforehand. Our study is the most recent comprehensive analysis of refeeding strategies after UGIB using a rigorous methodology and including only RCTs. In addition, we performed a subgroup analysis based on bleeding source, providing more detailed data.

9.4 Limitations

9.4.1 Study 1

Considering the limitations of this work, the definitions of HI and shock were different among the included studies or were even missing. Different characteristics of the included population led to high heterogeneity in almost all analyses. The presence of low certainty of evidence in some domains is another limitation.

9.4.2 Study 2

The majority of respondents, 446 (83%), identified themselves as gastroenterologists, as we encountered difficulties in reaching emergency medicine physicians. Additionally, self-reported data may be subject to response bias, and our survey did not capture institutional protocols that could influence decision-making. While we analyzed key factors affecting endoscopy timing, we did not assess other variables, such as local availability of resources and physician workload.

9.4.3 Study 3

Only a few studies with a low number of cases could be included. In addition, the EN and DN definitions varied among the studies, and different nutrition modalities and regimens were used. Generalizing the findings might be challenging due to variations in the severity of bleeding among the included patients, which could impact the appropriate timing for refeeding. Other limitations include a high risk of bias in some of the domains and the low quality of evidence.

10 CONCLUSIONS

10.1 Study 1

Our study has provided clear evidence that hemodynamic instability and shock are common presentations and complications of GIB. Based on our findings, a high majority of patients are affected; one in five, one in four, and one in eight patients develop shock or hemodynamic instability on admission or during the hospital stay in the case of non-variceal, variceal, and colonic diverticular bleeding, respectively. Patients need a more proactive treatment strategy and require continuous monitoring to prevent untoward outcomes.

10.2 Study 2

Our findings reveal a consistent trend: the more hemodynamically unstable the patients are, the earlier physicians tend to perform endoscopy for acute UGIB. More experienced physicians, those working in university-based hospitals, and those managing high UGIB patient volumes tend to favor earlier endoscopy, particularly in hemodynamically unstable patients. Poor adherence to international guideline recommendations was observed, especially among clinicians with more than 15-20 years of experience. This study highlights opportunities to improve consistency in clinical practice and identifies potential areas for further research.

10.3 Study 3

Compared to delayed nutrition, early nutrition (within 24 hours) is a safe intervention that reduces the LOHS without increasing the risk of complications such as rebleeding, mortality, newly onset ascites, newly onset bacterial infections, or blood transfusion requirements following hemostasis of UGIB.

11 IMPLEMENTATIONS FOR PRACTICE

11.1 Study 1

Based on our results, we suggest standardizing the definition of HI and shock and establishing a protocol to proactively screen and monitor the affected patients in routine management. Physicians involved in the treatment of the affected patients should focus more on early and rapid correction of hemodynamics because it significantly decreases mortality (68). Therefore, a careful pre-endoscopic assessment and strong adherence to risk stratification scores need to be highlighted. Furthermore, cautious care and continuous monitoring of the affected patients should be emphasized, especially for high-risk patients.

11.2 Study 2

Our findings underscore the need for clearer guidance on the optimal timing of endoscopy in UGIB, particularly in hemodynamically unstable patients. Standardizing definitions of HI and promoting adherence to evidence-based protocols may help reduce variability in practice. Additionally, proficient on-call GI endoscopists and support staff with technical expertise should be available 24/7 to ensure the timely and effective performance of endoscopy. Trainees performing the procedure should always be closely supervised by a senior attending.

11.3 Study 3

Risk-stratification systems have been developed to differentiate between patients with a high or low risk of mortality or rebleeding in cases of GIB. However, many of these scores rely on endoscopic findings, which makes them less suitable for early patient evaluation. Fortunately, several risk scores, such as the AIMS65 and Glasgow-Blatchford scores, can be used prior to endoscopy. Therefore, it is crucial to introduce these risk-stratification systems into clinical practice and apply them to determine the optimal timing for initiating enteral nutrition.

12 IMPLEMENTATION FOR RESEARCH

12.1 Study 1

Future studies should adopt a standardized definition of hemodynamic instability. Additionally, further research is needed to determine the optimal timing of endoscopy based on patients' hemodynamic status, whether they are stable, unstable but responsive to resuscitation, or unstable and unresponsive, as current evidence on this topic is lacking.

12.2 Study 2

Future research should focus on exploring the impact of hospital resources on decision-making. RCTs comparing different endoscopy timings based on bleeding severity, with consistent definitions of endoscopy timing (from the onset of bleeding or time of patient presentation), and endoscopy timeframes (emergent, urgent, early, very early, delayed), may provide more definitive evidence. Future studies should incorporate real-world patient outcome data to better understand the impact of different timing strategies on clinical endpoints.

12.3 Study 3

Our results suggest that EN is a safe intervention; however, further high-quality prospective data collection and reporting are needed to assess this clinical question more accurately, including clinical trials reporting the investigated outcomes based on the severity assessment with longer follow-up periods, others on the diet types and their effects on new-onset ascites, and hepatic encephalopathy might give additional insight into this field. In addition, the emphasis on adherence to risk stratification scores prior to endoscopy ensures appropriate management of those patients.

13 IMPLEMENTATION FOR POLICYMAKERS

13.1 Study 1

Based on the findings of this study, policymakers should prioritize the development of standardized definitions and clinical protocols for assessing hemodynamic instability in patients with gastrointestinal bleeding. With nearly one in four patients experiencing hemodynamic compromise, there is a clear need to integrate early hemodynamic assessment into clinical decision-making and guideline development. Policymakers should also support investments in emergency care infrastructure, staff training, and the implementation of structured triage systems that incorporate hemodynamic criteria. Furthermore, funding should be directed toward research investigating the optimal timing of endoscopy based on patients' hemodynamic status, as current evidence in this area remains insufficient. These actions would contribute to more efficient resource utilization and improved patient outcomes.

13.2 Study 2

Policymakers should prioritize the development and dissemination of clear, evidence-based protocols that account for hemodynamic status when determining the timing of endoscopy. Our survey revealed significant variability in clinical decision-making and poor adherence to guideline recommendations, particularly in unstable patients. We recommend investing in the implementation of structured clinical pathways, promoting training programs that emphasize risk stratification and physiologically informed decision-making, and ensuring 24/7 access to emergency endoscopy services. Additionally, a standardized definition of hemodynamic instability should be integrated into national and international guidelines to support consistent, high-quality care across healthcare settings. In addition, healthcare systems should allocate resources to support on-call endoscopy teams and essential infrastructure in both tertiary and non-tertiary centers to ensure timely intervention regardless of setting. Finally, the collection and integration of real-world outcome data into national databases should be encouraged to refine future guidelines, identify gaps in care, and drive continuous quality improvement initiatives.

13.3 Study 3

The results of this study suggest that early refeeding after successful hemostasis in UGIB is safe and may shorten hospital stay without increasing the risk of rebleeding or mortality. For policymakers, these findings support the integration of early nutritional support into clinical guidelines and hospital protocols. By promoting early refeeding as a standard practice, healthcare systems can enhance recovery, reduce unnecessary fasting periods, and optimize resource utilization, particularly by potentially decreasing the length of hospital stay. Policymakers should also encourage further research and dissemination of these findings to inform evidence-based updates to current gastrointestinal bleeding management guidelines.

14 FUTURE PERSPECTIVES

Future research should focus on establishing a standardized, universally accepted definition of hemodynamic instability in patients with GIB to enhance comparability across studies and improve clinical decision-making. Additionally, prospective studies and randomized trials are needed to determine the optimal timing of endoscopy based on distinct hemodynamic profiles, including stable patients, those who respond to resuscitation, and those who do not. In parallel, further investigation into refeeding practices is warranted, particularly through well-designed RCTs stratified by bleeding source (variceal vs. non-variceal) and severity, to identify which subgroups benefit most from early versus delayed nutritional support. These future directions will help refine clinical guidelines and support more personalized and effective management strategies for patients with GIB.

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IF: 4.3 (2023)

Hemodynamic Status as a Determinant Factor of Optimal Endoscopy Timing in Upper Gastrointestinal Bleeding: Results from an International Survey of 533 Clinicians

Mahmoud Obeidat, Diana-Elena Floria, Brigitta Teutsch, Zsolt Abonyi-Tóth, Péter Hegyi, Bálint Erőss, International Advisory Group of The Survey: (Stig B. Laursen, Marine Camus, Franck Verdonk, Áron Vincze, Zsolt Bognár, Vasile Drug, Keith Siau, Ian M. Gralnek)

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DOI: 10.1053/j.gastro.2025.07.044

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In Reply: Antibiotic-Impregnated Ventriculoperitoneal Shunts Decrease Bacterial Shunt Infection: A Systematic Review and Meta-Analysis

J. Kovács, V. Máté, **M. Obeidat**, R. Nagy, G. Agócs, S. Kiss-Dala, et al.

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IF: 5.0 (2024)

17 ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to my supervisors, Dr. Bálint Erőss and Dr. Brigitta Teutsch, for their unwavering support, guidance, and encouragement throughout every stage of this journey. Dr. Erőss, your mentorship, vision, and dedication have profoundly shaped both my research and my personal growth. Dr. Teutsch, your expertise and patient guidance in research methodology have been invaluable, and I am sincerely thankful for your consistent involvement and constructive feedback.

I am equally grateful to my family for their unconditional love, patience, and belief in me, especially during the most challenging times. Your constant encouragement has been the foundation upon which I built this work.

To my friends and colleagues, thank you for being my anchor and source of strength. Your support, understanding, and occasional distractions made this long journey not only bearable but also meaningful.

This accomplishment would not have been possible without the collective support of each and every one of you.