SEMMELWEIS EGYETEM

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UNDERRECOGNIZED RISK FACTORS IN ACUTE GASTROENTEROLOGICAL CONDITIONS REQUIRING ENDOSCOPIC INTERVENTION

Ph.D. Thesis

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Budapest

2026

“The present is theirs; the future, for which I really worked, is mine.”

Nikola Tesla

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1. LIST OF ABBREVIATIONS

CI Confidence Interval

DOI Digital Object Identifier

ERCP Endoscopic Retrograde Cholangiopancreatography

GIB Gastrointestinal Bleeding

GRADE Grading of Recommendations Assessment, Development and Evaluation

HI Hemodynamic Instability

HR Hazard Ratio

LGIB Lower Gastrointestinal Bleeding

LOH Length of Hospitalization

M-W Mallory-Weiss

NA Not Available

NVUGIB Non-Variceal Upper Gastrointestinal Bleeding

OR Odds Ratio

PAD **Periampullary Diverticulum**

PEP Post-ERCP Pancreatitis

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO International Prospective Register of Systematic Reviews

PUB Peptic Ulcer Bleeding

RCT Randomized Controlled Trial

SD Standard Deviation

QUIPS Quality in Prognostic Studies

UGIB Upper Gastrointestinal Bleeding

VUGIB Variceal Upper Gastrointestinal Bleeding

2. STUDENT PROFILE

2.1. Vision and mission statement

In my vision, interventional endoscopists work in a multidisciplinary environment alongside collaborative partners to improve patient care outcomes in the field and ensure the highest quality of care. By systematically evaluating clinical predictors and procedure-related risks, decision-making becomes more structured, reproducible, and patient-centered. My mission in this work is to contribute to this approach by generating high-quality evidence and translating relevant findings into practical guidance that supports safer and more effective endoscopic care.

2.2. Specific goals

The specific goals of my work were to evaluate clinically relevant risk factors and outcome determinants in acute and interventional gastroenterology through evidence-based synthesis and quantitative analysis. My research focused on identifying simple, readily assessable clinical and anatomical parameters that support objective risk stratification and guide endoscopic decision-making, with the aim of generating structured, clinically applicable knowledge for everyday practice.

2.3. Scientometrics

Number of all publications:	8
Cumulative IF:	30
Av IF/publication:	3.75
Ranking (SCImago; year of publication):	D1: 3, Q1: 8
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.8
Av IF/publication:	4.4
Ranking (Scimago; year of publication):	D1:1, Q1: 2
Number of citations on Google Scholar:	64
Number of citations on MTMT (independent):	45
H-index:	6

The detailed bibliography of the student can be found on pages 72-74.

2.4. Future plans

In the coming years, my primary professional goal is to complete my advanced training in interventional endoscopy and to obtain board certification in gastroenterology. Building on the international experience gained during my fellowships, I aim to further strengthen my clinical expertise in complex pancreaticobiliary and emergency endoscopic procedures, while continuing to develop a strong international professional network.

Alongside my clinical career, I intend to further expand my academic activity by supervising early-career researchers and strengthening their competencies in clinical research methodology. I plan to continue and complete my ongoing international clinical studies, including the PROSECCO trial (Prophylactic Endoscopic Sphincterotomy in Patients with Acute Biliary Pancreatitis Unfit for Surgery: A Randomized Controlled Clinical Trial), and to initiate additional multicentric, practice-oriented research projects in the field of acute gastroenterology and interventional endoscopy.

My long-term objective is to integrate high-level clinical practice with research leadership and education. I aspire to play an active role in training the next generation of gastroenterologists, fostering international scientific collaboration, and translating research findings into improved clinical pathways and patient outcomes at both national and international levels.

3. SUMMARY OF THE THESIS

Acute gastroenterological conditions requiring urgent intervention demand rapid yet structured clinical decision-making. In these settings, simple and readily identifiable risk factors are often recognized in routine practice but are not systematically incorporated into procedural planning or formal risk stratification. Papilla morphology assessed at the start of ERCP (endoscopic retrograde cholangiopancreatography) and hemodynamic instability (HI) at presentation in acute gastrointestinal bleeding (GIB) represent two such parameters that may substantially influence procedural and clinical outcomes

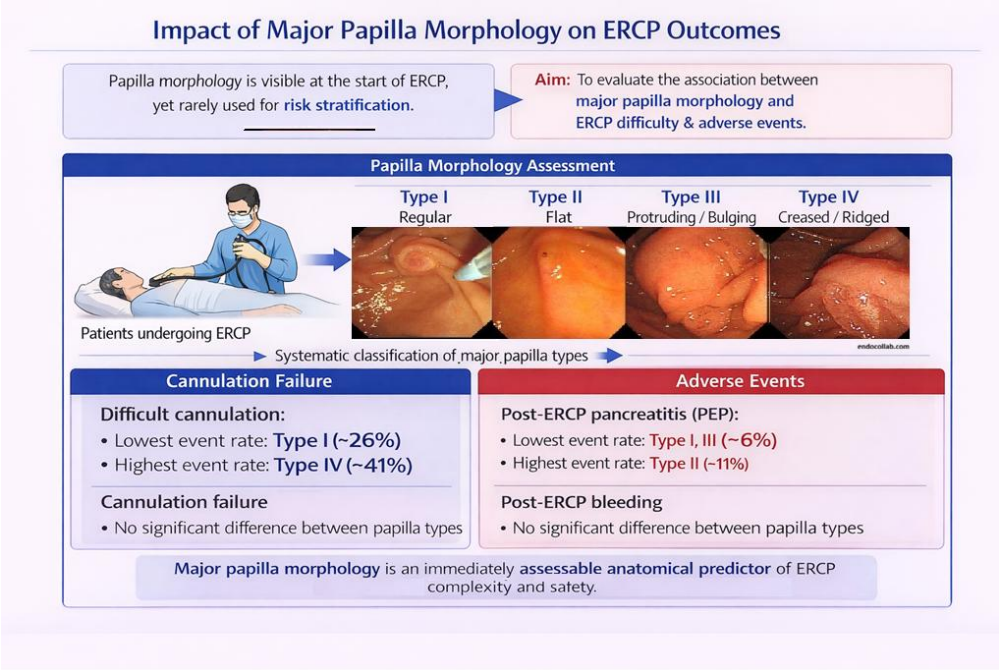
In this thesis, we investigated the role of major papilla morphology in determining the safety and efficacy of ERCP, and the prognostic significance of HI at admission in patients with acute GIB. To address these questions, two systematic reviews and meta-analyses were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and the methodological guidance of the Cochrane Handbook, with both protocols prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO).

Across a substantial international evidence base, papilla morphology was found to be associated with ERCP complexity and adverse-event risk. Type I papillae were consistently linked to lower rates of difficult cannulation, whereas type II papillae were associated with an increased risk of post-ERCP pancreatitis. In contrast, HI in acute GIB was strongly associated with worse clinical outcomes, including higher in-hospital and short-term mortality, increased rebleeding rates, and a greater likelihood of requiring surgical intervention.

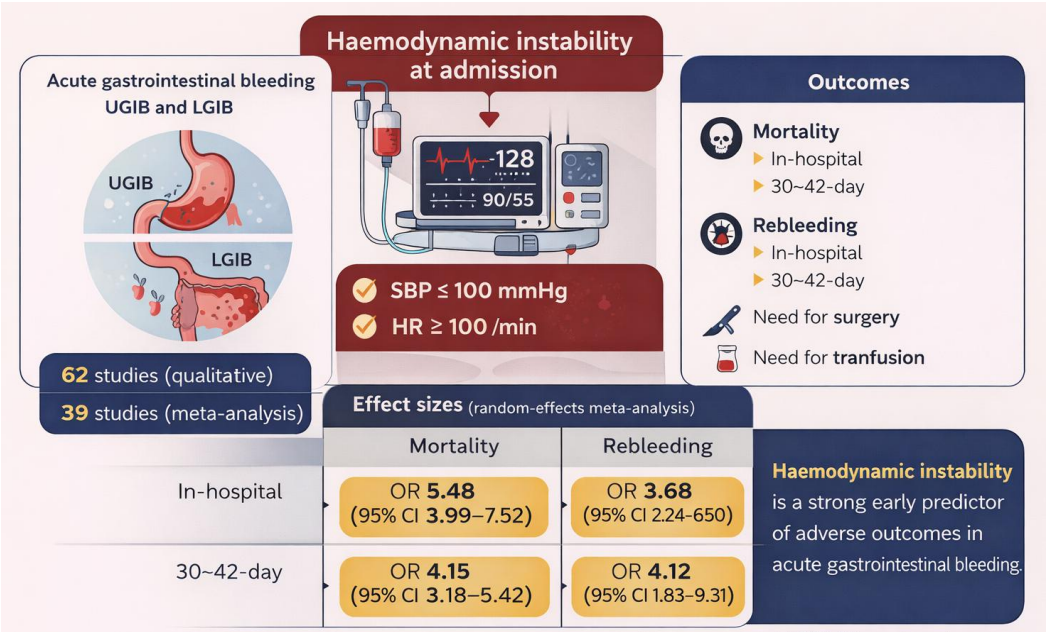
Taken together, these findings indicate that papilla morphology in ERCP and HI in acute GIB constitute clinically meaningful anatomical and physiological risk factors. Their systematic assessment, structured documentation, and integration into endoscopic decision-making pathways may support more individualized, risk-adapted management and contribute to improved patient safety and outcomes in acute gastroenterological care.

4. GRAPHICAL ABSTRACT

4.1. Study 1



4.2. Study 2



5. INTRODUCTION

5.1. Acute gastrointestinal conditions and urgent endoscopic decision-making

Acute gastrointestinal conditions frequently require urgent endoscopic intervention. Despite substantial advances in endoscopic techniques and peri-procedural management, clinical outcomes remain highly variable and are strongly influenced by patient-related and anatomical risk factors that are often underrecognized in routine clinical practice.

Endoscopic retrograde cholangiopancreatography (ERCP) and acute gastrointestinal bleeding (GIB) represent distinct clinical entities that occur in high-risk settings and require rapid endoscopic decision-making. In these scenarios, simple and readily available parameters such as papilla morphology or the presence of hemodynamic instability (HI) at presentation may critically influence procedural success and patient outcomes. The structured integration of these factors into evidence-based endoscopic management strategies remains limited.

5.2. Anatomical risk stratification in ERCP

ERCP is one of the most frequently performed endoscopic procedures for pancreaticobiliary disorders. Despite continuous technical refinement over recent decades, biliary cannulation remains a critical step of the procedure, with reported failure rates of 5–20% even in experienced hands (1). ERCP is also associated with a substantial risk of adverse events, most notably post-ERCP pancreatitis (PEP), which occurs in approximately 10% of procedures and in more than 14% of high-risk patients, with evidence indicating that its incidence has remained largely unchanged over the past decades (2).

Variations in the macroscopic appearance of the major duodenal papilla have long been recognized during routine endoscopic practice, raising the possibility that anatomical factors may influence cannulation difficulty and procedural risk (3). This assumption has been supported by the development of validated endoscopic classification systems and by prospective data suggesting an association between papilla anatomy, cannulation complexity, and adverse events (4, 5).

However, despite the availability of these data, papilla morphology is rarely considered as part of structured procedural planning or formal risk assessment. As a result, its potential role as a readily assessable anatomical risk factor has not yet been consistently translated into structured procedural decision-making.

5.3. Underrecognized risk factors in acute GIB

Acute GIB is a frequent and potentially life-threatening emergency in gastroenterology, with reported mortality rates of 2–10% (6, 7). Early risk stratification is therefore essential, as delayed recognition and inadequate initial resuscitation are associated with increased mortality and higher rates of rebleeding (8).

Approximately 25% of patients presenting with acute GIB develop HI, reflecting significant blood loss and circulatory compromise (9). This condition is easily identifiable at the bedside and is widely perceived as a marker of severe disease. However, despite its frequent recognition in clinical practice, the prognostic relevance of HI has not been consistently defined across studies, and its role in guiding early management decisions remains insufficiently addressed in current guidelines (10-12).

Consequently, HI is often acknowledged but not systematically integrated into structured risk stratification or endoscopic decision-making algorithms. This lack of standardization has contributed to uncertainty regarding its true impact on clinically relevant outcomes, including mortality and rebleeding, in patients with acute GIB.

5.4. Rationale and aims of the thesis

The common challenge across ERCP and acute GIB lies in the lack of structured integration of simple, readily identifiable risk factors into evidence-based endoscopic decision-making. Both papilla morphology and HI are easily assessable parameters that may substantially influence outcomes, yet their prognostic and procedural relevance has not been consistently quantified or standardized. The overarching aim of this thesis is to evaluate underrecognized risk factors in acute gastroenterological conditions requiring urgent endoscopic intervention and to clarify their impact on clinically relevant outcomes.

Through systematic evidence synthesis and meta-analytical approaches, this work seeks to improve the understanding of how anatomical risk profiling in ERCP and early

identification of HI in acute GIB may contribute to more informed clinical decision-making, improved procedural outcomes, and enhanced patient safety.

6. OBJECTIVES

6.1. Study 1 – Morphology of the papilla can predict procedural safety and efficacy of ERCP: a systematic review and meta‑analysis

We aimed to systematically evaluate the available evidence on the role of papilla morphology in ERCP and to clarify its clinical relevance for biliary cannulation outcomes. Therefore, we investigated whether different papilla morphology types are associated with an increased risk of difficult or unsuccessful cannulation and with a higher incidence of post-ERCP adverse events, particularly PEP. We hypothesized that specific papilla morphologies represent anatomical risk factors that predispose to more challenging cannulation and less favorable procedural outcomes during ERCP.

6.2. Study 2 – At admission hemodynamic instability is associated with increased mortality and rebleeding rate in acute gastrointestinal bleeding: a systematic review and meta-analysis

We aimed to systematically evaluate the available evidence on the prognostic role of HI at presentation in acute GIB and to clarify its impact on clinically relevant outcomes. Therefore, we investigated whether the presence of HI or shock at admission is associated with an increased risk of mortality and rebleeding, as well as other adverse outcomes, including the need for surgery, transfusion, and prolonged hospitalization. We hypothesized that HI at presentation represents a strong prognostic factor and is associated with significantly worse short- and medium-term outcomes in patients with acute GIB.

7. METHODS

Two independent systematic reviews and meta-analyses were conducted to address the predefined research questions. Both studies were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (13, 14).

The protocols of the two reviews were prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration numbers CRD42021285727 and CRD42022360894, respectively.

7.1. Information sources and search strategy

7.1.1. Study 1

Three databases — MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) — were systematically searched from inception to September 29, 2022. No filters or restrictions were applied. The main parts of the search query included terms related to ERCP and papilla morphology, with the following search key: (papilla) AND (cannulation OR endoscopic retrograde OR ERCP). Additionally, relevant articles were identified by manually screening the reference lists and citation records of all included studies.

7.1.2. Study 2

Three databases, MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched from inception to October 22, 2021. We did not apply any filters or restrictions to our search. The main parts of the search query included terms in connection with HI/shock and GIB, with the following 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))). In addition, we manually searched for relevant articles and checked the bibliographic reference lists of studies selected for inclusion.

7.2. Eligibility Criteria

7.2.1. Study 1

The condition–context–population (CoCoPop) framework was applied to define eligibility criteria (15). The conditions of interest included difficult biliary cannulation, cannulation attempts, cannulation time, cannulation failure, PEP, and other ERCP-related adverse events (bleeding, perforation, and infection), evaluated in the context of different papilla morphologies. The population comprised adult patients (≥18 years) undergoing ERCP with a native papilla. Randomized controlled trials (RCTs), case–control studies, cross-sectional studies, and cohort studies were considered eligible. Both full-text publications and conference abstracts providing sufficient extractable data were included. Definitions of difficult cannulation, cannulation failure, and post-ERCP adverse events were accepted as reported in the individual studies.

7.2.2. Study 2

The population–exposure–outcome (PEO) framework was applied to define eligibility criteria (15). The population of interest comprised adult patients (≥18 years) presenting with GIB. Studies were considered eligible if they reported outcomes in patients with HI or shock at admission. The primary outcome was mortality, while secondary outcomes included rebleeding, need for surgery, need for transfusion, length of hospitalization (LOH), and the need for rescue endoscopic therapy. Outcomes were assessed separately in upper GIB (UGIB), lower GIB (LGIB), and mixed populations including both UGIB and LGIB patients. Definitions of HI or shock were accepted as reported in the individual studies; based on these definitions, HI and shock were considered synonymous, and the term HI was used throughout this review. RCTs, case–control, cross-sectional, and cohort studies were eligible for inclusion in the systematic review, while only cohort studies were included in the meta-analysis. Only full-text articles were considered eligible.

7.3. Study Selection and Data Extraction

For both studies, all records retrieved from the systematic search were imported into a reference management software (EndNote X7.4, Clarivate Analytics, Philadelphia, PA, USA), and duplicates were removed using automated and manual procedures. Two independent reviewers subsequently screened the remaining records based on title and

abstract, followed by full-text assessment. Inter-reviewer agreement was evaluated at both stages using Cohen's kappa coefficient (κ) (16). Data extraction was performed independently by two investigators using a purpose-designed Microsoft Excel 2016 spreadsheet (Office 365, Microsoft, Redmond, WA, USA).

7.3.1. Study 1

7.3.1.1. Study selection and data extraction

Data were extracted on the first author, year of publication, digital object identifier (DOI), data collection period, study location, number of centers, study design, patient age (reported as mean or median with corresponding standard deviation (SD) or interquartile range), total sample size, number of female patients, number of patients in each papilla morphology category, and data on primary and secondary outcomes reported separately for the different papilla types.

7.3.1.2. Morphology of the papilla

Papilla morphology was classified using the Haraldsson system, the first classification with validated intra- and interobserver agreement (5). According to this system, papillae are categorized into four types: regular (type 1), small (type 2), protruding or pendulous (type 3), and creased or ridged (type 4).

As a secondary analysis, a comparison between the Haraldsson classification and other papilla morphology classification systems identified in the literature was performed. For this purpose, two endoscopists independently reviewed the morphological descriptions and available images reported in the included studies and assigned corresponding Haraldsson papilla types. In cases of disagreement, consensus was achieved through adjudication by a third reviewer. Based on this comparison, additional analyses were conducted.

7.3.2. Study 2

Data were extracted on the first author, year of publication, study location, study design, enrollment period, study population, sample size, patient age, source of bleeding, duration of follow-up, numbers of patients with and without HI or shock at admission, and the definitions of HI or shock applied in each study. Effect estimates, including odds ratios

(ORs) and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), were also collected.

When multiple publications originated from the same patient cohort, the study reporting the largest sample size was included.

7.4. Risk of Bias and Quality of Evidence Assessment

All assessments were conducted independently by two reviewers. In cases of disagreement, consensus was reached through discussion; if disagreement persisted, a third reviewer was consulted.

7.4.1. Study 1

The risk of bias for each outcome was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence (17). The overall certainty of the evidence was evaluated in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (18).

7.4.2. Study 2

The risk of bias for each outcome was assessed using the Quality In Prognostic Studies (QUIPS) tool (19).

7.5. Data Synthesis and Analysis

Statistical analyses were performed by a biostatistician using the R programming language (R Core Team, 2022; version 4.2.1). Forest plots were used to present the results of the meta-analyses. A minimum of three studies was required to perform a meta-analysis.

7.5.1. Study 1

Event rates with corresponding 95% CIs were used as effect size measures. Anticipated between-study heterogeneity was addressed using random-effects meta-analysis to obtain pooled estimates. Publication bias was evaluated by visual inspection of funnel plots, and sensitivity analyses were conducted using the leave-one-out approach.

As multiple papilla morphology subgroups were reported within individual studies, a three-level random-effects meta-analysis was applied to account for the non-

independence of effect size estimates derived from the same study (20). Statistical heterogeneity was quantified using the I^2 statistic, and subgroup differences between papilla morphology types were assessed using the Cochrane Q test. A two-sided p value <0.05 was considered statistically significant.

7.5.2. Study 2

In-hospital mortality, 7-day mortality, and both 6-week and 30-day mortality were pooled. The same analytical approach was applied to rebleeding outcomes. Pooled ORs with 95% CIs were calculated using random-effects models. Between-study heterogeneity was assessed using the I^2 statistic, as described by Thompson and Higgins (21). Publication bias was evaluated by visual inspection of funnel plots and by Egger's test, with additional analyses performed when a potential small-study effect was suspected (22). Sensitivity analyses were conducted using the leave-one-out method. Subgroup analyses were performed in studies in which the bleeding subtype was specified. Additional analyses were conducted in studies defining HI as a systolic blood pressure ≤100 mmHg and/or a pulse rate ≥100/min.

8. RESULTS

8.1. Study 1: Morphology of the papilla can predict procedural safety and efficacy of ERCP: a systematic review and meta‑analysis

8.1.1. Study search and selection

The study selection process is presented in the PRISMA flow chart (see Figure 1). In total, 6,952 records were retrieved from the database search. After the screening and eligibility assessment, 17 studies were retained for the narrative synthesis (3, 4, 23-37), and 14 of these could be incorporated into the quantitative analysis (3, 4, 23, 24, 26, 28-36).

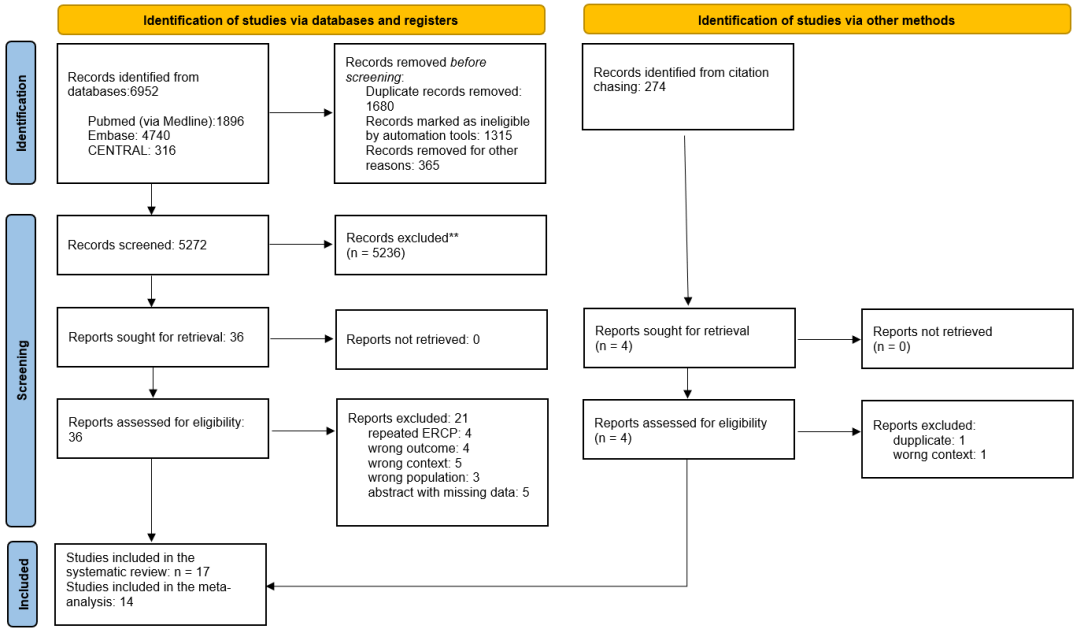


Figure 1. *PRISMA 2020 flowchart representing the detailed systematic search and study selection process (38).*

8.1.2. Basic characteristics of the included studies

The main characteristics of the included studies are summarised in Table 1. The eligible studies were published between 2016 and 2022. Of the 17 studies, 15 followed a cohort design, including eight prospective (3, 4, 23-25, 29, 31, 32) and seven retrospective investigations (27, 28, 30, 34-37). In addition, one case–control study (33) and one cross-sectional study (26) were identified. Thirteen studies were available as full-text articles

(3, 4, 23, 24, 26-29, 31, 33, 35-37), while four were published as conference abstracts (25, 30, 32, 34).

Seven studies applied the Haraldsson classification (3, 4, 26, 28, 31, 33, 34), and a further seven used classification systems that were comparable to it (23, 24, 29, 30, 32, 35, 36). In three studies, the applied classifications were not directly comparable to the Haraldsson system (25, 27, 37). The sample size varied widely across studies, ranging from 72 to 11,090 participants.

Table 1. Basic characteristics of the included articles in Study 1 (38).

Author	Year	Centers	Study type	Age (*:mean; #:median)	Sex (female%)	Number of patients	Classification	Outcomes
Balan et al. (23)	2020	1	prospective cohort	NA	NA	322	Regular: 52% Canard type I 11% Canard type II: 19% Canard type III: 10% Canard type IV: 8%	difficult cannulation cannulation time cannulation attempts post-ERCP pancreatitis, bleeding, infection
Canena et al. (24)	2021	3	prospective cohort	*69.6	56.8%	361	Viana type I: 13% Viana type IIa: 35% Viana type IIb: 30% Viana type IIc:10% Viana type IIIa: 4% Viana type IIIb: 4% Viana type IV: 4%	cannulation failure cannulation time post-ERCP pancreatitis, bleeding, perforation
Chen et al. (3)	2020	1	prospective cohort	*64 (SD: 16.5)	47.5%	286	Haraldsson type I: 41% Haraldsson type II: 9% Haraldsson type III: 22% Haraldsson type IV: 28%	cannulation failure cannulation time post-ERCP pancreatitis, bleeding, perforation, cholangitis
Fernandes et al. (25)	2018	3	prospective cohort	#79	59.4%	106	Leés type I: 50% Leés type II: 32% Leés type III: 12% Leés type IV: 6%	cannulation time
Gutierrez- De Aranguren et al. (26)	2021	1	retrospective cross-sectional	*55 (SD: 20)	66.5%	188	Haraldsson type I: 32% Haraldsson type II: 25% Haraldsson type III: 27% Haraldsson type IV: 16%	difficult cannulation
Haraldsson et al. (4)	2019	9	prospective cohort	66 (SD: 16)	52%	1377	Haraldsson type I: 56% Haraldsson type II: 13% Haraldsson type III: 23% Haraldsson type IV: 8%	difficult cannulation cannulation time post-ERCP pancreatitis

Liu et al. (27)	2021	1	retrospective cohort	NA	NA	11 090	Normal: 44% Thick and long: 11% Peridiverticular: 27% Intradiverticular: 5% Ectopic: 1% Edematous 10% Ulcerative: 2%	difficult cannulation
Mohamed et al. (28)	2021	1	retrospective cohort	NA	51.8%	637	Haraldsson type I: 62% Haraldsson type II: 5% Haraldsson type IIIa: 9% Haraldsson type IIIb: 9% Haraldsson type IV: 3% Type D: 12%	cannulation failure cannulation time cannulation attempts post-ERCP pancreatitis, bleeding, cholangitis or sepsis
Nakeeb et al. (29)	2016	1	prospective cohort	*58.4 (SD: 14.7)	44.4%	996	Normal: 60% Atrophic: 3% Pregnant: 7% Tumour: 7% Redundant: 8% Juxtadiverticular: 8% Small: 6% Long: 1%	post-ERCP pancreatitis
Onilla et al. (30)	2021	1	retrospective cohort	NA	NA	347	Regular protrusion: 57% Small protrusion: 31% Large protrusion: 12% Annular pattern: 72% Unstructured pattern: 11% Longitudinal pattern 11% Isolated pattern: 1% Gyrus pattern: 5%	difficult cannulation, cannulation failure
Quiroga-Purizaca et al. (31)	2022	1	prospective cohort	*51.5 (CI: 48.8-54.1)	68.4%	138	Haraldsson type I: 59% Haraldsson type II: 8% Haraldsson type III: 29% Haraldsson type IV: 4%	difficult cannulation cannulation time cannulation attempts post-ERCP pancreatitis, bleeding, perforation

Sadeghi et al. (32)	2019	1	prospective cohort	*62.3 (SD: 15.5)	51.4%	72	Small: 33% Bulging: 28% Long: 39%	cannulation success
Saito et al. (33)	2022	3	retrospective case-control	*74.9	47.5%	1406	Haraldsson type I: 45% Haraldsson type II: 44% Haraldsson type III: 7% Haraldsson type IV: 4%	difficult cannulation
Thongsuwan et al. (34)	2021	1	retrospective cohort	NA	50.4%	558	Haraldsson type I: 66% Haraldsson type II: 16% Haraldsson type III: 12% Haraldsson type IV: 6%	difficult cannulation cannulation failure post-ERCP pancreatitis, bleeding, infection
Watanabe et al. (35)	2019	1	retrospective cohort	#70	36%	589	Regular protrusion: 12% Small protrusion: 78% Large protrusion: 10% Annular pattern: 67% Unstructured pattern: 7% Longitudinal pattern: 7% Isolated pattern: 1% Gyrus pattern:16% Unclassified pattern: 2%	difficult cannulation cannulation failure cannulation attempts
Zhang et al. (36)	2016	1	retrospective cohort	*75 (SD: 2.2)	42.7%	82	bulging: 44% normal: 22% small: 16% unusual location: 18%	cannulation success cannulation time
Zheng et al. (37)	2020	1	retrospective cohort	NA	46.1%	2385	others:18% villous: 74% granular: 8%	post-ERCP pancreatitis

NA: not available; SD: standard deviation; CI: confidence interval; ERCP: endoscopic retrograde cholangiopancreatography

8.1.3. Quantitative Synthesis

8.1.3.1. Difficult cannulation

Nine studies reported data on the rate of difficult cannulation (4, 23, 26, 27, 30, 31, 33-35), of which eight were eligible for quantitative synthesis (4, 23, 26, 30, 31, 33-35). In analyses restricted to studies applying the Haraldsson classification, difficult cannulation occurred less frequently in type I papillae (26%; CI 18–37) compared with the other papilla types (type III: 35%; CI 25–48; type II: 39%; CI 28–52; type IV: 41%; CI 28–55). Although this difference did not reach statistical significance, the p-value indicated a trend toward higher rates of difficult cannulation in certain papilla types (p = 0.075). Heterogeneity was considerable (total I^2 = 89%; CI 48–98). Sensitivity analyses did not identify outlier studies or relevant changes in the pooled effect estimates (see Figure 2).

A similar pattern, but with a statistically significant difference and no outlier studies, was observed when all studies using various classification systems were included (p = 0.019; total I^2 = 87%; CI 55–96; see Figure 3).

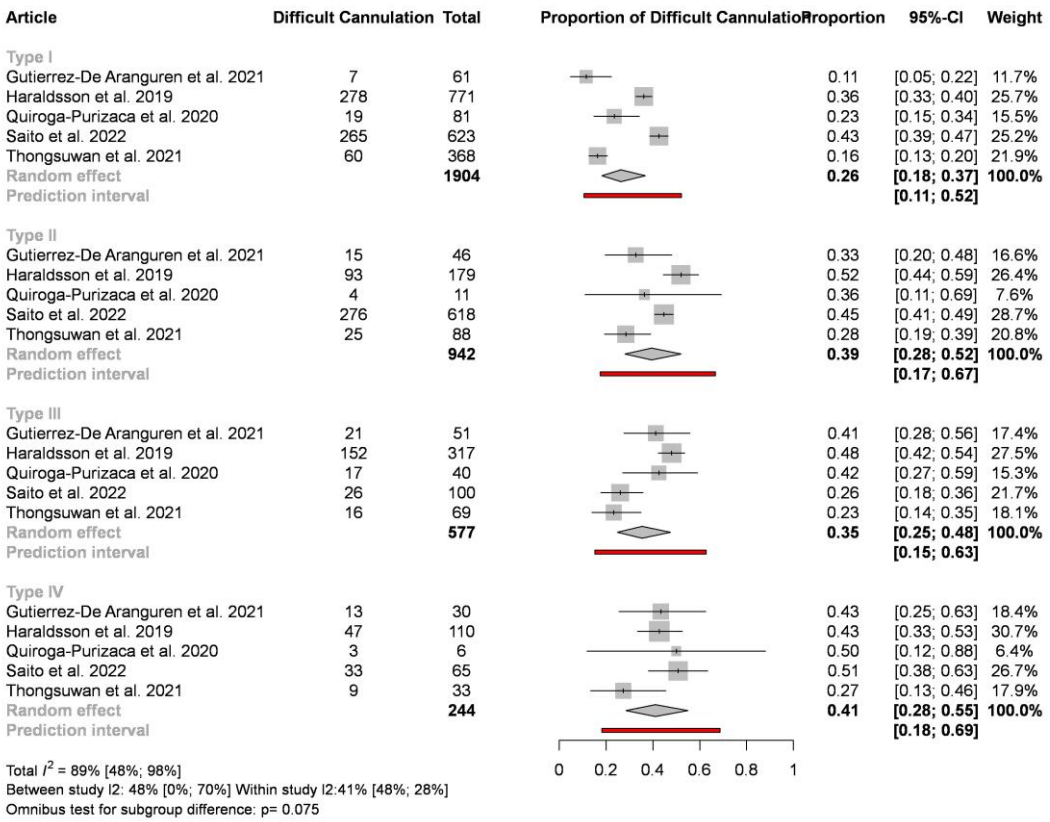


Figure 2. *Forest plot representing the pooled event rate of difficult cannulation in the different papilla types in studies using the Haraldsson classification, showing a lower tendency for difficult cannulation in type I papilla compared to the other papilla types (38). CI: confidence interval.*

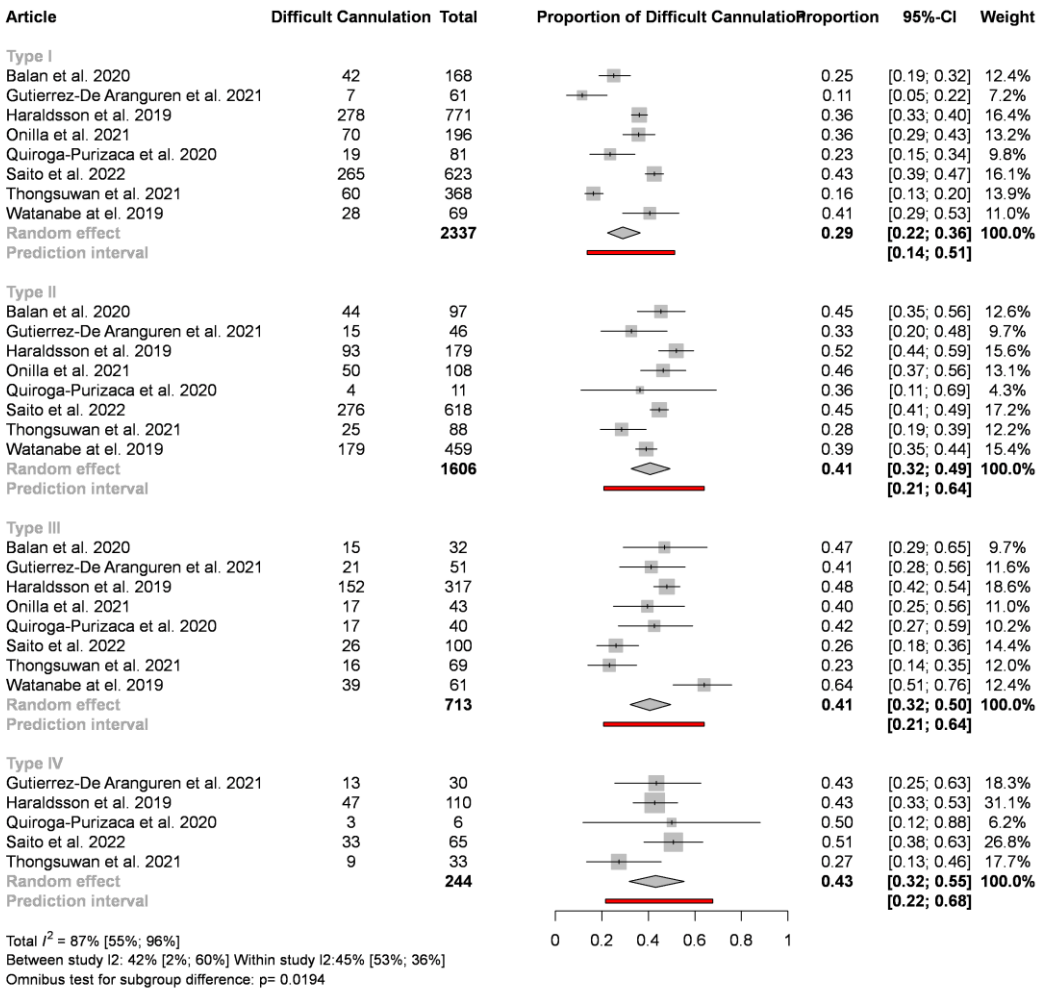


Figure 3. *Forest plot representing the pooled event rate of difficult cannulation in the different papilla types in studies using different classification systems, showing statistically significantly lower rate in type I papilla, compared to the other papilla types (38). CI: confidence interval.*

8.1.3.2. Cannulation failure

Eight studies reported the rate of cannulation failure, all applying the Haraldsson classification or a comparable system (3, 24, 28, 30, 32, 34-36). When the analysis was restricted to studies

using the Haraldsson classification, no statistically significant differences were detected in cannulation failure rates across papilla types (p = 0.262; total I^2 = 61%; CI 0–97; see Figure 4).

When all eight studies were included, the difference became statistically significant (p = 0.047; I^2 = 64%; CI 0–91). In this pooled analysis, cannulation failure occurred most frequently in type II papillae (8%, CI 4–14) and least frequently in type I papillae (3%, CI 2–6; see Figure 5). Sensitivity analyses did not identify outlier studies or relevant changes in the pooled effect estimates.

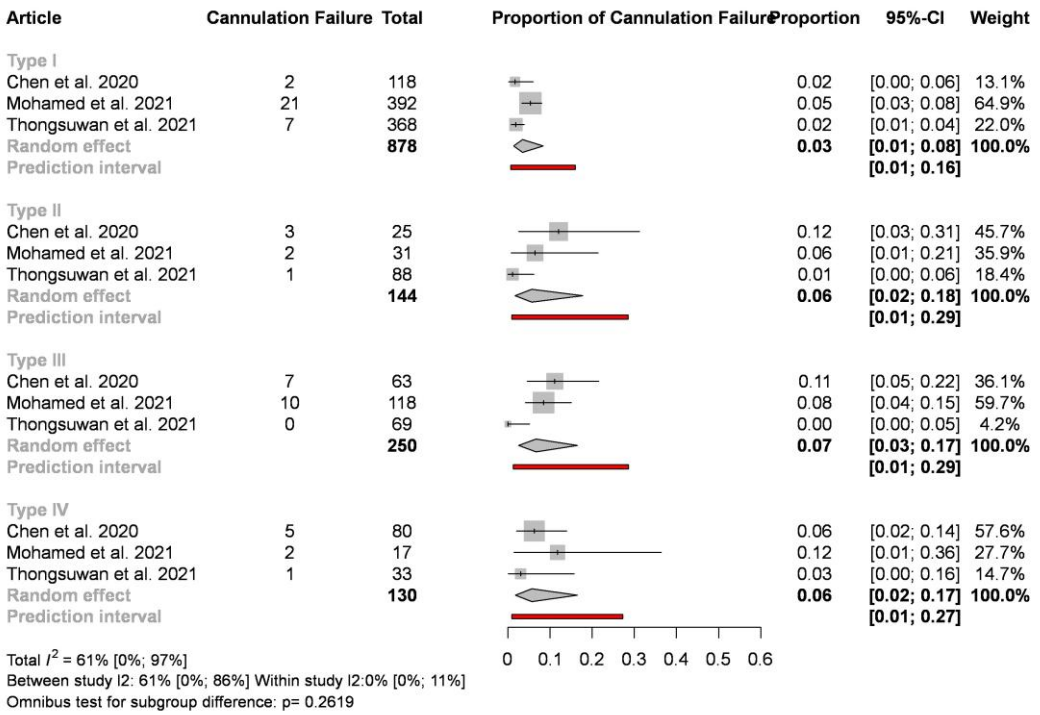


Figure 4. *Forest plot representing the pooled event rate of cannulation failure in the different papilla types in studies using the Haraldsson classification, showing no statistically significant difference in the event rates between the papilla types (38). CI: confidence interval.*

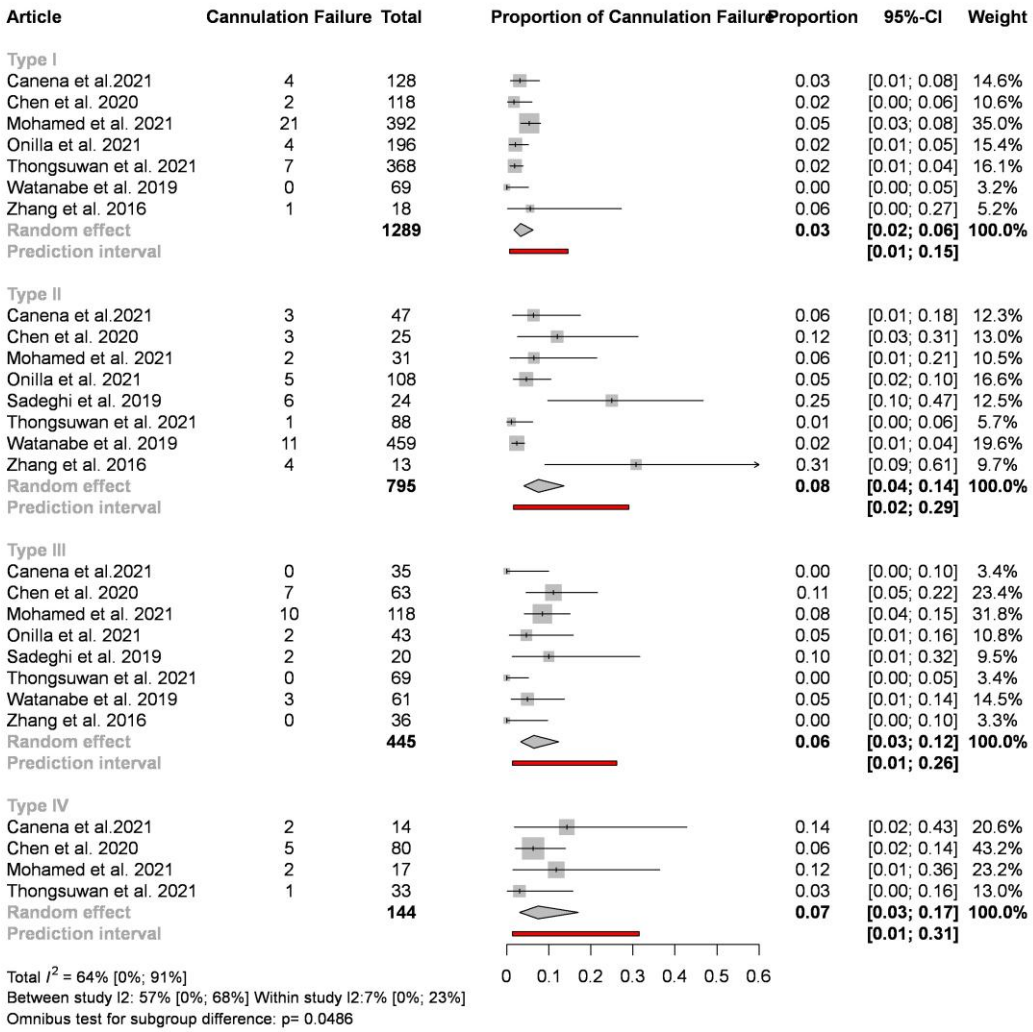


Figure 5. *Forest plot representing the pooled event rate of cannulation failure in the different papilla types in studies using different classification systems, showing statistically significant difference in the event rates between the papilla types (38). CI: confidence interval.*

8.1.3.3. Post-ERCP pancreatitis

Nine of the included studies reported the rate of PEP across different papilla types (3, 4, 23, 24, 28, 29, 31, 34, 37), eight of which were suitable for quantitative synthesis (3, 4, 23, 24, 28, 29, 31, 34). In analyses limited to studies applying the Haraldsson classification, PEP occurred more frequently in type II papillae (11%; CI 8–15) compared with the other papilla types (type IV: 7%; CI 4–12; type I: 6%; CI 5–8; type III: 6%; CI 4–8). This difference was statistically significant (p = 0.0441), and heterogeneity was negligible (total I^2 = 0%; see Figure 6).

When all eight studies using different classification systems were included, a similar pattern was observed; however, the difference between papilla types was not statistically significant (p

= 0.103; see Figure 7). Sensitivity analyses did not identify any influential outliers or relevant changes in the effect estimates.

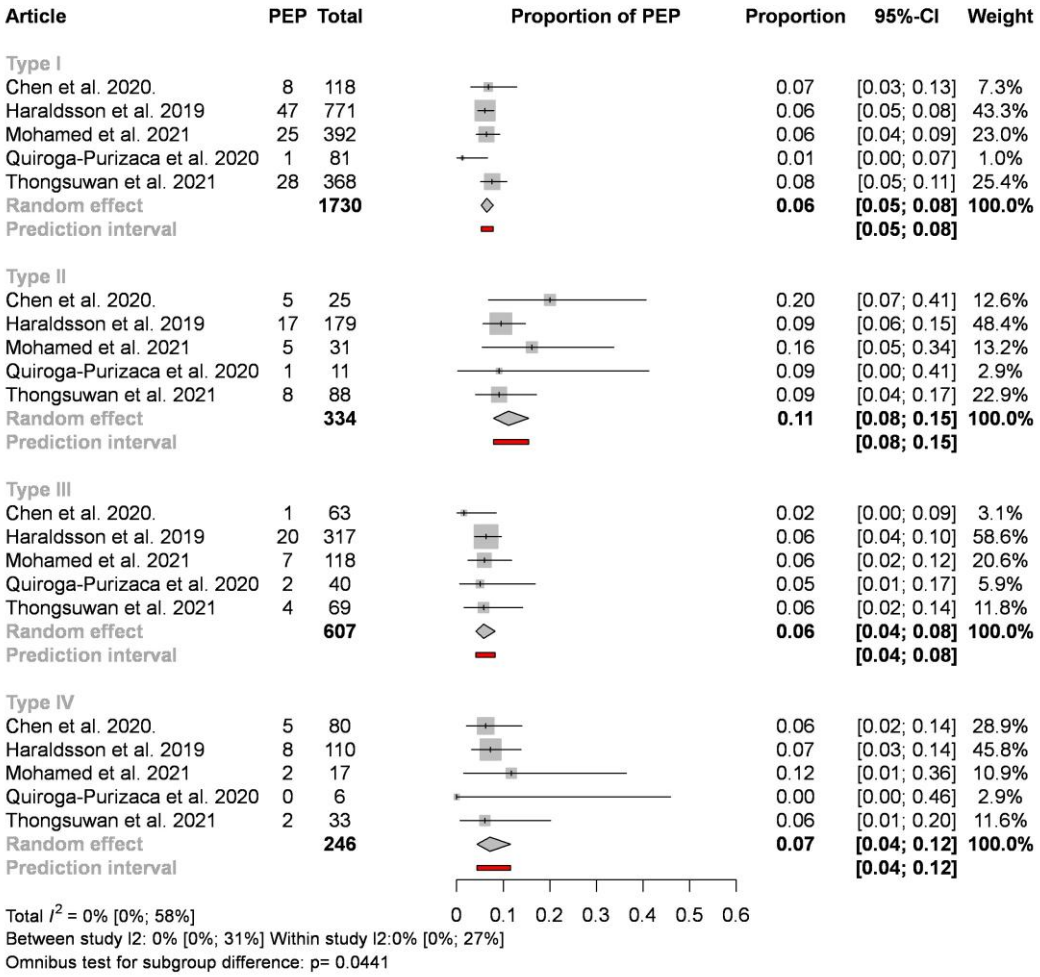


Figure 6. *Forest plot representing the pooled event rate of post-ERCP pancreatitis in the different papilla types in studies using the Haraldsson classification, showing a statistically significantly higher rate of post-ERCP pancreatitis in type II papilla, compared to the other papilla types (38). CI: confidence interval; PEP: post-ERCP pancreatitis.*

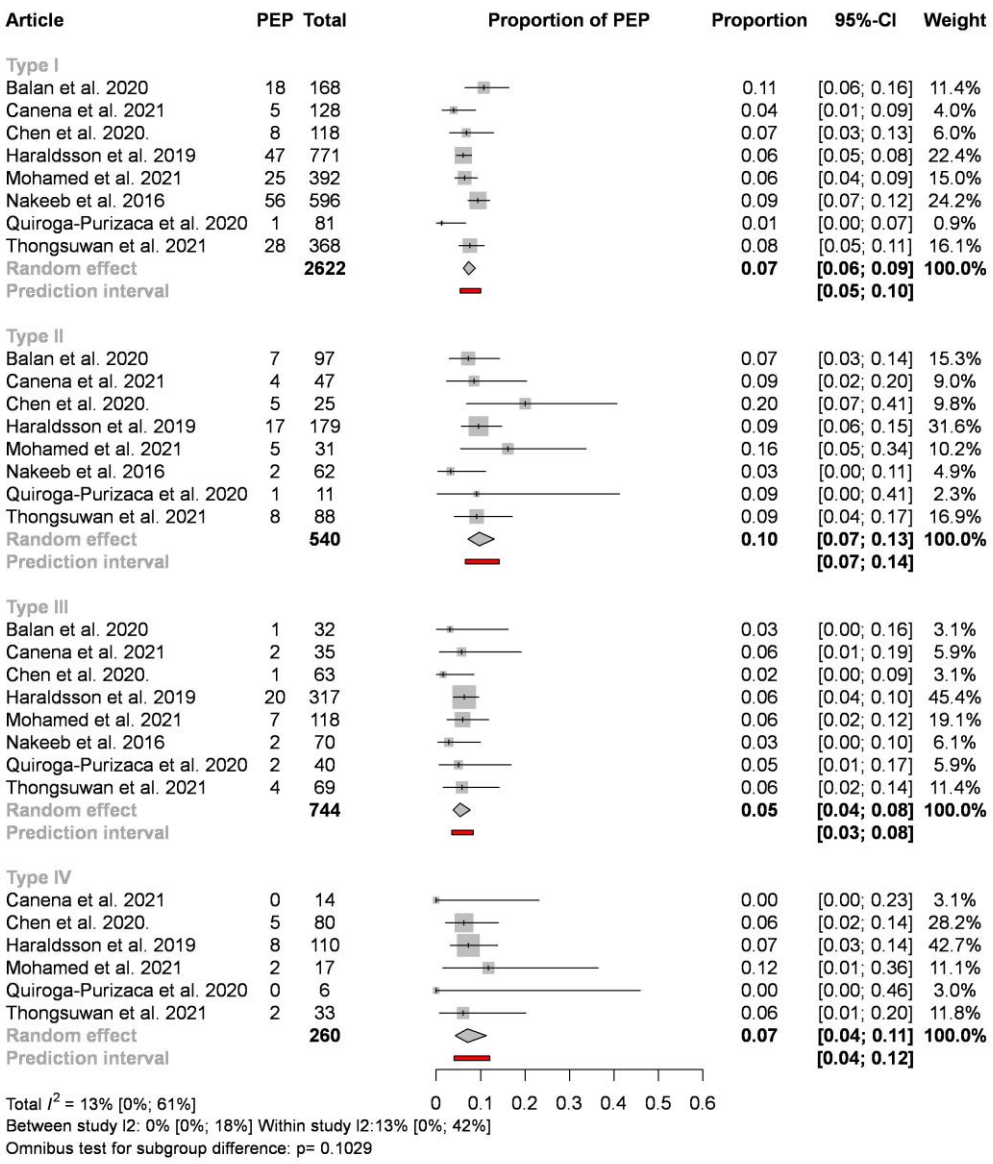


Figure 7. *Forest plot representing the pooled event rate of post-ERCP pancreatitis in the different papilla types in studies using different classification systems, showing a higher tendency for post-ERCP pancreatitis in type II papilla, compared to the other papilla types (38). CI: confidence interval; PEP: post-ERCP pancreatitis.*

8.1.3.4. Post-ERCP bleeding

Six studies provided data on post-ERCP bleeding and all of them applied the Haraldsson classification or a comparable system (3, 23, 24, 28, 31, 34). When the analysis was restricted to studies using the Haraldsson classification, as well as when the different classifications were pooled, no significant differences were detected in bleeding rates across papilla types (p =

0.8585 and p = 0.8078, respectively; see Figures 8 and 9). Sensitivity analyses did not identify any influential outliers or relevant changes in the effect estimates.

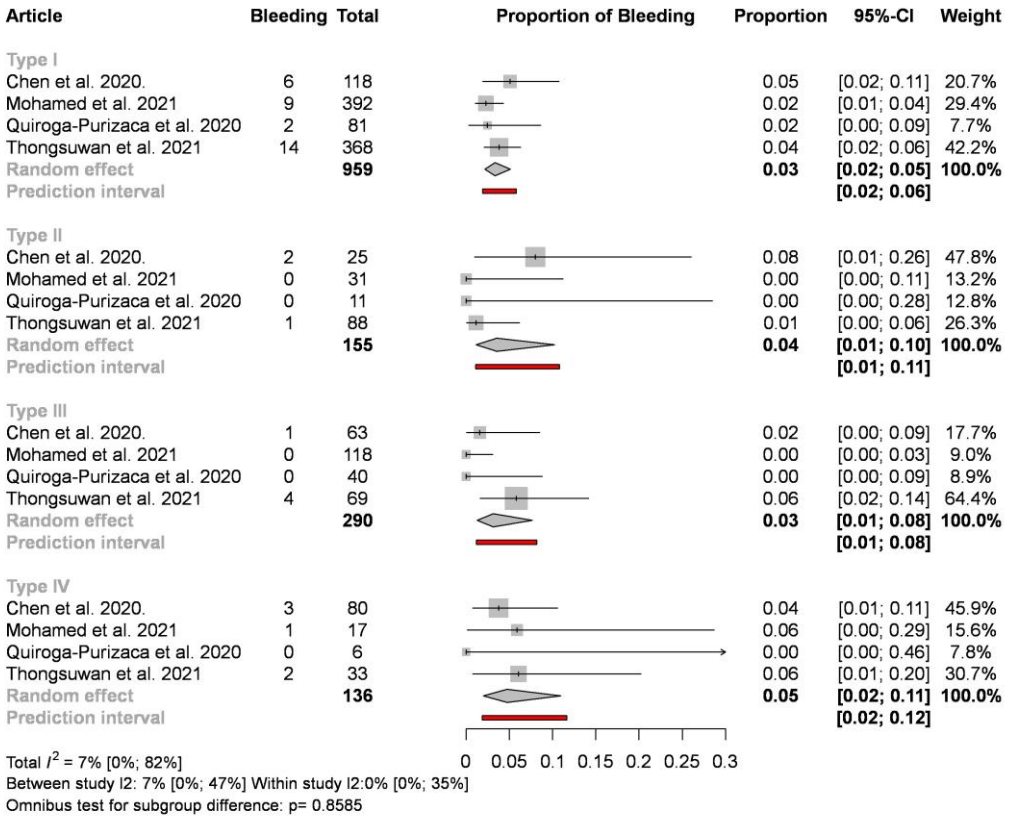


Figure 8. *Forest plot representing the pooled event rate of post-ERCP bleeding in the different papilla types in studies using the Haraldsson classification, showing no statistically significant difference in the event rates between the papilla types (38). CI: confidence interval.*

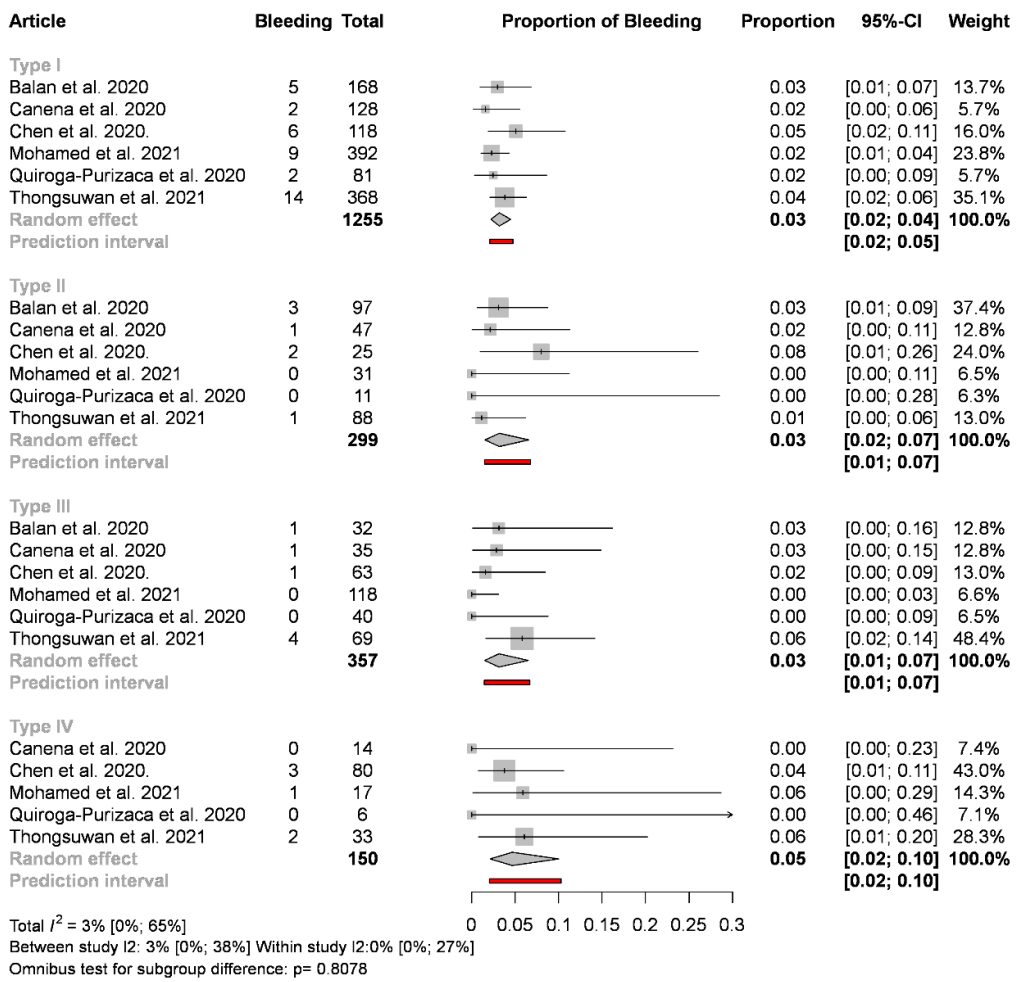


Figure 9. *Forest plot representing the pooled event rate of post-ERCP bleeding in the different papilla types in studies using different classification systems, showing no statistically significant difference in the event rate between the papilla types (38). CI: confidence interval.*

8.1.4. Qualitative synthesis

8.1.4.1. Cannulation time

Eight studies assessed cannulation time in relation to papilla morphology (3, 4, 23-25, 28, 31, 36), four of which applied the Haraldsson classification (3, 4, 28, 31). Across all studies, type I papillae were associated with the shortest cannulation times. Two studies reported the longest cannulation times in type II papillae (3, 4), while another two studies found the highest values in type IV papillae (28, 31).

8.1.4.2. Cannulation attempts

Four studies examined the number of cannulation attempts in relation to papilla morphology (23, 28, 31, 35), of which two applied the Haraldsson classification (28, 31). Across these analyses, cannulation attempts were consistently highest in type IV papillae, whereas the lowest numbers were reported for type I and type III papillae.

8.1.4.3. Post‑ERCP perforation

Three studies evaluated the rate of perforation following ERCP, all applying the Haraldsson classification (3, 24, 31). Meta-analysis could not be performed due to the presence of zero events across the studies.

8.1.4.4. Post‑ERCP infection

Four studies reported on post-ERCP infectious complications (3, 23, 28, 34), with three of these studies applying the Haraldsson classification (3, 28, 34). In the study by Chen et al., cholangitis occurred most frequently in type I papillae (2.5%), while no events were observed in type II or type III papillae (3). By contrast, Mohamed et al. found the highest rate of cholangitis and/or sepsis in type II papillae (3.2%), with no reported events in types III and IV (28). In the study of Thongsuwan et al., infections were most frequent in type III papillae (10.5%) and least frequent in type I papillae (6%) (34).

8.1.5. Risk of Bias and Quality of Evidence Assessment

The majority of the included studies showed a low risk of bias according to the applied assessment criteria across the reported outcomes. In addition, the conducted analyses did not indicate the presence of publication bias.

As only observational cohort studies were available, the certainty of evidence was limited and ranged from very low to low across the evaluated outcomes.

8.2. Study 2: At admission hemodynamic instability is associated with increased mortality and rebleeding rate in acute gastrointestinal bleeding: a systematic review and meta-analysis

8.2.1. Study search and selection

A total of 11,583 records were retrieved through the database search. After removing duplicates and screening titles and abstracts, 218 articles were selected for full-text review. An additional three studies were identified through reference screening and manual searches. In the end, 62 studies were included in the qualitative synthesis (39-100), of which 39 were eligible for quantitative analysis (40-48, 50, 52-54, 56-59, 63-67, 69, 72, 74, 76, 80, 82, 84, 86, 87, 92, 93, 95-100). The full study selection process is presented in the PRISMA flow diagram (see Figure 10).

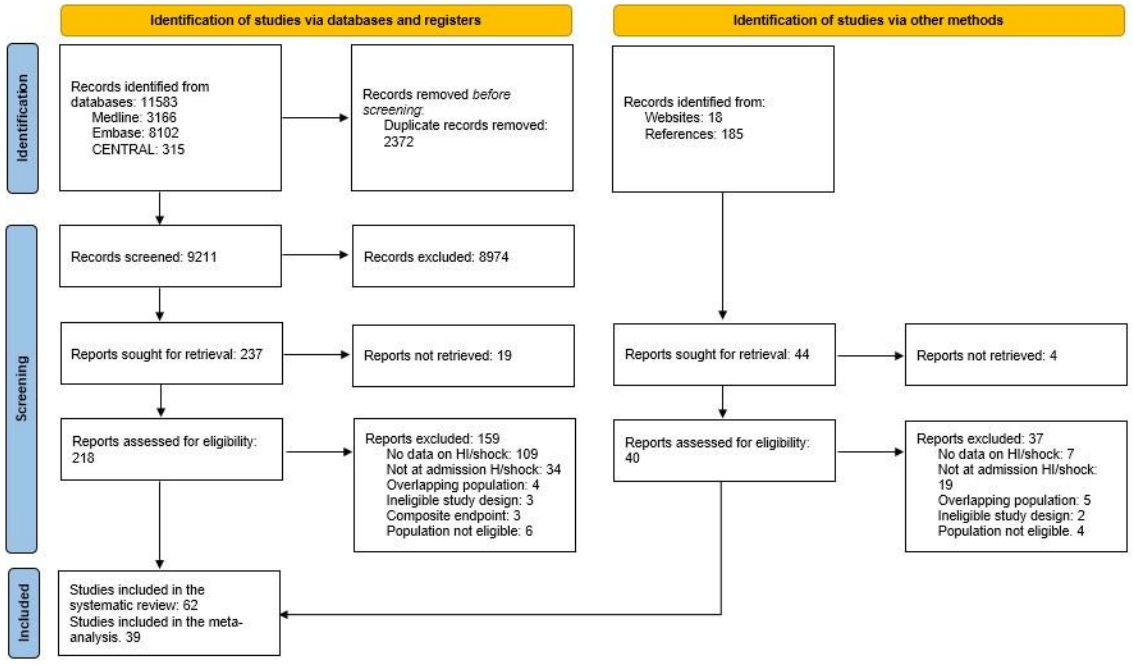


Figure 10. *PRISMA 2020 flowchart representing the detailed systematic search and study selection process (101).*

8.2.2. Basic characteristics of included studies

The main characteristics of the included studies are summarized in Table 2. The eligible publications were published between 1977 and 2021, and the number of participants per study ranged from 56 to 12,601. Most of the identified studies followed a cohort design, including 23 prospective (40-42, 44, 45, 48, 52, 53, 55, 56, 59, 64, 65, 67, 72, 74, 75, 78, 80, 84, 88, 94, 98) and 32 retrospective investigations (39, 43, 46-51, 54, 58, 60, 63, 66, 68-71, 73, 76, 82, 83, 85-

87, 89-93, 95-97, 99), while two were conducted in an ambidirectional manner (57, 100). In addition, the review comprised one randomized controlled trial (79), one case–control study (77), and three cross-sectional studies (61, 62, 81).

The reported proportion of patients with HI or shock varied widely across the studies, ranging from 1.2% to 68.3%. In terms of bleeding source, 54 studies focused on UGIB (40-59, 61-69, 71-82, 84, 86, 87, 89, 92-100), while 7 studies investigated LGIB (39, 60, 70, 85, 88, 90, 91), and one study included both patient groups within the same population (83).

Regarding outcomes, 44 studies reported mortality (40, 42-45, 47, 49-53, 55-57, 59, 61-68, 71-74, 76, 78-82, 84, 86, 88, 92-96, 98-100), 27 studies examined rebleeding (39, 41-43, 45, 46, 48, 51, 56, 58, 60, 67, 69, 70, 72, 74, 75, 77, 79, 81-85, 88, 89, 100), and 5 studies assessed the need for surgical intervention (39, 54, 87, 90, 97). Furthermore, two studies provided data on transfusion requirements (72, 89), and another two studies reported information on the length of hospitalization (39, 91).

Table 2. Basic characteristics of the included articles in Study 2 (101).

Author	Year	Study type	Type of bleeding	N⁰ of patients	Shock/HI (%)	Outcomes	Results
Albeldawi et al. (39)	2014	retrospective cohort	LGIB	56	51.8%	in-hospital rebleeding need for surgery length of hospitalization	HR: 3.80 (CI: 1.06–13.70) HR: 13.5 (CI: 3.2–56.5) HR: 1.1 (CI: 1.05–1.2)
Ardevol et al. (40)	2017	prospective cohort	UGIB	790	27.3%	6-week mortality	OR: 2.82 (CI: 1.94–4.09)
Bornman et al. (41)	1985	prospective cohort	PUB	177	14.5%	in-hospital rebleeding	OR: 14.67 (CI: 5.21–41.25)
Branicki et al. (42)	1992	prospective cohort	PUB	842	17.5%	in-hospital mortality in-hospital rebleeding	OR: 1.96 (CI: 0.92–4.17) OR: 1.60 (CI: 1.01–2.52)
Bratanic et al. (43)	2013	retrospective cohort	PUB	251	1.2%	in-hospital mortality in-hospital rebleeding	OR: 29.00 (CI: 2.49–337.18) OR: 13.50 (CI: 1.19–153.19)
Brullet et al. (44)	1996	prospective cohort	PUB	106	23.6%	in-hospital mortality	OR: 3.34 (CI: 1.00–11.10)
Budimir et al. (45)	2017	prospective cohort	PUB	796	9.7%	30-day mortality in-hospital rebleeding	OR: 5.56 (CI: 2.75–11.24) OR: 12.81 (CI: 7.28–22.53)
Bunchorntavakul et al. (46)	2017	retrospective cohort	NVUGIB VUGIB	180 106	8.3% 16%	30-day rebleeding	OR: 10.65 (CI: 3.57–31.78) OR: 1.99 (CI: 0.37–10.65)
Chaabane et al. (47)	2011	retrospective cohort	UGIB	401	9.5%	in-hospital mortality	OR: 19.70 (CI: 6.43–60.32)
Chandnani et al. (48)	2019	prospective cohort	UGIB	300	35.3%	30-day rebleeding	OR: 2.54 (CI: 1.37–4.71)
Charatcharoenwitthaya et al. (49)	2011	retrospective cohort	UGIB	526	59.5%	30-day mortality	HR: 2.57 (CI: 1.05–7.76)
Cheng et al. (50)	2014	retrospective cohort	PUB	785	12.9%	in-hospital mortality	OR: 5.66 (CI: 2.86–11.21)
Chirapongsathorn et al. (51)	2021	retrospective cohort	VUGIB	713	72.5%	5-day mortality 6-week mortality 5-day rebleeding 6-week rebleeding	HR: 12.25 (CI: 7.09–21.16) HR: 12.91 (CI: 7.95–20.97) HR: 2.32 (CI: 1.30–4.15) HR:2.14 (CI: 1.27–3.64)
Chiu et al. (52)	2009	prospective cohort	PUB	3220	20%	in-hospital mortality	OR: 2.85 (CI: 2.15–3.77)
Clason et al. (53)	1986	prospective cohort	UGIB	326	18%	in-hospital mortality	OR: 9.33 (CI. 4.49–19.37)
Danne et al. (54)	1984	retrospective cohort	UGIB	153	22.9%	need for surgery	OR: 3.23 (CI: 1.27–8.21)
Del Piano et al. (55)	2013	prospective cohort	NVUGIB	1413	9.3%	in-hospital mortality	OR: 2.89 (CI: 0.93–8.94)
Djuranovic et al. (56)	2007	prospective cohort	NVUGIB	315	21.6%	in-hospital mortality in-hospital rebleeding	OR: 18.69 (CI: 3.93–88.78) OR: 2.43 (CI: 1.28–4.61)
Elloumi et al. (58)	2003	retrospective cohort	PUB	208	6.7%	in-hospital rebleeding	OR: 3.91 (CI: 1.11–13.75)

El Mekkaoui et al. (57)	2011	ambidirectional cohort	UGIB	1303	2%	in-hospital mortality	OR: 5.60 (CI: 2.29–13.72)
Elsebaey et al. (59)	2018	prospective cohort	UGIB	286	56.6%	in-hospital mortality	OR: 4.47 (CI: 1.49–13.38)
Fujino et al. (60)	2013	retrospective cohort	LGIB	90	41.1%	30-day rebleeding	OR: 5.56 (CI: 2.00–15.57)
Gado et al. (62)	2014	cross-sectional	PUB	62	48.4%	2-week mortality	OR: 1.67 (CI: 0.26–10.74)
Gado et al. (61)	2014	cross-sectional	VUGIB	224	17.4%	2-week mortality	OR: 4.08 (CI: 1.52–10.96)
Hassanien et al. (63)	2018	retrospective cohort	VUGIB	725	28.7%	in-hospital mortality	OR: 7.69 (CI: 5.29–11.17)
Hunt et al. (64)	1983	prospective cohort	PUB	633	29.1%	in-hospital mortality	OR: 14.96 (CI: 6.12–36.55)
Hwang et al. (65)	2016	prospective cohort	NVUGIB	1584	9.8%	30-day mortality	OR: 2.75 (CI: 1.42–5.34)
Ishikawa et al. (66)	1995	retrospective cohort	PUB	75	56%	in-hospital mortality	OR: 11.93 (CI: 0.65–219.99)
Katschinski et al. (67)	1994	prospective cohort	UGIB	2217	NA	in-hospital mortality in-hospital rebleeding	OR: 4.40 (CI: 3.06–6.33) OR: 4.60 (CI: 3.90–5.43)
Kim et al. (69)	2005	retrospective cohort	M-W syndrome	159	22.6%	30-day rebleeding	OR: 6.37 (CI: 2.22–18.31)
Kim et al. (68)	2021	retrospective cohort	VUGIB	1373	6.3%	6-week mortality	HR: 4.43 (CI: 3.19–7.60)
Kitagawa et al. (70)	2019	retrospective cohort	LGIB	144	9%	90-day rebleeding	OR: 6.20 (CI: 1.75–21.97)
Koch et al. (71)	2013	retrospective cohort	UGIB	463	NA	in-hospital mortality	OR: 4.26 (CI: 1.11–16.3)
Lakatos et al. (72)	2021	prospective cohort	NVUGIB	688	NA	in-hospital mortality in-hospital rebleeding need for transfusion	OR: 1.80 (CI: 1.11–2.92) OR: 2.15 (CI: 1.33–3.47)
Lanas et al. (73)	2013	retrospective cohort	PUB	539	6.7%	30-day mortality	OR: 4.36 (CI: 0.02–6.09)
Laursen et al. (74)	2017	prospective cohort	PUB	12601 6643	23.3% 22.7%	in-hospital mortality in-hospital rebleeding 30-day mortality	OR: 3.60 (CI: 3.09–4.18) OR: 2.12 (CI: 1.91–2.36) OR: 2.95 (CI: 2.48–3.51)
Lausevic et al. (75)	2007	case-control	PUB	80	30%	in-hospital rebleeding	OR: 52.76 (CI: 6.58–423.02)
Lee et al. (76)	1992	retrospective cohort	VUGIB	101	56.7%	in-hospital mortality	OR: 2.28 (CI: 1.01–5.16)
Liang et al. (77)	2012	retrospective case-control	PUB	413	52.8%	30-day rebleeding	OR: 1.42 (CI: 0.88–2.28)
Lohse et al. (78)	2015	prospective cohort	PUB	3580	25.7%	90-day mortality	OR: 2.03 (CI: 1.69–2.43)
Mäkelä et al. (79)	1996	RCT	PUB	78	19.2%	30-day mortality	OR: 11.09 (CI:1.80–68.10)
Marmo et al. (80)	2014	prospective cohort	NVUGIB	2317	7%	30-day mortality	OR: 5.52 (CI: 3.47–8.79)
Minakari et al. (81)	2017	retrospective cross-sectional	UGIB	4747	39.8%	in-hospital mortality in-hospital rebleeding	OR: 39.84 (CI: 21.71–73.09) OR: 3.50 (CI: 2.98–4.10)

Mungan et al. (82)	2012	retrospective cohort	NVUGIB	423	NA	30-day mortality 30-day rebleeding	OR: 7.28 (CI: 1.81–29.24) OR: 3.49 (CI: 1.13–10.80)
Nagata et al. (83)	2017	retrospective cohort	GIB	157	20.4%	90-day rebleeding	OR: 2.90 (CI: 1.10–7.70)
Nahon et al. (84)	2012	prospective cohort	UGIB	3298	7.7%	in-hospital mortality in-hospital rebleeding	OR: 4.24 (CI: 3.07–5.85)
Nykänen et al. (85)	2018	retrospective cohort	LGIB	NA	NA	30-day rebleeding	OR: 0.59 (CI: 0.17–2.06)
Ogasawara et al. (86)	2014	retrospective cohort	PUB	428	10.3%	in-hospital mortality	OR: 13.98 (CI: 2.27–86.08)
Parreira et al. (87)	2002	retrospective cohort	PUB	200	13.5%	need for surgery	OR: 3.86 (CI: 1.47–10.15)
Radaelli et al. (88)	2021	prospective cohort	LGIB	1198	9.2%	in-hospital mortality in-hospital rebleeding	OR: 5.07 (CI: 2.54–10.11) OR: 1.85 (CI: 1.01–3.42)
Restellini et al. (89)	2012	retrospective cohort	NVUGIB	1677	31.9%	in-hospital rebleeding need for transfusion	OR: 1.10 (CI: 0.80–1.50) OR: 3.42 (CI: 2.73–4.28)
Rios et al. (90)	2007	retrospective cohort	LGIB	171	17%	need for surgery	OR: 4.81 (CI: 1.87–12.37)
Schmulewitz et al. (91)	2003	retrospective cohort	LGIB	565	68.3%	length of hospitalization	HR: 0.80 (CI: 0.70–1.00)
Sereda et al. (92)	1977	retrospective cohort	UGIB	513	24.2%	in-hospital mortality	OR: 8.93 (CI: 4.57–17.46)
Shih et al. (93)	2018	retrospective cohort	UGIB	202	22.3%	in-hospital mortality	OR: 7.60 (CI: 2.40–24.05)
Sombié et al. (94)	2015	prospective cohort	UGIB	265	33.6%	30-day mortality	OR: 4.80 (CI: 1.90–11.70)
Stupin et al. (95)	2013	retrospective cohort	PUB	895	28.4%	30-day mortality	OR: 6.80 (CI: 4.87–9.49)
Thomopoulos et al. (97)	2004	retrospective cohort	PUB	191	16.8%	need for surgery	OR: 3.85 (CI: 1.68–8.81)
Thomopoulos et al. (96)	2006	retrospective cohort	VUGIB	141	18.4%	6-week mortality 1-year mortality	OR: 6.18 (CI: 2.39–16.03) OR: 1.70 (CI: 0.70–4.06)
Tsoi et al. (98)	2002	prospective cohort	PUB	8222	8.7%	30-day mortality	OR: 3.62 (CI: 2.77–4.70)
Vuachet et al. (99)	2015	retrospective cohort	VUGIB	121 112	11.6% 10.7%	6-week mortality 6-month mortality 6-month rebleeding	OR: 4.60 (CI: 1.40–15.13) OR: 3.42 (CI: 1.09–10.70) OR: 3. 76 (CI: 1.09–12.86)
Wierchowski et al. (100)	2013	ambidirectional cohort	NVUGIB	482	19.3%	in-hospital mortality in-hospital rebleeding	OR: 11.50 (CI: 5.43–24.36) OR: 3.30 (CI: 1.91–5.72)

LGIB: lower gastrointestinal bleeding; UGIB: upper gastrointestinal bleeding; PUB: peptic ulcer bleeding; NVUGIB: non-variceal upper gastrointestinal bleeding; VUGIB: variceal upper gastrointestinal bleeding; M-W: Mallory-Weiss; NA: not available; HR: hazard ratio; OR: odds ratio

8.2.3. Mortality

8.2.3.1. In-hospital mortality

A total of 27 studies assessed the association between HI and in-hospital mortality in UGIB (42-44, 47, 50-53, 55-57, 59, 63, 64, 66, 67, 71, 72, 76, 81, 84, 86, 88, 92, 93, 100, 102), of which 22 provided sufficient data to be included in the meta-analysis (42-44, 47, 50, 52, 53, 56, 57, 59, 63, 64, 66, 67, 72, 76, 84, 86, 92, 93, 100, 102). The pooled results demonstrated a significantly increased odds of in-hospital mortality among patients presenting with HI (OR: 5.48; CI: 3.99–7.52; I^2 = 74%) (see Figure 11). Subgroup analyses were conducted for overall UGIB, non-variceal UGIB (NVUGIB), and PUB (peptic ulcer bleeding). In studies including all UGIB cases, the odds of in-hospital mortality were higher (OR: 6.18; CI: 4.11–9.28) compared with studies restricted to PUB patients (OR: 4.79; CI: 2.62–8.97). In the NVUGIB subgroup, the association did not reach statistical significance (OR: 6.52; CI: 0.29–144.21). Influence analysis did not identify any outlying study that would have substantially affected the pooled estimate.

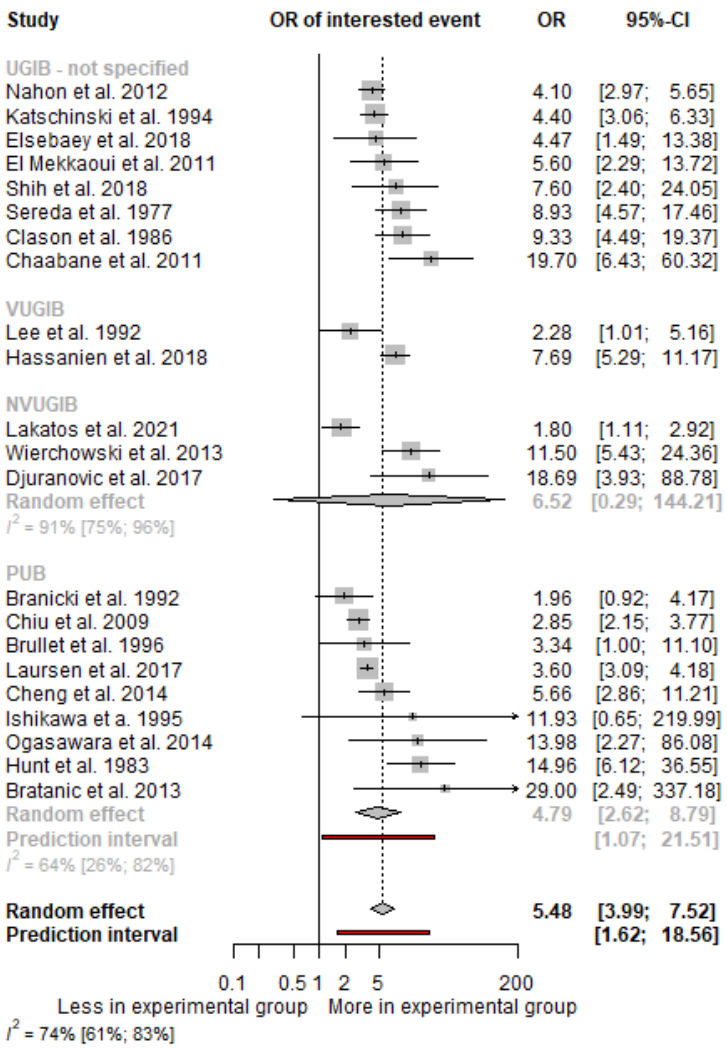


Figure 11. *Forest plot representing the odds of in-hospital mortality in patients with upper gastrointestinal bleeding, demonstrating a substantially higher odds of death in the presence of hemodynamic instability. NVUGIB: non-variceal upper gastrointestinal bleeding; PUB: peptic ulcer bleeding; UGIB: upper gastrointestinal bleeding; VUGIB: variceal upper gastrointestinal bleeding; OR: odds ratio; CI: confidence interval (101).*

In the subgroup of studies defining HI as a systolic blood pressure ≤ 100 mmHg and/or a pulse rate ≥ 100/min, the odds of in-hospital mortality remained significantly increased, although at a lower magnitude (OR: 4.14; CI: 2.47–6.94; $I^2 = 67\%$) (see Figure 12).

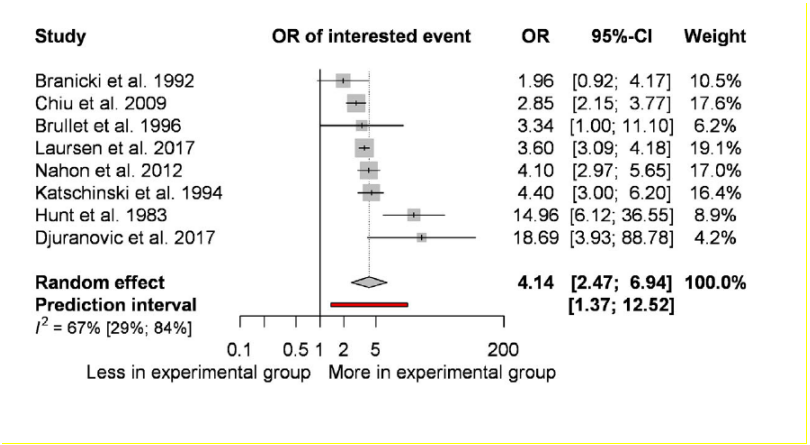


Figure 12. *Forest plot representing the odds of in-hospital mortality in upper gastrointestinal bleeding in studies defining hemodynamic instability as a systolic blood pressure ≤ 100 mmHg and/or a pulse rate ≥ 100/min, demonstrating a significantly increased odds of death in the presence of hemodynamic instability. OR: odds ratio; CI: confidence interval (101).*

In addition to the studies included in the meta-analysis, four cohort studies and one cross-sectional study — which could not be pooled quantitatively — likewise reported higher odds of in-hospital mortality among UGIB patients presenting with HI (51, 55, 71, 81, 88).

Furthermore, one study that examined a mixed cohort of patients with UGIB and LGIB, also demonstrated increased odds of in-hospital mortality in hemodynamically unstable patients (OR: 5.07; CI: 2.54–10.11) (83).

8.2.3.2. Follow-up mortality

A total of 19 studies evaluated follow-up mortality, all involving patients with UGIB (40, 45, 49, 51, 61, 62, 65, 68, 73, 74, 78-80, 82, 94-96, 98, 99). Of these, 16 reported outcomes at 30–42 days (40, 45, 49, 51, 65, 69, 73, 74, 79, 80, 82, 94-96, 98, 99), and 10 provided sufficient data to be included in the meta-analysis (40, 45, 65, 74, 80, 82, 95, 96, 98, 99). The pooled analysis demonstrated increased odds of mortality during the follow-up period (OR: 4.15; CI: 3.18–5.42; I^2 = 68%) (see Figure 13). Influence analysis did not identify any outlying study that would have substantially altered the pooled estimate.

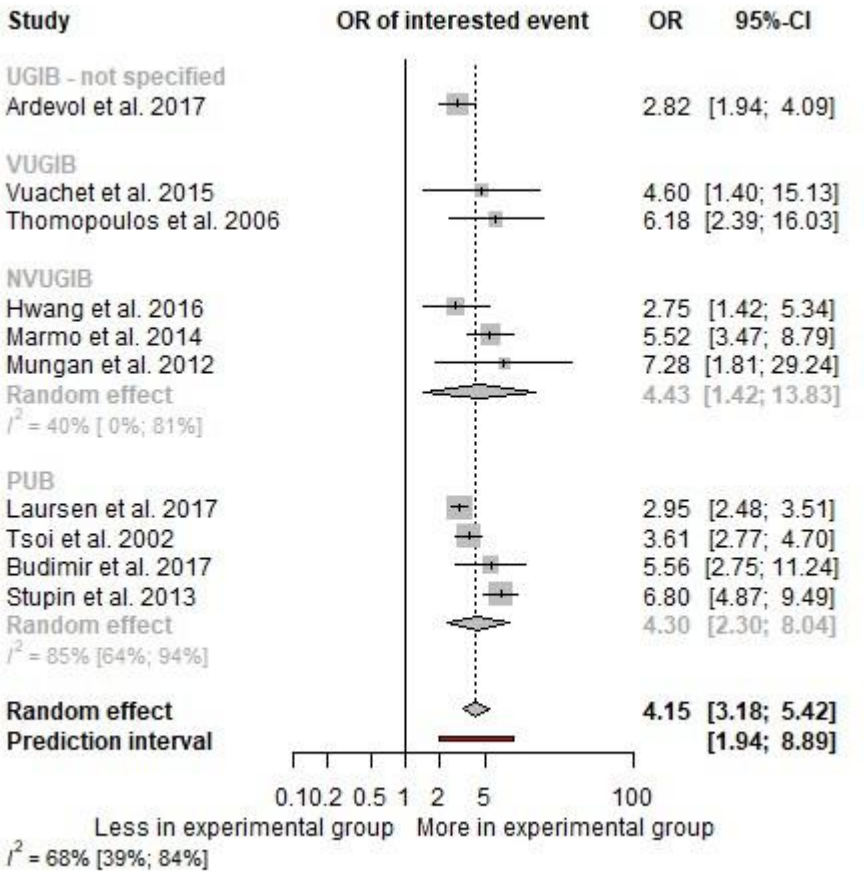


Figure 13. *Forest plot illustrating the odds of 30–42-day mortality in upper gastrointestinal bleeding, demonstrating a significantly increased odds of death during the follow-up period among patients presenting with hemodynamic instability. NVUGIB: non-variceal upper gastrointestinal bleeding; PUB: peptic ulcer bleeding; UGIB: upper gastrointestinal bleeding; VUGIB: variceal upper gastrointestinal bleeding; OR: odds ratio; CI: confidence interval (101).*

In the subgroup of studies defining HI as a systolic blood pressure ≤ 100 mmHg and/or a pulse rate ≥ 100/min, the association with 30–42-day mortality remained statistically significant (OR: 4.03; CI: 2.68–6.05; $I^2 = 58\%$) (see Figure 14).

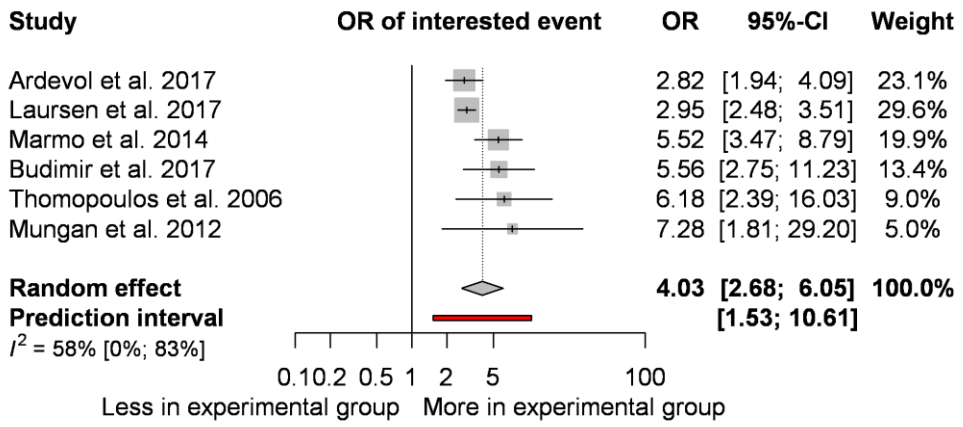


Figure 14. *Forest plot illustrating the odds of 30–42-day mortality in upper gastrointestinal bleeding among studies that defined hemodynamic instability as a systolic blood pressure ≤ 100 mmHg and/or a pulse rate ≥ 100/min, demonstrating an increased odds of mortality in patients presenting with hemodynamic instability. OR: odds ratio; CI: confidence interval (101).*

In addition, six further eligible studies — five cohort studies and one randomized controlled trial — also reported increased mortality among patients with HI (49, 51, 68, 73, 79, 94).

Two studies assessed 2-week mortality, one in PUB and one in variceal UGIB (VUGIB). In the VUGIB population, HI was associated with a higher odds of 2-week mortality (OR: 4.08; CI: 1.52–10.96), whereas in PUB the association did not reach statistical significance (OR: 1.67; CI: 0.26–10.74) (61, 62).

Furthermore, Lohse et al. reported an increased odds of 90-day mortality in PUB patients with HI (OR: 2.03; CI: 1.69–2.43) (78).

8.2.4. Rebleeding

8.2.4.1. In-hospital rebleeding

In total, 17 studies investigated the association between in-hospital rebleeding and HI, of which 15 focused on UGIB and 2 on LGIB (39, 41-43, 45, 51, 56, 58, 67, 72, 74, 75, 81, 84, 88, 89, 100). Among the studies with UGIB as the bleeding source, 11 were included

in the meta-analysis (41-43, 45, 56, 58, 67, 72, 74, 84, 100). Our findings demonstrated higher odds of in-hospital rebleeding in the presence of HI in UGIB (OR 3.68; CI 2.24–6.50; I^2 = 91%) (see Figure 15). Subgroup analyses were conducted for NVUGIB and PUB, showing that the odds were higher in PUB patients compared with those with NVUGIB (OR 4.95; CI 1.70–14.44 vs. OR 2.55; CI 1.44–4.50). The influence analysis identified the study by Budimir et al. as an outlier; however, no clinical explanation could be determined for this finding (45).

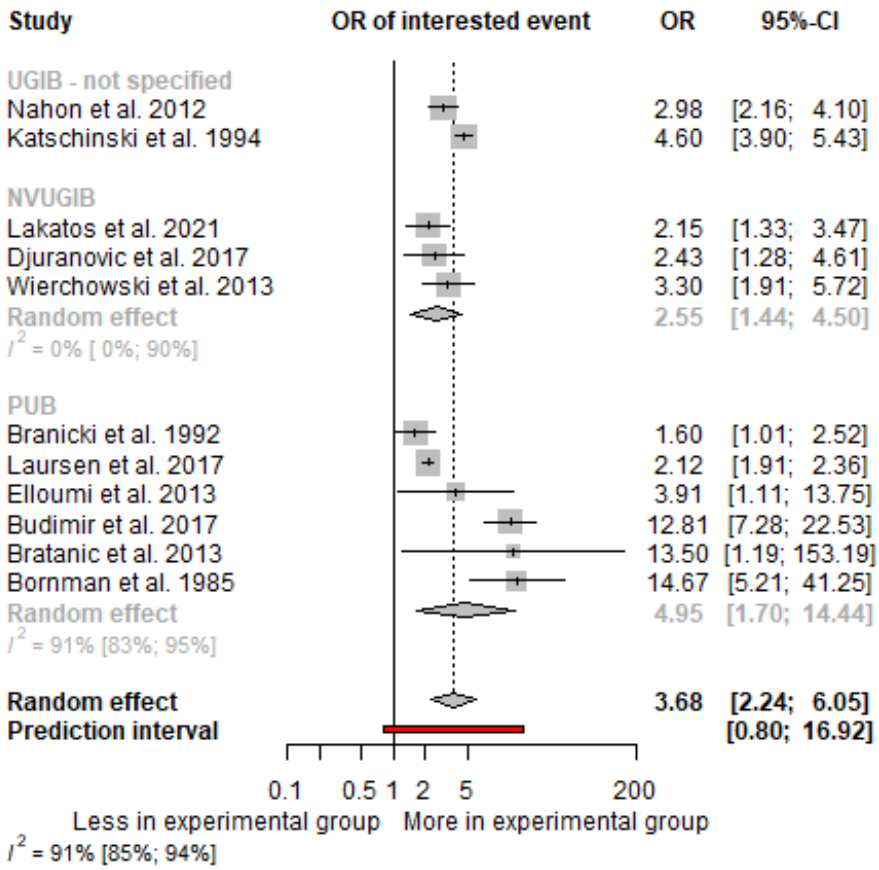


Figure 15. *Forest plot representing the odds of in-hospital rebleeding in patients with UGIB, demonstrating an increased odds of rebleeding in the presence of hemodynamic instability. Subgroup analyses indicated higher odds among patients with PUB compared with those with NVUGIB. NVUGIB: non-variceal upper gastrointestinal bleeding; PUB: peptic ulcer bleeding; UGIB: upper gastrointestinal bleeding; VUGIB: variceal upper gastrointestinal bleeding; OR: odds ratio; CI: confidence interval (101).*

In the subgroup of studies defining HI as a systolic blood pressure ≤100 mmHg and/or a pulse rate ≥100/min, significantly increased, although comparatively lower, odds of in-hospital rebleeding were observed in unstable patients (OR 3.92; CI 1.80–8.55; $I^2 = 94\%$) (see Figure 16).

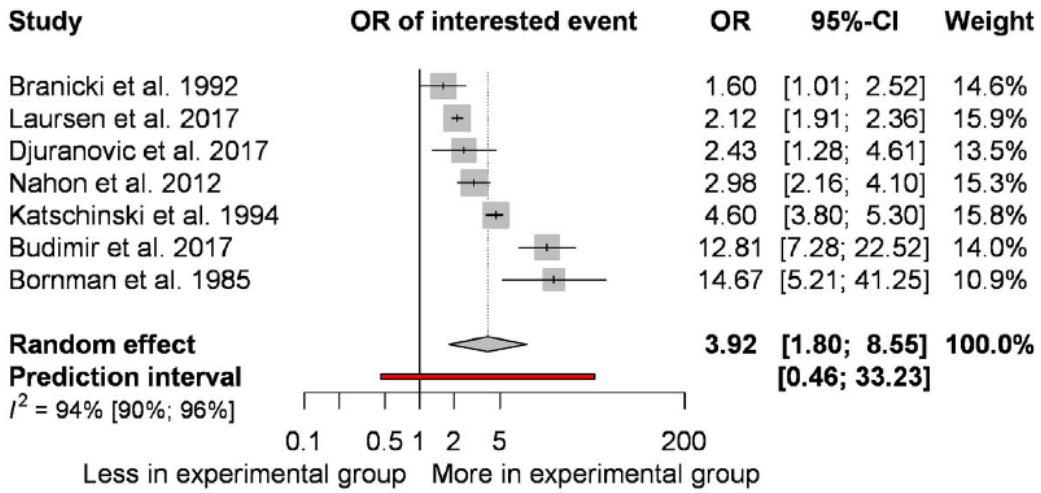


Figure 16. *Forest plot representing the odds of in-hospital rebleeding in patients with upper gastrointestinal bleeding in studies defining hemodynamic instability as a systolic blood pressure ≤100 mmHg and/or a pulse rate ≥100/min, showing significantly increased odds of rebleeding in hemodynamically unstable patients. OR: odds ratio; CI: confidence interval (101).*

In addition, four studies that were not included in the meta-analysis also reported higher odds of in-hospital rebleeding (51, 75, 81, 89). Two further studies examining hemodynamically unstable patients with LGIB likewise demonstrated increased rebleeding risk (HR 3.78; CI 1.06–13.7; OR 1.85; CI 1.01–3.42) (39, 88).

8.2.4.2. Follow-up rebleeding

Eight studies evaluated the association between HI and 30-42-day rebleeding, seven in patients with UGIB and one in LGIB (46, 48, 51, 60, 69, 77, 82, 85). Four UGIB studies were eligible for inclusion in the meta-analysis, resulting in an odds ratio of 4.12 (CI 1.83–9.31; $I^2 = 39\%$) (see Figure 17). Due to the limited number of studies, the leave-one-out sensitivity analysis had restricted interpretability.

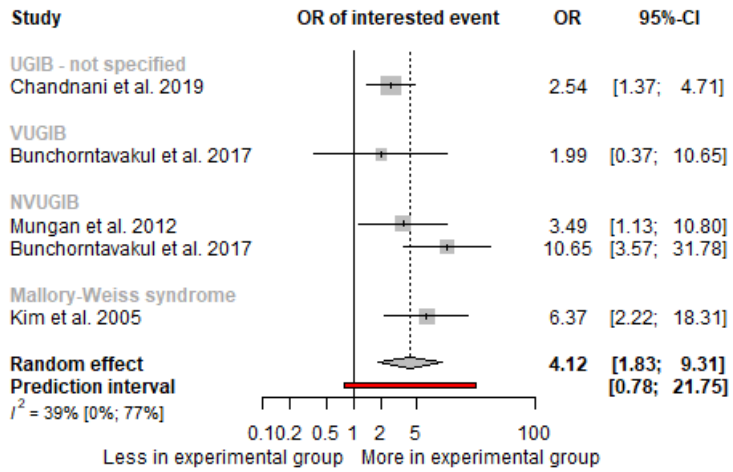


Figure 17. *Forest plot representing the odds of 30–42-day rebleeding in patients with upper gastrointestinal bleeding, showing increased odds in the presence of hemodynamic instability. VUGIB: variceal upper gastrointestinal bleeding; UGIB: upper gastrointestinal bleeding; NVUGIB: non-variceal upper gastrointestinal bleeding; OR: odds ratio; CI: confidence interval (101).*

In the subgroup of studies defining HI as a systolic blood pressure ≤100 mmHg and/or a pulse rate ≥100/min, comparable estimates were obtained (OR 5.44; CI 2.38–12.43; I^2 = 0%) (see Figure 18).

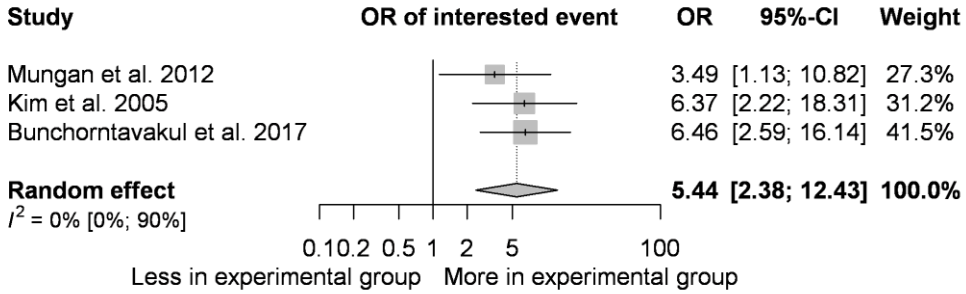


Figure 18. *Forest plot representing the odds of 30–42-day rebleeding in patients with upper gastrointestinal bleeding in studies defining hemodynamic instability as a systolic blood pressure ≤100 mmHg and/or a pulse rate ≥100/min, showing increased odds of rebleeding in hemodynamically unstable patients. OR: odds ratio; CI: confidence interval (101).*

The remaining four studies — three conducted in UGIB and one in LGIB — also demonstrated increased odds of 30- to 42-day rebleeding in case of HI (51, 60, 77, 85). Furthermore, two studies assessing 90-day rebleeding, one in LGIB and one in general GIB, similarly reported a higher odds of rebleeding among hemodynamically unstable patients (OR 6.20; CI 1.75–21.97; OR 2.90; CI 1.10–7.70) (70, 83).

8.2.5. Need for surgery

Five studies evaluated the requirement for surgical intervention in the context of HI. Among patients with UGIB, hemodynamic compromise was associated with an increased need to undergo surgery (OR 3.65; CI 2.17–6.14) (see Fig. 19) (54, 87, 97).

For LGIB, the two available studies similarly indicated an increased need for surgery in patients with HI (HR 13.5; CI 3.2–56.5 and OR 4.81; CI 1.87–12.37) (39, 90).

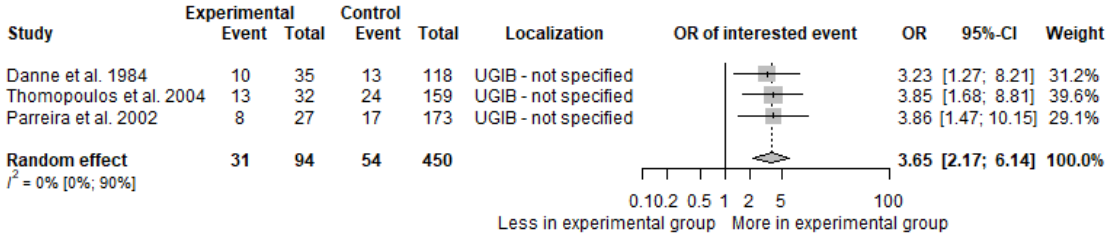


Figure 19. *Forest plot representing the odds of requiring surgery in patients with upper gastrointestinal bleeding, demonstrating a higher likelihood of surgical intervention in the presence of hemodynamic instability (101).*

8.2.6. Need for transfusion

Two studies reported on the need for blood transfusion. In both, the bleeding source was UGIB, and HI was associated with higher odds of requiring transfusion (OR 3.57; CI 2.6–5.0 and OR 3.42; CI 2.73–4.28) (72, 89).

8.2.7. Length of hospitalization

Two studies reporting on the length of hospitalization were identified, both involving patients with LGIB. Abeldawi et al. found that HI was associated with longer hospital stays (HR 1.1; CI 1.05–1.20) (39). In contrast, Schmulewitz et al. observed a tendency

toward shorter hospitalization in hemodynamically unstable patients (HR 0.8; CI 0.7–1.0), although this association did not reach statistical significance (91).

8.2.8. Need for endoscopic rescue therapy

We did not identify any studies that reported the use of endoscopic rescue therapy in hemodynamically unstable patients with GIB.

8.2.9. Risk of bias and publication bias assessment

Among the 27 studies reporting in-hospital mortality, one study (4%) was judged to have a high risk of bias, 13 (48%) a moderate risk, and 13 (48%) a low risk of bias. For follow-up mortality, two of the 19 studies (11%) were rated as high risk, eight (42%) as moderate risk, and nine (47%) as low risk. Of the 17 studies reporting in-hospital rebleeding, seven (42%) were classified as having a moderate risk of bias and ten (58%) as low risk. Regarding rebleeding during follow-up, three of the 11 studies (27%) were assessed as moderate risk, while eight (73%) were considered low risk. For the need for surgery, one of the five studies (20%) was categorized as low risk, whereas four (80%) were considered to have a moderate risk of bias. All four studies reporting on transfusion requirements and length of hospital stay were assessed as having a moderate risk of bias.

9. DISCUSSION

9.1. Summary of Findings, International Comparisons

Acute gastroenterological conditions often require urgent or semi-urgent diagnostic and therapeutic endoscopic interventions, in which procedural complexity and the risk of adverse events are determined by clinical factors and procedure-relevant anatomical characteristics identifiable at presentation. Early recognition of these factors is essential for procedural planning, appropriate allocation of expertise, and the implementation of risk-adapted preventive strategies, ultimately improving patient safety and clinically meaningful outcomes.

In this context, this PhD work synthesizes evidence from two systematic reviews and meta-analyses examining distinct but conceptually related risk factors in acute gastroenterological and endoscopic settings. Although the analyses address different clinical scenarios, both highlight the relevance of early, readily identifiable factors in guiding endoscopic management strategies. Collectively, these findings emphasize the role of risk stratification as an integral component of decision-making in acute gastrointestinal diseases.

The first systematic review and meta-analysis evaluated the role of papilla morphology in ERCP-related outcomes. Based on international data applying the Haraldsson classification, regular (type I) papillae were associated with a significantly lower rate of difficult cannulation, whereas type II papillae demonstrated an approximately twofold increased risk of post-ERCP pancreatitis. In contrast, no significant differences were observed between papilla types with respect to cannulation failure or post-ERCP bleeding. These findings are consistent with and extend results from previous international cohort studies, supporting papilla morphology as a relevant anatomical determinant of ERCP performance and safety.

The international literature has long debated the factors influencing ERCP success and safety, including patient-related characteristics, certain disease etiologies, and procedure-related variables (103). Within this framework, anatomical features of the papilla, including papilla morphology, have gained increasing attention as potential contributors to procedural complexity.

Several studies have explored the interaction between papilla type and endoscopist experience. Among the studies included in this analysis, the impact of endoscopist expertise on cannulation difficulty remains inconsistent. While some cohorts reported no clear association between difficult cannulation rates and operator experience, others observed higher rates of difficult cannulation and procedure-related adverse events in papilla types more frequently managed by less experienced endoscopists (4, 28). These observations are in line with broader evidence indicating that increasing endoscopist experience is associated with improved ERCP performance and safety (104, 105). These data suggest that papilla morphology should be considered both in procedural planning and in the context of endoscopic training.

In addition, international studies have reported differences in the use of rescue cannulation techniques across papilla morphologies. This variability may partly explain the absence of significant differences in cannulation failure rates between papilla types. Morphology-adapted strategies, such as needle-knife fistulotomy or precut sphincterotomy in regular papillae, transpancreatic sphincterotomy in small papillae, and needle-knife techniques in protruding or ridged papillae, have been proposed in the literature, supporting a more individualized approach to advanced biliary cannulation (106, 107).

Several papilla classification systems have been described in the literature; however, the Haraldsson classification remains the most widely used and well-recognized and therefore served as the basis of the present analysis. A key limitation of this classification is the lack of consideration of periampullary diverticulum (PAD). Recent data suggest that PAD may represent a distinct anatomical entity and is associated with an increased risk of cannulation failure and post-ERCP adverse events (28, 108). These observations indicate that classification systems incorporating PAD may allow a more comprehensive assessment of anatomical risk and should be considered in future studies and clinical practice.

The second systematic review and meta-analysis examined haemodynamic instability as a prognostic factor in acute GIB. Across a large international body of evidence, haemodynamic instability at presentation was consistently associated with a substantially increased risk of in-hospital and short-term mortality, rebleeding, and the need for

surgery, with the strongest associations observed in UGIB. These findings quantitatively confirm earlier observations from international cohort studies and further emphasize the prognostic relevance of early haemodynamic compromise in acute bleeding episodes.

In the international literature, haemodynamic instability has been defined heterogeneously, most commonly using systolic blood pressure and heart rate thresholds. Despite this variability, these parameters are universally and rapidly available in emergency settings and require no specialized equipment. The present meta-analysis demonstrates that abnormalities in these simple clinical markers at presentation are sufficient to identify patients at markedly increased risk of adverse outcomes. This observation is consistent with their incorporation into widely used pre-endoscopic risk scores, such as the Rockall and Glasgow–Blatchford scores, supporting their continued clinical relevance in early risk stratification (50, 109).

Importantly, the present findings indicate that haemodynamic parameters assessed at presentation alone are associated with an approximately fourfold increase in the odds of in-hospital mortality and rebleeding in acute GIB. This highlights the central prognostic role of early physiological assessment and supports the concept that haemodynamic instability represents a robust marker of disease severity, largely independent of subsequent therapeutic interventions.

From a clinical perspective, these results underscore the importance of prompt recognition, resuscitation, and stabilization of haemodynamically unstable patients presenting with acute GIB. Adequate early management may reduce the risk of severe adverse outcomes; however, several aspects of initial care remain insufficiently defined. In particular, uncertainty persists regarding the optimal rate and intensity of fluid resuscitation, the role of vasopressor therapy, and the most appropriate choice of resuscitation fluids, as reflected in current guideline recommendations (10).

The prognostic impact of haemodynamic instability also has important implications for the timing of endoscopy. Evidence from international studies indicates worse outcomes, including higher in-hospital mortality, when endoscopy is performed too early in inadequately stabilized patients, particularly in UGIB (102). In this context, current European guidelines emphasize the importance of adequate haemodynamic stabilization prior to endoscopic intervention (10). A plausible explanation is insufficient correction

of haemodynamic derangement before the procedure, potentially exacerbating circulatory compromise during endoscopy.

Overall, the findings of this work demonstrate that readily identifiable anatomical and physiological factors play a central role in risk stratification in acute gastroenterological conditions requiring endoscopic intervention. Papilla morphology represents a relevant anatomical determinant of ERCP complexity and procedure-related adverse events, whereas haemodynamic instability constitutes a strong prognostic marker of adverse outcomes in acute GIB. Recognition of these factors at presentation may support improved procedural planning, appropriate allocation of expertise, and more individualized, risk-adapted patient management in acute endoscopic practice.

9.2. Strengths

Both studies have several important strengths. Each addresses a clinically relevant yet previously underexplored risk factor in acute gastroenterological and endoscopic settings, providing quantitative evidence for its association with clinically meaningful outcomes.

A rigorous and transparent methodology was applied in both analyses. Comprehensive systematic searches were performed across multiple databases, study selection and data extraction were conducted according to predefined criteria, and appropriate meta-analytical methods were used. Between-study heterogeneity and potential sources of bias were systematically assessed, and sensitivity and subgroup analyses were performed where feasible.

In addition, both studies are based on a large body of evidence derived from diverse patient populations, enhancing the robustness and generalizability of the findings across different clinical contexts.

9.3. Limitations

Both studies have limitations that should be considered when interpreting the findings. First, in several analyses substantial between-study heterogeneity was observed. This likely reflects clinical and methodological differences across the included cohorts, such as variations in outcome definitions, procedural classifications and patient populations. Although standardized definitions were applied where feasible, definitions were not

uniform across studies, particularly for haemodynamic instability. This may have contributed to the observed heterogeneity.

Second, a considerable proportion of the included evidence originated from retrospective cohort studies. While these provide valuable real-world data, retrospective designs are inherently more susceptible to confounding, selection bias and incomplete reporting.

Third, for some outcomes the available evidence remained limited, and in certain analyses the risk of bias was moderate or high. Therefore, the results should be interpreted with appropriate caution.

Finally, variability in reporting and data granularity constrained the scope of some subgroup and sensitivity analyses.

Taken together, these limitations underline the need for prospective studies with more uniform definitions and more complete reporting.

10. CONCLUSIONS

10.1. Study 1

In conclusion, the morphology of the major papilla is associated with ERCP outcomes and procedure-related adverse events. Difficult cannulation occurred less frequently in type I papillae (26%) compared with other papilla types, whereas PEP was significantly more frequent in type II papillae (11%). In studies using the Haraldsson classification, no significant difference in cannulation failure rates was observed between papilla types.

10.2. Study 2

In conclusion, HI is strongly associated with worse clinical outcomes in patients with acute GIB. Hemodynamically compromised patients had increased odds of in-hospital mortality, with an approximately fivefold higher risk (OR 5.48; CI 3.99–7.52). In addition, HI was associated with higher odds of in-hospital rebleeding (OR 3.68; CI 2.24–6.50) and a higher need for surgical intervention in UGIB (OR 3.65; CI 2.84–4.68).

11. IMPLICATIONS FOR PRACTICE

11.1. Study 1

Based on our results, papilla morphology should be routinely assessed and documented prior to or at the start of ERCP. During the training of fellow endoscopists, procedures should initially be performed in patients with type I papillae, which are associated with the lowest rate of difficult cannulation.

In contrast, type II papillae, which are associated with the highest rates of PEP, should preferably be managed by more experienced endoscopists. Given the increased risk of PEP in this papilla type, these cases require particular caution, including careful cannulation strategies, strict adherence to prophylactic measures, and enhanced post-procedural monitoring, as well as thorough patient education regarding procedure-related adverse events.

Furthermore, the use of a unified and validated classification system for papilla morphology is recommended to improve transparency, communication, and reproducibility in both clinical practice and training.

11.2. Study 2

Based on our results, patients presenting with HI should be identified early and managed as a high-risk population. In particular in UGIB, hemodynamically compromised patients require prompt assessment, early resuscitation, and close monitoring in an emergency or high-dependency setting.

The integration of a unified and clearly defined definition of HI or shock into routine clinical practice may improve early risk stratification and facilitate timely decision-making.

Given the markedly increased risks of in-hospital mortality, rebleeding, and the need for surgical intervention, early and aggressive stabilization, multidisciplinary involvement, and appropriate triage to higher levels of care are essential to improve clinical outcomes.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

12.1.1. Study 1

Large, well-characterized cohorts are needed to further validate the modified papilla morphology classification, including the assessment of PAD involvement. Beyond overall event rates, future studies should also evaluate the severity of PEP across different papilla types to better capture clinically relevant outcomes.

12.1.2. Study 2

High-quality RCTs are needed to define optimal early resuscitation strategies in hemodynamically unstable patients with acute GIB. In addition, future interventional studies should examine the interaction between resuscitation intensity and the timing of endoscopy to better delineate safe and effective early management strategies.

12.2. New Areas

12.2.1. Study 1

Future research should consider the development of morphology-based recommendation systems for advanced biliary cannulation techniques to support procedural planning and technique selection. Beyond procedural guidance, the role of papilla morphology as a component of integrated ERCP risk stratification frameworks deserves further investigation.

12.2.2. Study 2

Further prospective cohort studies should investigate modifiable factors contributing to the development of initial HI, including comorbidities, medication use, and delays in early care. Moreover, research focusing on prehospital and emergency department triage parameters may improve early identification of high-risk patients and enable more timely escalation of care.

13. IMPLICATIONS FOR POLICY MAKERS

13.1. Study 1

From a policy perspective, our findings underline the importance of structured education, standardization, and data-driven quality improvement in ERCP practice. Given the impact of papilla morphology on procedural difficulty and adverse events, dedicated training programs should be supported, with particular emphasis on hands-on simulation and cadaver-based courses that allow trainees to safely practice fundamental cannulation techniques before performing high-risk procedures in clinical settings.

Furthermore, structured supervision frameworks and competency-based progression in ERCP training may contribute to improved patient safety and more consistent procedural outcomes.

In parallel, the development and dissemination of standardized patient education materials addressing potential ERCP-related adverse events, including post-ERCP pancreatitis, should be encouraged to improve informed consent and patient awareness.

At a system level, the implementation of uniform endoscopic reporting standards, including mandatory documentation of papilla morphology using a validated classification system, may enhance transparency and comparability across centers. The establishment or further development of national endoscopy registries with standardized data collection could facilitate continuous quality monitoring, benchmarking, and research.

13.2. Study 2

At a health system level, our findings support the implementation of standardized, pathway-based emergency management for acute GIB with HI. Because HI at presentation — particularly in UGIB — identifies a subgroup with markedly increased odds of mortality, rebleeding, and the need for surgery, patients meeting HI criteria should be triaged as high priority and managed within dedicated resuscitation pathways. A unified, operational definition of HI and shock should be embedded into routine clinical practice and reporting to enable consistent risk stratification and timely escalation of care.

In addition, system-level protocols should prioritize early recognition, prompt resuscitation, and stabilization before proceeding to definitive endoscopic therapy. Finally, standardized monitoring and post-acute care pathways, combined with registry-based quality indicators (e.g., time to stabilization and outcomes among patients with HI), may facilitate benchmarking and continuous quality improvement across centers.

14. FUTURE PERSPECTIVES

Acute gastrointestinal conditions represent some of the most time-critical and complex scenarios in gastroenterology, where early decision-making and procedural performance have a direct impact on patient outcomes. As an interventional endoscopist in training, my long-term goal is to contribute to the optimization of acute gastrointestinal care, with particular emphasis on the early phase of patient assessment and intervention.

The findings of this thesis highlight two complementary pillars of high-quality acute care: precise risk stratification at presentation and technically informed endoscopic management. In patients undergoing ERCP, systematic assessment of major papilla morphology at the start of the procedure may support safer cannulation strategies, improve training pathways, and reduce procedure-related adverse events. In parallel, early recognition of HI in acute GIB is crucial for identifying high-risk patients who require prompt resuscitation, intensified monitoring, and appropriately timed endoscopic intervention.

Building on these results, I aim to support the integration of these principles into routine clinical practice through targeted education, improved standardization, and collaborative, data-driven approaches. This includes structured training focusing on anatomical recognition and risk-adapted technique selection, the use of unified definitions and standardized documentation in acute gastrointestinal emergencies, and active participation in prospective registries and multicenter collaborations. Ultimately, these efforts aim to enhance early clinical and endoscopic decision-making, thereby contributing to safer and more consistent acute gastrointestinal care, and supporting the development and implementation of evidence-based care pathways.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

1. **Tari, Edina** ; Gagyi, Endre Botond ; Rancz, Anett ; Veres, Dániel Sándor ; Váncsa, Szilárd ; Hegyi, Péter Jenő ; Hagymási, Krisztina ; Hegyi, Péter ; Erőss, Bálint
Morphology of the papilla can predict procedural safety and efficacy of ERCP-a systematic review and meta-analysis.
SCIENTIFIC REPORTS (2024)
Publication: 34763940
Journal subject: Scopus - Multidisciplinary Rank: Q1
IF: 3.9

2. **Tari, Edina** ; Frim, Levente ; Stolcz, Tünde ; Teutsch, Brigitta ; Veres, Dániel Sándor ; Hegyi, Péter ; Erőss, Bálint
At admission hemodynamic instability is associated with increased mortality and rebleeding rate in acute gastrointestinal bleeding : a systematic review and meta-analysis
THERAPEUTIC ADVANCES IN GASTROENTEROLOGY (2023)
Publication: 34123722
Journal subject: Scopus - Gastroenterology Rank: Q1
IF: 3.9

16.2. Publications not related to the thesis

3. **Tari, E.** ; Vörhendi, N. ; Kiss, S. ; Teutsch, B. ; Váradi, A. ; Sisák, K. ; Alizadeh, H. ; Hegyi, P. ; Erőss, B.
Anaemia Is Associated with an Increased Risk of Fractures, a Systematic Review, and Meta-Analysis
GERONTOLOGY (2023)
Publication: 32758286
Journal subject: Scopus - Geriatrics and Gerontology Rank: Q2
Journal subject: Scopus - Aging Rank: Q3
IF: 3.1

4. Boros, Eszter ; Pintér, József ; Molontay, Roland ; Prószéky, Kristóf Gergely ; Vörhendi, Nóra ; Simon, Orsolya Anna ; Teutsch, Brigitta ; Pálinkás, Dániel ; Frim, Levente ; **Tari, Edina** et al.
New machine-learning models outperform conventional risk assessment tools in Gastrointestinal bleeding
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Publication: 35785849
Journal subject: Scopus - Multidisciplinary Rank: Q1
IF: 3.9

5. Floria, Diana-Elena ; Fogarasi, Beatrix ; **Tari, Edina** ; Szabó, László ; Sándor Veres, Dániel ; Sára Bognár, Anna ; Sikó, Beáta ; Erőss, Bálint ; Teutsch, Brigitta ; Hegyi, Péter
Psychological interventions improve mental health in inflammatory digestive diseases : a systematic review and meta-analysis of randomized controlled trials
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Publication: 36411906
Journal subject: Scopus - Gastroenterology Rank: Q1
IF: 3.4

6. Gagyi, Endre Botond ; Obeidat, Mahmoud ; **Tari, Edina** ; Váncsa, Szilárd ; Veres, Daniel Sandor ; Banovcin, Peter ; Hegyi, Peter Jeno ; Hegyi, Peter ; Eross, Balint
Progression from acute to chronic pancreatitis in children : a systematic review and meta-analysis
CLINICAL AND EXPERIMENTAL PEDIATRICS (2025)
Publication: 36490540
Journal subject: Scopus - Pediatrics Rank: D1
Journal subject: Scopus - Pediatrics, Perinatology and Child Health Rank: Q1
IF: 3.6

7. Teutsch, B. ; Tóth, Z.A. ; Ferencz, O. ; Vörhendi, N. ; Simon, O.A. ; Boros, E. ; Pálinkás, D. ; Frim, L. ; **Tari, E**. ; Kalló, P. et al.

Hemoglobin decrease predicts untoward outcomes better than severity of anemia

SCIENTIFIC REPORTS (2024)

Publication: 35663428

Journal subject: Scopus - Multidisciplinary Rank: Q1

IF: 3.9

8. Obeidat, Mahmoud ; Teutsch, Brigitta ; Rancz, Anett ; **Tari, Edina** ; Márta, Katalin ; Veres, Dániel Sándor ; Hosszúfalusi, Nóra ; Mihály, Emese ; Hegyi, Péter ; Erőss, Bálint

One in four patients with gastrointestinal bleeding develops shock or hemodynamic instability : A systematic review and meta-analysis

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Morphology of the papilla can predict procedural safety and efficacy of ERCP—a systematic review and meta-analysis

Edina Tari[1,2], Endre Botond Gagyi[1,3], Anett Rancz[1], Dániel Sándor Veres[1,4], Szilárd Váncsa[1,2,5], Péter Jenő Hegyi[1,2,5], Krisztina Hagymási[1,6], Péter Hegyi[1,2,5] & Bálint Erőss[1,2,5]✉

Endoscopic Retrograde Cholangiopancreatography (ERCP) is the primary therapeutic procedure for pancreaticobiliary disorders, and studies highlighted the impact of papilla anatomy on its efficacy and safety. Our objective was to quantify the influence of papilla morphology on ERCP outcomes. We systematically searched three medical databases in September 2022, focusing on studies detailing the cannulation process or the rate of adverse events in the context of papilla morphology. The Haraldsson classification served as the primary system for papilla morphology, and a pooled event rate with a 95% confidence interval was calculated as the effect size measure. Out of 17 eligible studies, 14 were included in the quantitative synthesis. In studies using the Haraldsson classification, the rate of difficult cannulation was the lowest in type I papilla (26%), while the highest one was observed in the case of type IV papilla (41%). For post-ERCP pancreatitis, the event rate was the highest in type II papilla (11%) and the lowest in type I and III papilla (6–6%). No significant difference was observed in the cannulation failure and post-ERCP bleeding event rates between the papilla types. In conclusion, certain papilla morphologies are associated with a higher rate of difficult cannulation and post-ERCP pancreatitis.

Endoscopic Retrograde Cholangiopancreatography (ERCP) is the most used therapeutic procedure for pancreaticobiliary disorders. However, how to best achieve safe and effective bile duct cannulation is still debated. Despite notable developments in the past decades, the failure rate is still 5–20% in experienced hands[1]. Moreover, the incidence of the procedure's adverse events is high; post-ERCP pancreatitis (PEP) has an incidence rate of 9.7%, with a mortality rate of 0.7%[2].

Endoscopists performing ERCP recognize the differences in the macroscopic appearance of the major papilla. This has led to a conception that certain appearances of the papilla are more challenging to cannulate and, therefore, more prone to adverse events. Despite the essential role of bile duct cannulation in procedural safety and success, research on this topic is still limited.

A Scandinavian research group published the first inter- and intraobserver-validated classification of the major papilla's endoscopic appearance in 2017[3]. In the same year, they also published a multicentric prospective cohort study, indicating that the anatomy of the major papilla affects both the difficulty of the bile duct cannulation and the procedural adverse events[4]. Further, their results suggest that the morphology of the papilla should be considered in the training of fellow endoscopists[4]. Other identified studies support their results[5,6].

Recently, several articles have been published assessing the influence of papilla morphology on ERCP outcomes, with contradicting results. Therefore, we aimed to systematically review and quantify the magnitude of its effect and investigate its importance and relevance in the endoscopic practice.

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Methods

A systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (see Supplementary Table 12) and the recommendations of the Cochrane Handbook[7,8]. The review protocol was registered in advance on PROSPERO with the registration number CRD42022360894.

Systematic search

Three databases: MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched from inception until the 29th of September 2022. We did not apply any filters or restrictions to our search. The main parts of the search query included terms in connection with ERCP and papilla morphology. For the detailed search strategy, see Table S1. Additionally, we systematically searched for relevant articles by reviewing the included articles' bibliographic references and citation lists.

Eligibility criteria

The condition-context-population (CoCoPop) framework was used to identify eligible studies[9]. The conditions were (Co): difficult cannulation, cannulation attempts, cannulation time, cannulation failure, post-ERCP pancreatitis, and other post-ERCP adverse events (bleeding, perforation, infection) in the context of the different papilla morphologies (Co). Studies with adult patients (> 18) undergoing ERCP with a native papilla (Pop) were selected.

Randomized controlled trials, case–control, cross-sectional, and cohort studies were eligible for inclusion. Both full-text articles and conference abstracts with sufficient data were considered eligible. Regarding the definition of difficult cannulation, cannulation failure, and post-ERCP adverse events, the definitions provided in the included studies were used.

Morphology of the papilla

Primarily, for the classification of the morphology of the papilla, as the first validated intra- and interobserver classification, the Haraldsson system was used[4]. They classified the papilla into four types: regular (type 1), small (type 2), protruding or pendulous (type 3), and creased or ridged (type 4)[3].

Secondarily, a comparison between the Haraldsson and the other identified classification systems was attempted with the following method: two endoscopists (PJH, EB) assessed the description of the morphology and the imagery of the studies. They chose the identical papilla types to Haraldsson's. In case of any disagreement, a third reviewer was included in the decision process (ET). After the comparison, additional analyses were conducted.

Study selection and data extraction

After the systematic search, the yielded articles were imported into a reference management program (EndNote X7.4, Clarivate Analytics, Philadelphia, PA, USA) to remove the duplicates automatically and manually. After removing duplicates, two independent authors (ET, EBG) screened the remaining publications first by title and abstract and then by full text. We used Rayyan for the selection process[10]. Cohen's kappa coefficient (κ) was calculated on both levels of selection to measure inter-reviewer reliability[11].

Two investigators extracted data independently (ET, EBG) and manually populated it into a purpose-designed Excel 2016 sheet (Office 365, Microsoft, Redmond, WA, USA). Data were collected on the first author, year of publication, digital object identifier, period of data collection, study location, number of centers, study design, the mean or median age of the patients (with standard deviation or interquartile range), the total number of patients, the number of women, the number of patients with each papilla morphology, and data regarding the primary and secondary outcomes in the context of the different papilla types. For statistical analysis, raw data were extracted into two-by-four tables (condition yes/no; papilla morphologies).

Statistical analysis

The statistical analysis was performed by a biostatistician (DSV) with *R* (R Core Team 2022, v4.2.2)[12]. Forest plots were used to display the results of the meta-analytical calculations. The minimum study number to perform the meta-analytical calculation were three. Event rates with a 95% confidence interval (CI) were used for the effect size measure. As we anticipated considerable between-study heterogeneity, a random-effects model was used to pool effect sizes. For assessing the small study publication bias, funnel plots were used with a visual inspection. Additional sensitivity analyses were conducted using the leave-one-out method, with a minimum study number of four (see additional details in the supplementary material).

See supplementary material for additional details on the statistical analyses.

Risk of bias assessment

Two investigators (ET, EBG) independently assessed the risk of bias for each outcome using the Joanna Briggs Institute Critical Appraisal tool for studies reporting prevalence[13].

Quality of evidence

Certainty of evidence was assessed following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendation[14]. Two independent investigators (ET, EBG) evaluated all criteria for all outcomes. Disagreements were resolved by the senior review author (BE).

Results

Search and selection

The details of the study selection process are summarised in the PRISMA flow chart shown in Fig. 1.

A total of 6,952 studies were identified through database searching. Finally, our narrative synthesis comprised 17 studies[4–6,15–28]. Of those, 14 could be included in the quantitative synthesis[4–6,15–17,19,21–27].

Basic characteristics of included studies

The main characteristics of the included studies are summarised in Table 1. Eligible studies were reported between 2016 and 2022. Of the 17 studies, 15 were cohort studies, eight had prospective (5, 6, 19–22, 26, 27), and seven had retrospective designs. There was also one case–control[24] and one cross-sectional study[19]. 13 of the studies were full-text articles[4–6,15–17,19,21,22,24,26–28], and four of them were conference abstracts[18,21,23,25]. Seven studies used the Haraldsson classification[4–6,19,22,24,25], with seven additional ones using comparable classifications[15–17,21,23,26,27]. Three studies used classification systems that were not comparable to the Haralddson classification. The number of study participants ranged from 72 to 11,090.

Quantitative synthesis

Difficult cannulation

Nine studies were identified regarding the event rate of difficult cannulation[4,15,19–22,24–26], of which eight were included in the quantitative synthesis[4,15,19,21,22,24–26]. In the case of studies using the classification proposed by Haraldsson, in type I papilla, the rate of difficult cannulation was lower (26%; CI 18–37) compared to the other papilla types (type III: 35%; CI 25–48; type II: 39%; CI 28–52; type IV: 41%; CI 28–55). The difference was statistically no significant; however, the p-value referred for a higher tendency for difficult cannulation in certain papilla types (p: 0.075). The heterogeneity was high (total I^2: 89%; CI 48–98). Sensitivity analyses did not reveal outlier studies or relevant changes in the estimate (see Figs. 2 and S1).

A similar but statistically significant result with no outlier study was observed, including all the studies with different classifications (p: 0.019; total I^2: 87%; CI 55–96) (see Figures S2-3).

Cannulation failure

Eight studies detailed the event rate of cannulation failure, all using Haraldsson's or classifications comparable to it[5,6,16,21,23,25,26,28]. In the analysis, including studies only using the Haraldsson classification, no statistically significant difference was observed in the rate of failed cannulation between the different papilla types (p: 0.262, total I^2: 61%; CI 0–97) (see Fig. 3).

In the case of including all eight studies, the difference was statistically significant (p: 0.047, I^2: 64%; CI 0–91). The rate of cannulation failure was the highest in the case of type II papilla (8%, CI 4–14) and the lowest

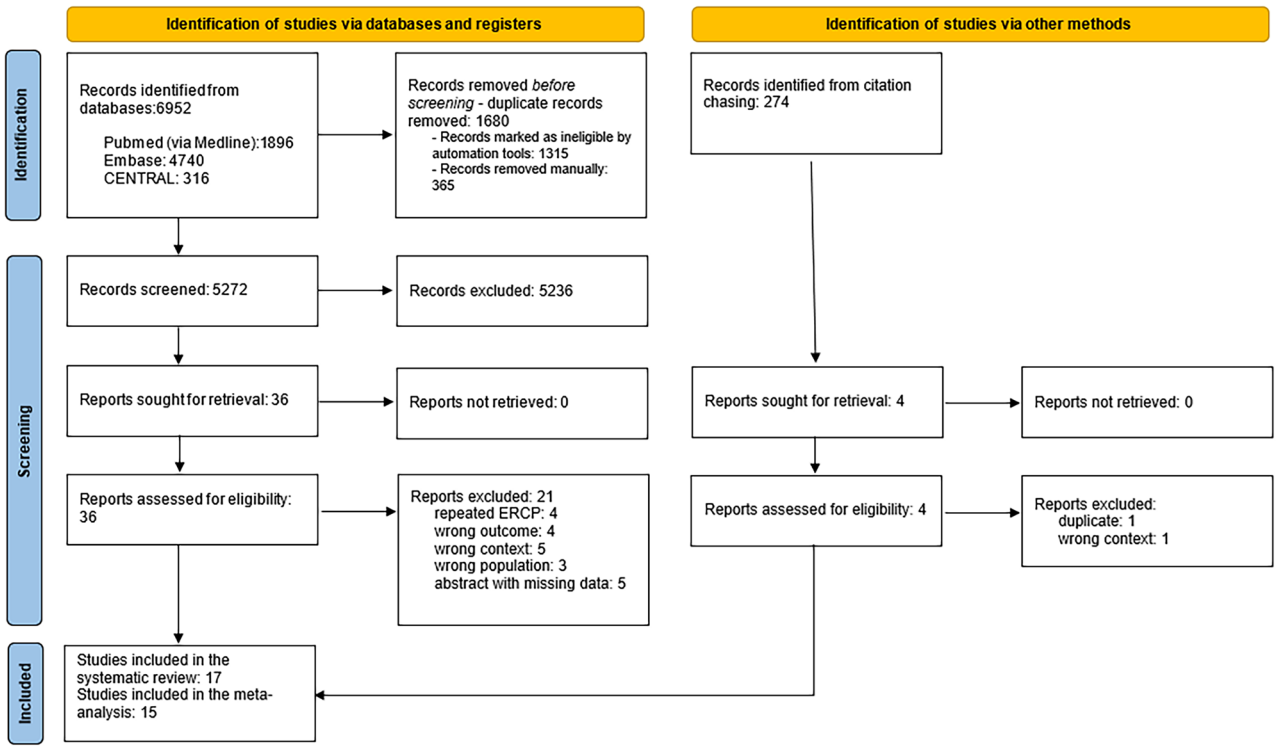

Figure 1. PRISMA 2020 flowchart representing the study selection process.

Author	Year	Country	Centers	Study type	Study period	Age (*:mean; #:median)	Sex (female %)	Number of patients	Classification	Outcomes
Balan et al.[15]	2020	Romania	1	Prospective cohort	January 2018 to August 2018	NA	NA	322	Regular: 52% Canard type I 11%: Canard type II: 19% Canard type III: 10% Canard type IV: 8%	Difficult cannulation Cannulation time Cannulation attempts Post-ERCP pancreatitis Post-ERCP bleeding Post-ERCP infection
Canena et al.[16]	2021	Portugal	3	Prospective cohort	May 2018 to October 2020	*69.6	56.8%	361	Viana type I: 13% Viana type IIa: 35% Viana type IIb: 30% Viana type IIc:10% Viana type IIIa: 4% Viana type IIIb: 4% Viana type IV: 4%	Cannulation failure Cannulation time Post-ERCP pancreatitis Post-ERCP bleeding Post-ERCP perforation
Chen et al.[5]	2020	Taiwan	1	Prospective cohort	October 2017 to October 2018	*64 (SD: 16.5)	47.5%	286	Haraldsson type I: 41% Haraldsson type II: 9% Haraldsson type III: 22% Haraldsson type IV: 28%	Cannulation failure Cannulation time Post-ERCP pancreatitis Post-ERCP bleeding Post-ERCP perforation Post-ERCP cholangitis
Fernandes et al.[18]	2018	Portugal	3	Prospective cohort	August 2017 to January 2018	#79	59.4%	106	Leés type I: 50% Leés type II: 32% Leés type III: 12% Leés type IV: 6%	Cannulation time
Gutierrez- De Aranguren et al.[19]	2021	Peru	1	Retrospective cross-sectional	July 2019 to April 2021	*55 (SD:2 0)	66.5%	188	Haraldsson type I: 32% Haraldsson type II: 25% Haraldsson type III: 27% Haraldsson type IV: 16%	Difficult cannulation
Haraldsson etal.[4]	2019	Nordic countries	9	Prospective cohort	NA	66 (SD: 16)	52%	1377	Haraldsson type I: 56% Haraldsson type II: 13% Haraldsson type III: 23% Haraldsson type IV: 8%	Difficult cannulation Cannulation time Post-ERCP pancreatitis
Liu et al.[20]	2021	China	1	Retrospective cohort	January 2008 to December 2017	NA	NA	11 090	Normal: 44% Thick and long: 11%: Peridiverticular: 27% Intradiverticular: 5% Ectopic: 1% Edematous 10%: Ulcerative: 2%	Difficult cannulation

Continued

Author	Year	Country	Centers	Study type	Study period	Age (*:mean; #:median)	Sex (female %)	Number of patients	Classification	Outcomes
Mohamed et al.[6]	2021	Canada	1	Retrospective cohort	September 2018 to January 2020	NA	51.8%	637	Haraldsson type I: 62% Haraldsson type II: 5% Haraldsson type IIIa: 9% Haraldsson type IIIb: 9% Haraldsson type IV: 3% Type D: 12%	Cannulation failure Cannulation time Cannulation attempts Post-ERCP pancreatitis Post-ERCP bleeding Post-ERCP infection Post-ERCP cholangitis or sepsis
Nakeeb et al.[17]	2016	Egypt	1	Prospective cohort	August 2012 to September 2014	*58.4 (SD: 14.7)	44.4%	996	Normal: 60% Atrophic: 3% Pregnant: 7% Tumor: 7% Redundant: 8% Juxtadivertcular: 8% Small: 6% Long: 1%	Post-ERCP pancreattis
Onilla et al.[21]	2021	Philippines	1	Retrospective cohort	January 2017 to December 2019	NA	NA	347	Regular protrusion: 57% Small protrusion: 31% Large protrusion: 12% Annular pattern: 72% Unstructured pattern: 11% Longitudinal pattern 11%: Isolated pattern: 1% Gyrus pattern: 5%	Difficult cannulation Cannulation failure
Quiroga-Purizaca et al.[22]	2022	Peru	1	Propective cohort	NA	*51.5 (CI 48.8–54.1)	68.4%	138	Haraldsson type I: 59% Haraldsson type II: 8% Haraldsson type III: 29% Haraldsson type IV: 4%	Difficult cannulation Cannulation time Cannulation attempts Post-ERCP pancreatitis Post-ERCP bleeding Post-ERCP perforation
Sadeghi et al.[23]	2019	Iran	1	Prospective cohort	September 2017 to March 2018	*62.3 (SD: 15.5)	51.4%	72	Small: 33%: Bulging: 28% Long: 39%	Cannulation success
Saito et al.[24]	2022	Japan	3	Retrospective case–control	April 2012 to February 2020	*74.9	47.5%	1406	Haraldsson type I: 45% Haraldsson type II: 44% Haraldsson type III: 7% Haraldsson type IV: 4%	Difficult cannulation
Thongsuwan et al.[25]	2021	Thailand	1	Retrospective cohort	January 2013 to May 2017	NA	50.4%	558	Haraldsson type I: 66% Haraldsson type II: 16% Haraldsson type III: 12% Haraldsson type IV: 6%	Difficult cannulation Cannulation failure Post-ERCP pancreatitis, Post-ERCP bleeding Post-ERCP infection

Continued

Author	Year	Country	Centers	Study type	Study period	Age (*:mean; #:median)	Sex (female %)	Number of patients	Classification	Outcomes
Watanabe et al.[26]	2019	Japan	1	Retrospective cohort	September 2013 to June 2017	#70	36%	589	Regular protrusion: 12% Small protrusion: 78% Large protrusion: 10% Annular pattern: 67% Unstructured pattern: 7% Longitudinal pattern: 7% Isolated pattern: 1% Gyrus pattern:16% Unclassified pattern: 2%	Difficult cannulation Cannulation failure Cannulation attempts
Zhang et al.[27]	2016	China	1	Retrospective cohort	February 2012 to March 2015	*75 (SD: 2.2)	42.7%	82	bulging: 44% normal: 22% small: 16% unusual location: 18%	Cannulation failure Cannulation time
Zheng et al.[28]	2020	China	1	Retrospective cohort	January 2016 to December 2019	NA	46.1%	2385	others:18% villous: 74% granular: 8%	Post-ERCP pancreatitis

Table 1. Basic characteristics of included studies.

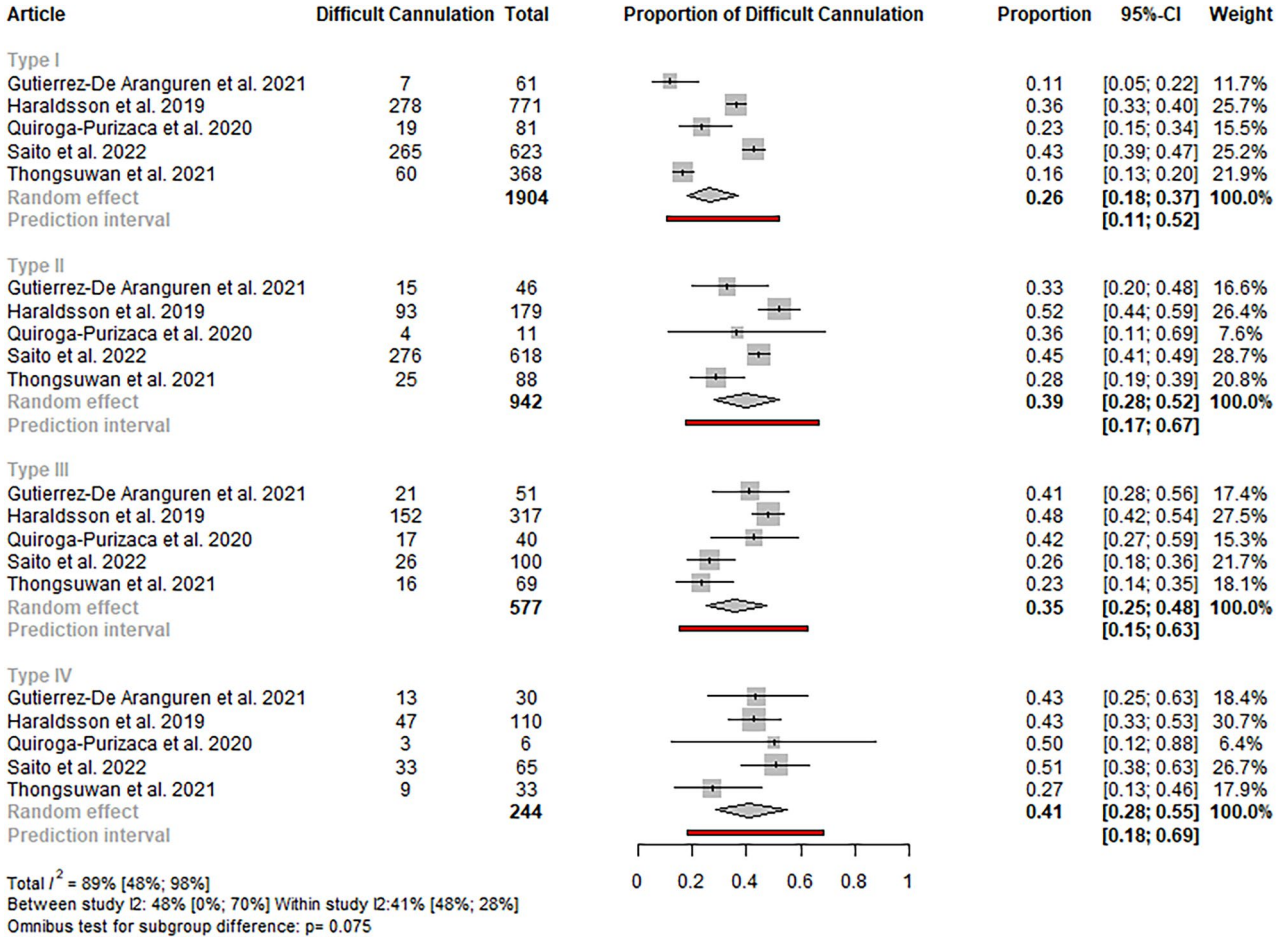

Figure 2. Forest plot representing the pooled event rate of difficult cannulation in the different papilla types in studies using the Haraldsson classification, showing a lower tendency for difficult cannulation in type I papilla compared to the other papilla types.

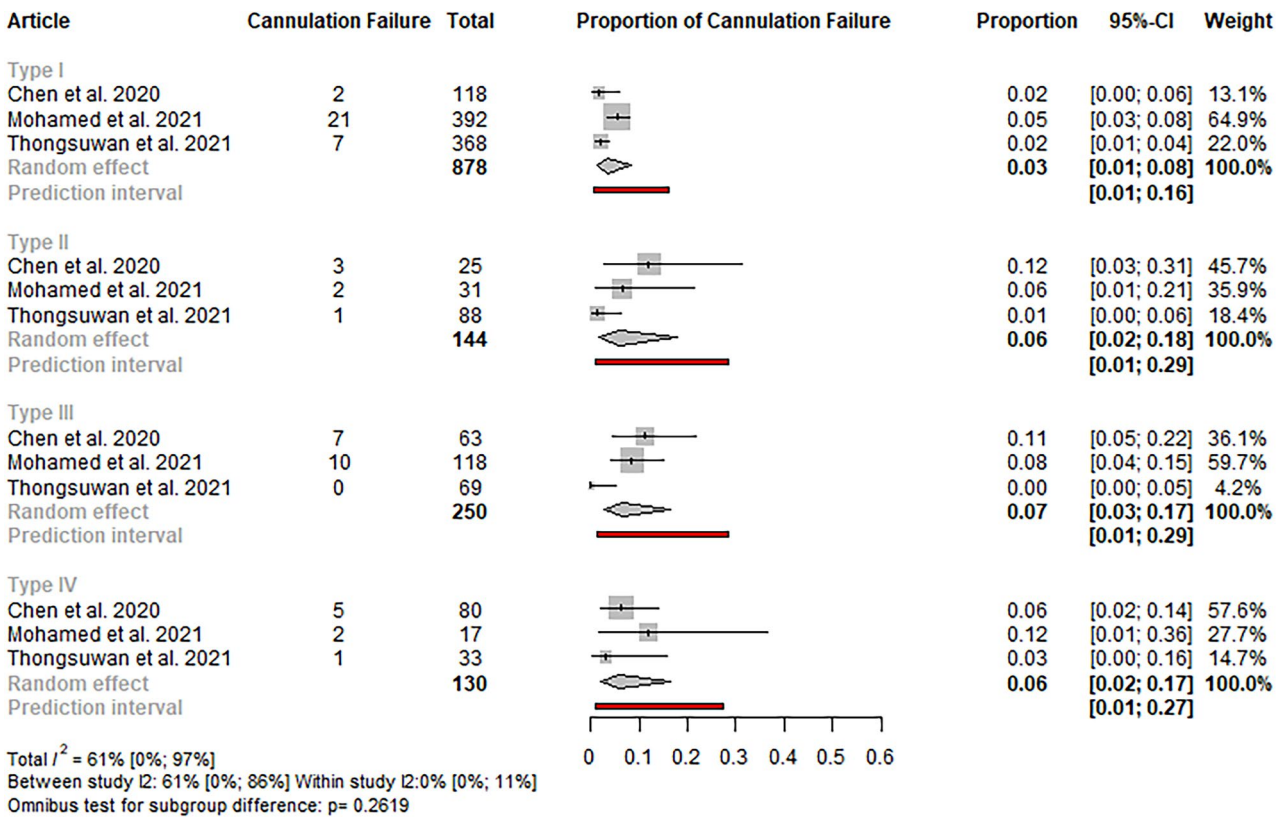

Figure 3. Forest plot representing the pooled event rate of cannulation failure in the different papilla types in studies using the Haraldsson classification, showing no statistically significant difference in the event rates between the papilla types.

in type I (3%; CI 2–6) (see Figure S4). Sensitivity analyses did not reveal outlier studies or relevant changes in the estimate (see Figure S5).

Post-ERCP pancreatitis

Nine of the identified studies reported the event rate of PEP in the different papilla types[4–6,15–17,22,25,28], of which eight articles were included in the quantitative synthesis[4–6,15–17,22,25]. In the case of studies using the Haraldsson classification, in type II papilla, the rate of post-ERCP pancreatitis was higher (11%; CI 8–15) compared to the other papilla types (type IV: 7%; CI 4–12; type I: 6%; CI 5–8; type III: 6%; CI 4–8). The result was statistically significant (p: 0.0441). Total homogeneity was observed (total I^2: 0.044) (see Fig. 4).

A similar tendency was observed in the case of including all eight studies; however, the difference between the papilla types was not statistically significant (p: 0.103) (see Figure S6). Sensitivity analyses did not reveal outlier studies or relevant changes in the estimate (see Figures S7-8).

Post-ERCP bleeding

Six eligible studies reported information about a bleeding episode after an ERCP procedure, all using the Haraldsson classification or classifications comparable to it[5,6,15,16,22,25]. In the analyses with only studies using the Haraldsson classification and with all classification systems, no statistically significant difference was observed in the event rate of the post-ERCP bleeding between the papilla types (p: 0.8585 and p: 0.8078, respectively) (see Figs. 5 and S9). Sensitivity analyses did not reveal outlier studies or relevant changes in the estimate (see Figures S10-11).

Qualitative synthesis

Cannulation time

Eight studies investigated cannulation time in the context of papilla morphology[4–6,15,16,18,22,27], and four used the Haraldsson classification[4–6,22]. The time for cannulation was the lowest in type I papilla, without exception. Two-two studies reported the highest cannulation time in type II[4,5] and type IV papilla[6,22].

Cannulation attempts

Four studies investigated the number of cannulation attempts in the context of papilla morphology[6,15,22,26], from which two used the Haraldsson classification[6,22]. In both cases, the cannulation attempts were the highest in type IV and the lowest in type I and III papillae.

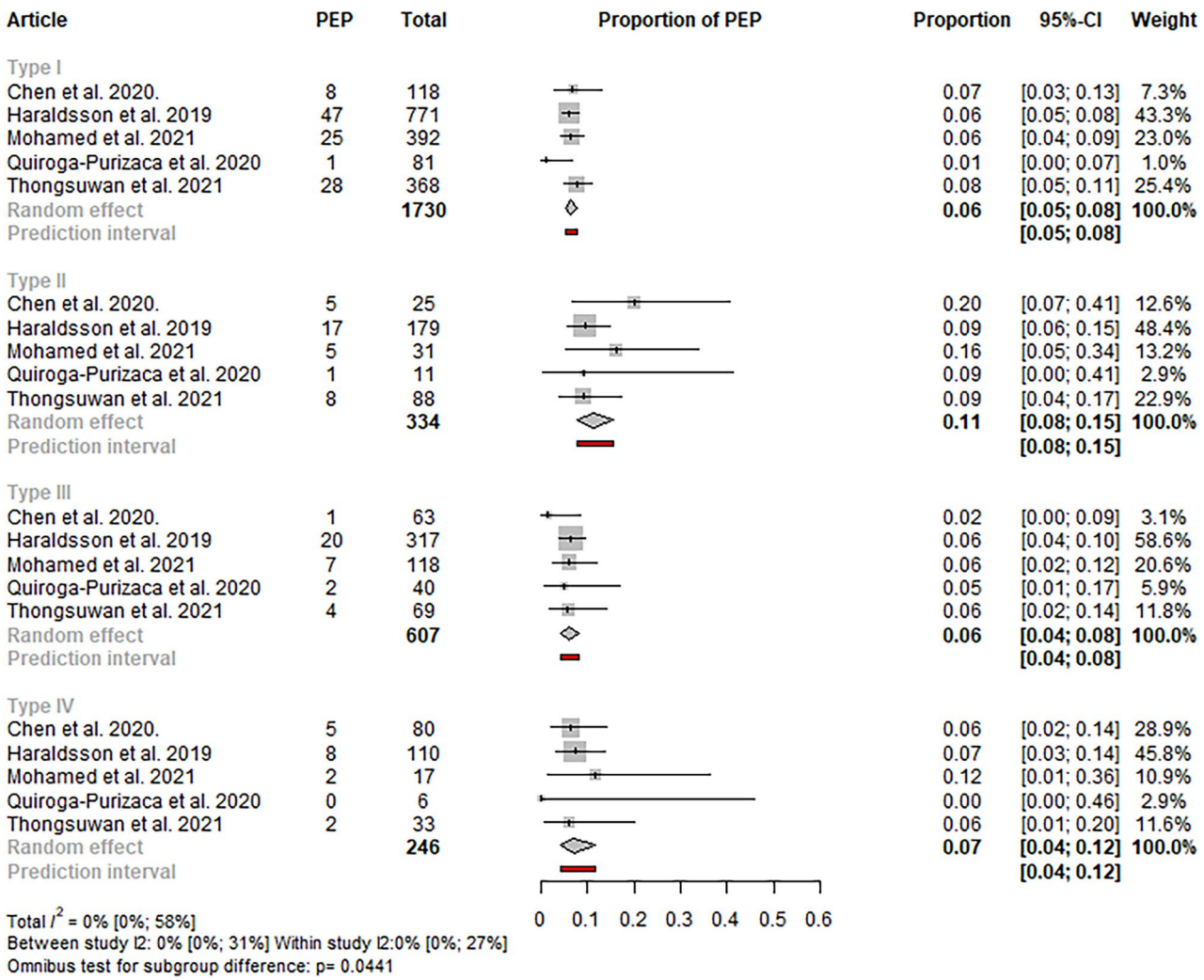

Figure 4. Forest plot representing the pooled event rate of post-ERCP pancreatitis in the different papilla types in studies using the Haraldsson classification, showing a statistically significantly higher rate of post-ERCP pancreatitis in type II papilla, compared to the other papilla types.

Post-ERCP perforation

Three studies investigated the perforation rate after an ERCP procedure, all using the Haraldsson classification[5,16,22]. The meta-analytical calculation was impossible due to the number of zero events.

Post-ERCP infection

Four studies reported the proportion of patients with an infection after ERCP[5,6,15,25]; of those, three studies used the Haraldsson classification[5,6,25]. Chen et al. reported the highest event rate of cholangitis in type I (2.5%) and no event in type II and III papillae[5]. Mohammed et al. found the highest event rate of cholangitis and/or sepsis in type II (3.2%) and no event in type III and IV papillae, meanwhile in the study by Thongsuwan et al., the event rate of infection was the highest in type III (10.5%) and the lowest in type I papilla (6%)[6,25].

Risk of bias and publication bias assessment

Most of the included studies carried a low risk of bias. Among the eight studies detailing difficult cannulation, two (25%) had high, and six (75%) had low risk of bias. The results of the risk of bias assessments are shown in Figures S12-19. Publication bias could not be observed in the conducted analyses. The results of the assessments are shown in Figures S20-27.

Quality of evidence

Since we included only cohort studies, the certainty of evidence ranged between very low and low for each outcome. Detailed results of the GRADE assessment can be found in Tables S4-11.

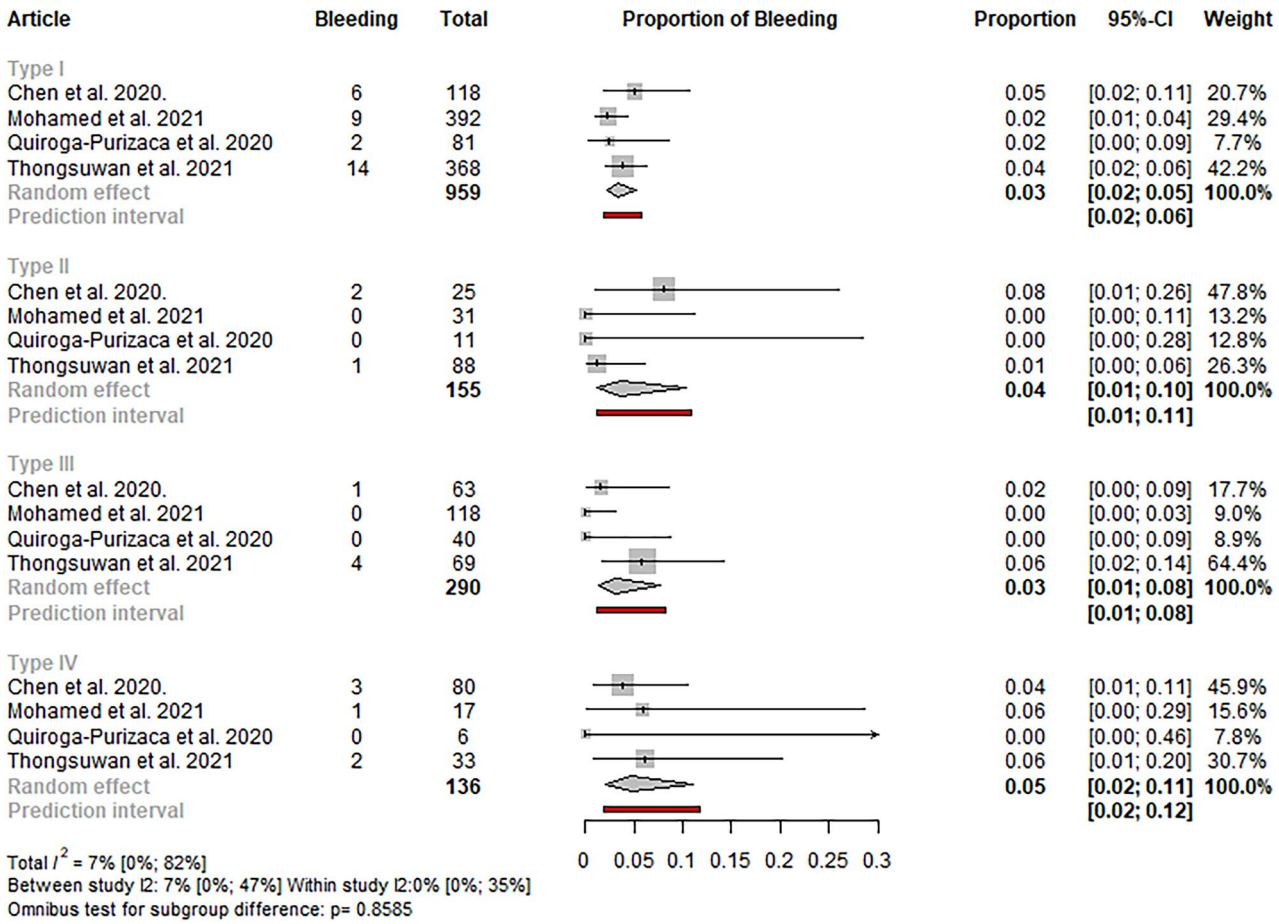

Figure 5. Forest plot representing the pooled event rate of post-ERCP bleeding in the different papilla types in studies using the Haraldsson classification, showing no statistically significant difference in the event rates between the papilla types.

Discussion

Our systematic review and meta-analysis assessed the impact of papilla morphology on ERCP and its outcomes. We found that in studies using the Haraldsson classification, compared to the other papilla types, the event rate of difficult cannulation was lower in type I papilla. Type II papilla was associated with a twofold increase in the event rate of PEP compared to the other papilla types. There was no difference in the cannulation failure and post-ERCP bleeding event rates between the different papilla types.

Since its introduction, there have been debates regarding ERCP's safety and success rate. Several factors seem to influence cannulation difficulties, such as age and age-related factors, including duodenal distortion; procedure-related aspects, such as duodenal positioning or certain etiologies, for example, malignant biliary obstruction. The morphology of the papilla is also assumed to be related to multiple perspectives of the procedure[29].

First, papilla morphology should be considered in the training of fellow endoscopists. In the studies selected for inclusion, there are contradicting data regarding how the endoscopist's expertise influences cannulation difficulty. Mohamed et al. found no relationship between the rate of difficult cannulation and the endoscopist's expertise (7). In contrast, in the study by Haraldsson et al., the rate of difficult cannulation was the highest in type II papilla, where the number of trainees starting the cannulation process was the highest (5). Other studies also suggest that the operator's experience may decrease the rate of difficult cannulation and cannulation failure (34, 35). Further data in the literature suggest that the rate of PEP and other adverse events also decreases with the endoscopist's experience (36).

Secondly, papilla morphology also influences the rate of PEP, the procedure's most common adverse event[2]. We found the highest rate of PEP in type II papilla, which is consistent with the result of the individual studies. However, the definite explanation for this pattern is still uncertain. According to Chen et al. hypothesis, it could be due to the fact that endoscopic papilla balloon dilatation (EPBD) was used more often in this papilla type in their cohort[5]. The same trend could be observed in the study by Mohamed et al.[6]. Further data in the literature suggest that EPBD with small-caliber balloons (diameter: 8–10 mm) increases the rate of PEP[30].

Lastly, all the included studies observed differences in rescue techniques' use in different papilla morphologies. It could be one of the explanations for the non-significant difference in cannulation failure between the different papilla types. We hypothesize that the morphology of the papilla should be considered when choosing a rescue cannulation technique since it decreases the difference in the tendency for cannulation failure or

difficult cannulation between the papilla types. Studies suggest that a pre-cut sphincterotomy or needle-knife fistulotomy (NKF) may be used in normal papillae. Trans-pancreatic sphincterotomy could be the recommended rescue technique in small papillae. In protruding/pendulous or creased/ridged papillae, also NKF could be the preferred method[31,32].

Several classification systems were identified; the Haraldsson was the most widely used and well-recognized one. Despite being the first validated classification system developed by expert endoscopists and, therefore, the basis of our analysis, it has one major limitation: it ignores the presence of a periampullary diverticulum. A modified version of the classification was proposed by Mohamed et al. in 2021, introducing an additional papilla type (type D) for papillae involved with a periampullary diverticulum[6]. In addition, a meta-analysis by Mui et al. found that the presence of PAD may increase the risk of cannulation failure and may also be associated with a higher risk for post-ERCP adverse events[33]. These results suggest that this modified version of the classification should be used.

Strengths

Despite the topic's importance, to our knowledge, this is the first meta-analysis focusing on papilla morphology and its relation to the most relevant endpoints of the ERCP cannulation process and the rate of adverse events. A rigorous methodology was applied, with a comprehensive search key. No publication bias or outlier study was detected in any conducted analyses, and most studies carried a low risk of bias. Moreover, the number of included patients was above 20,000.

Limitations

Regardless of all the strengths, this study also had some limitations: (1) In certain analyses, considerable statistical heterogeneity was observed. Its explanation could be the clinical heterogeneity across studies, such as the difference in the applied definitions in connection with the endoscopic procedure. Most studies used the definition of the European Society of Gastrointestinal Endoscopy for difficult cannulation; however, Thongsuwan et al. used its simplified version. (2) Some of the included cohort studies were retrospective analyses. (3) The certainty of the evidence was low or very low. (4) Abstracts were also eligible for inclusion; however, all were high-quality, containing all the necessary data.

Implication for practice

Based on our results, during training of fellow endoscopists**,** papilla morphology should be determined, and trainees should start their learning with type I ("regular") papillae. Using a unified classification system for papilla morphology is recommended to promote transparency in clinical practice.

Implication for research

Large sample cohorts are needed to validate the Mohammed version of the classification and assess the presence of a periampullary diverticulum. Besides the event rate, future research should also focus on the severity of PEP in the different papilla types. Furthermore, developing a recommendation system for advanced cannulation techniques in the context of papilla morphologies should be considered.

Conclusion

In conclusion, other types are associated with a higher rate of difficult cannulation compared to the regular papilla type. The small papilla is associated with a higher rate of post-ERCP pancreatitis.

Data availability

All data is provided within the manuscript or supplementary information files.

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Author contributions

TE: conceptualization, project administration, methodology, formal analysis, writing—original draft; EBG: formal analysis, visualization, writing—review & editing; AR: conceptualization, writing—review & editing; DSV: formal analysis, data curation, writing—review & editing; SzV: conceptualization, writing—review & editing; PJH: conceptualization, writing—review & editing; KH: conceptualization, writing—review & editing; PH: conceptualization, writing—review & editing; BE: conceptualization; supervision; writing—original draft. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the manuscript's concept, design, analysis, writing, or revision.

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At admission hemodynamic instability is associated with increased mortality and rebleeding rate in acute gastrointestinal bleeding: a systematic review and meta-analysis

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Abstract

Background: Acute gastrointestinal bleeding (GIB) is a life-threatening event. Around 20–30% of patients with GIB will develop hemodynamic instability (HI).

Objectives: We aimed to quantify HI as a risk factor for the development of relevant end points in acute GIB.

Design: A systematic search was conducted in three medical databases in October 2021.

Data sources and methods: Studies of GIB patients detailing HI as a risk factor for the investigated outcomes were selected. For the overall results, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated based on a random-effects model. Subgroups were formed based on the source of bleeding. The Quality of Prognostic Studies tool was used to assess the risk of bias.

Results: A total of 62 studies were eligible, and 39 were included in the quantitative synthesis. HI was found to be a risk factor for both in-hospital (OR: 5.48; CI: 3.99–7.52) and 30-day mortality (OR: 3.99; CI: 3.08–5.17) in upper GIB (UGIB). HI was also associated with higher in-hospital (OR: 3.68; CI: 2.24–6.05) and 30-day rebleeding rates (OR: 4.12; 1.83–9.31) among patients with UGIB. The need for surgery was also more frequent in hemodynamically compromised UGIB patients (OR: 3.65; CI: 2.84–4.68). In the case of in-hospital mortality, the risk of bias was high for 1 (4%), medium for 13 (48%), and low for 13 (48%) of the 27 included studies.

Conclusion: Hemodynamically compromised patients have increased odds of all relevant untoward end points in GIB. Therefore, to improve the outcomes, adequate emergency care is crucial in HI.

Registration: PROSPERO registration number: CRD42021285727.

Keywords: gastrointestinal bleeding, hemodynamic instability, meta-analysis, shock

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Introduction

Acute gastrointestinal bleeding (GIB) is a life-threatening event, often requiring emergency medical care.[1] The mortality rate ranges from 2% to 10%, varying between the countries, making it one of the acute gastrointestinal diseases with the most unfavorable prognosis.[2,3]

Current guidelines provide little to no information and recommendations on the optimal management

and resuscitation of hemodynamically unstable GIB patients.[4–6] The only randomized controlled trial (RCT) which investigated the early resuscitation of patients with upper GIB (UGIB) found that patients receiving early vasopressor treatment with more value-controlled fluid therapy reached hemodynamic stability significantly sooner. Moreover, these patients also had better laboratory values, developed fewer complications, and had an increased chance of survival.[7] These results suggest that the early detection and aggressive treatment of hemodynamic instability (HI) are crucial.

Approximately 20–30% of patients with acute GIB develop HI, which is thought to be associated with worse outcomes, including higher mortality and rebleeding rates than usual. Laursen *et al.*[8] found that hemodynamically unstable GIB patients had a mortality rate of 13%, compared to only 4% in stable patients. Several other identified studies suggested the same trend.[9,10] However, these values have never been systematically reviewed and quantified before.

Our systematic review and meta-analysis aimed to quantify the magnitude of the risk of developing the most relevant end points in the presence of HI in acute GIB.

Methods

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (see Supplemental Table S1) and the recommendations of the Cochrane Handbook.[11,12] The review protocol was registered in advance on PROSPERO with the registration number CRD42021285727.

Systematic search

Three databases, MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched from inception until the 22nd of October 2021. We did not apply any filters or restrictions to our search. The main parts of the search query included terms in connection with HI/shock and GIB. For the detailed search strategy, see Supplemental Table S2. In addition, we manually searched for relevant articles and checked the bibliographic reference lists of studies selected for inclusion.

Eligibility criteria

The population–exposure–outcome (PEO) framework was used to identify eligible studies.[13] We included studies with a population (P) of adult patients (age >18 years) with GIB. Studies were eligible if they contained data on the investigated outcomes in the presence (E) of HI/shock at admission. The primary outcome (O) was mortality, and the secondary outcomes were rebleeding, need for surgery, need for transfusion, length of hospitalization (LOH), and need for rescue endoscopic therapy.

The end points were investigated in UGIB, lower GIB (LGIB) patients, and in populations with UGIB and LGIB patients separately. For defining HI/shock, the individual definitions of the included studies were used. Based on their definitions, HI and shock were considered synonyms, and the term HI was used for both.

RCTs, case–control, cross-sectional, and cohort studies were eligible for the systematic review. Only cohort studies were included in the meta-analytical calculations. Full-text articles were considered eligible.

Study selection and data extraction

After the systematic search, the yielded articles were imported into a reference management program (EndNote X7.4, Clarivate Analytics, Philadelphia, PA, USA). After duplicate removal, two independent authors (ET and LF) screened the remaining publications first by title and abstract, and then by full text. Disagreements were resolved by consensus and the involvement of the senior review author (BE). Cohen's kappa coefficient (κ) was calculated at both levels of selection to measure inter-reviewer reliability.[14] In the case of multiple publications from the same cohort, the study with the highest number of cases was selected.

Two investigators independently extracted data (ET and LF) and manually uploaded them into a purpose-designed Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA). Disagreements were solved by the senior review author (BE).

Data were collected on the first author, year of publication, study location, study design, period of enrollment, study population, number and age of the enrolled patients, source of bleeding, follow-up

time, number of patients with and without HI/shock at admission, and on the definitions of HI/shock. For statistical analysis, raw data were extracted into two-by-two tables (outcome yes/no; HI/shock yes/no). Odds ratios (ORs) and hazard ratios (HRs) and their respective 95% confidence intervals (CIs) were also collected.

Statistical analysis

The statistical analysis was performed by a biostatistician (DSV) using the R programing language (R Core Team 2022, v4.2.1). Forest plots were used to display the results of the meta-analytical calculations. The minimum number needed to perform the meta-analytical calculation was three. In-hospital mortality and mortality in less than 7 days, as well as 6-week and 30-day mortality, were pooled. The same strategy was used for rebleeding. Pooled ORs with 95% confidence intervals were calculated using the random-effects model. I^2 statistics by Thompson and Higgings[15] were used to describe between-study heterogeneity. Publication bias was assessed by funnel plots and Egger's tests with additional analysis if a potential small study bias was suspected.[16] The leave-one-out method was used for sensitivity analyses. Subgroup analyses were performed for studies where the 'subtype' of bleeding was specified. Additional analyses were performed on articles with a definition of a blood pressure $\leqslant$100 mmHg and/or a pulse rate $\geqslant$100/min for HI.

Risk of bias assessment

The risk of bias assessment was carried out at the study level and across studies independently by two investigators (ET and TS) using the Quality of Prognostic Studies (QUIPS) tool for each outcome.[17] Disagreements were resolved by the senior review author (BE).

Results

Search and selection

A total of 11,583 studies were identified through database searching. After the duplicate removal and careful selection by title and abstract, 218 articles were found eligible for full-text assessment. Three additional studies were identified through cross-referencing and manual database searching. Finally, our qualitative synthesis comprised 62 studies, and 39 were included in the quantitative synthesis. The details of the study selection process are summarized in the PRISMA flow chart in Figure 1.

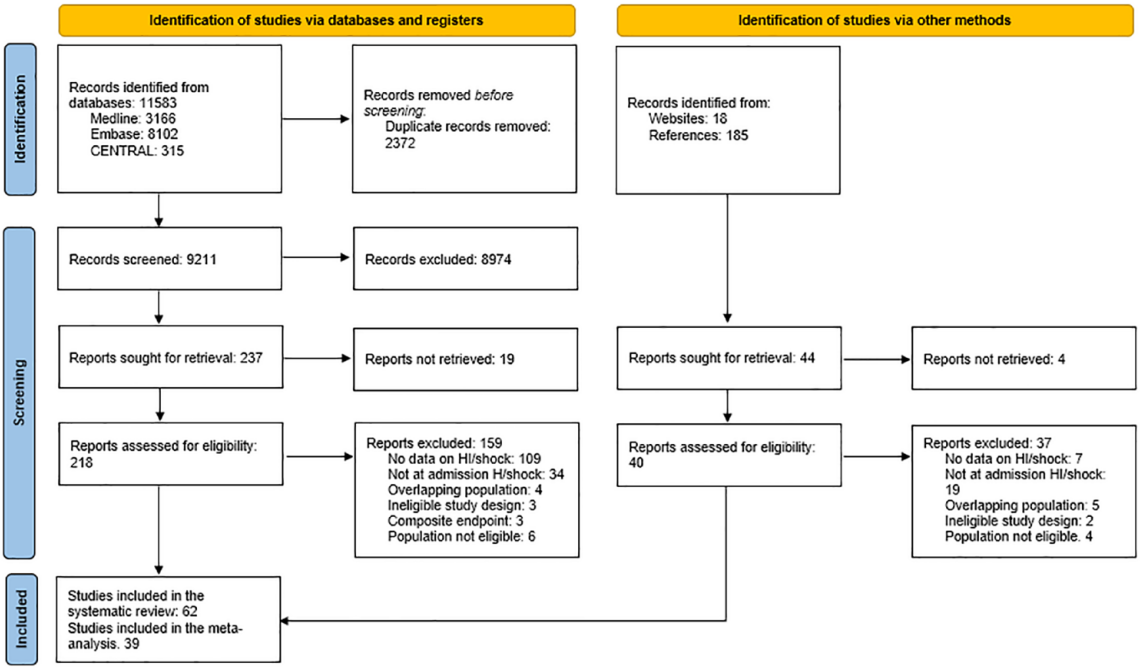

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 flowchart representing the study selection process.

Basic characteristics of included studies

The main characteristics of the included studies are summarized in Table 1. Eligible studies were reported between 1977 and 2021. The number of study participants ranged from 56 to 12,601. The majority of the identified studies were cohort studies, of which 22 were prospective,[8,10,18–37] 32 were retrospective,[9,38–68] and two were ambidirectional analyses.[69,70] One RCT,[71] one case–control,[72] and three cross-sectional studies[58,73–75] were also included in the systematic review.

The rate of HI/shock ranged between 1.2% and 68.3% of the eligible studies. The source of bleeding was UGIB in 54 of the included studies,[8–10,18–34,36,37,39–45,47–50,52–55,58–60,63–76] and LGIB in 7.[35,38,46,51,57,61,62] One study detailed a population including both UGIB and LGIB patients.[56]

In terms of outcomes, 44 studies reported mortality,[8–10,18,20–30,32–37,39,41–43,47–49,52–55,58,63–66,68–71,73–75] 27 rebleeding,[8,19,20,22,25,29–31,34,35,38–40,43,45,46,50,51,55–57,60,68,70,72,75,76] and 5 the need for surgery.[38,44,59,61,67] Two studies detailed the need for transfusion,[30,60] and another two the LOH.[38,62]

For the definitions in the included studies for HI/shock, see Supplemental Table S3.

Mortality

We identified 27 studies investigating in-hospital mortality in the presence and absence of HI in UGIB; 22 could be pooled and included in the meta-analytical calculation (see Figure 2). Our results suggested considerably increased odds of in-hospital mortality in patients with HI (OR: 5.48; CI: 3.99–7.52; I^2: 74%) (see Figure 2). Subgroup analyses were made in the cases of UGIB, non-variceal UGIB (NVUGIB), and peptic ulcer bleeding (PUB). In studies containing information about patients suffering from all types of UGIB, the odds were higher (6.18; CI: 4.11–9.28), compared to the studies only with PUB patients (4.79; CI: 2.62–8.97). In the case of NVUGIB, the results were not statistically significant (OR: 6.52; CI: 0.29–144.21). The influential analysis detected no outlier study (see Supplemental Figure S1).

In the analysis of studies with a definition of a blood pressure $\leqslant$100 mmHg and/or a pulse rate $\geqslant$100/min for HI, smaller, but still significantly increased odds were observed for in-hospital mortality (OR: 4.14; CI: 2.47–6.94; I^2: 67%) (see Figure 3).

Besides all other studies, four cohorts, and one cross-sectional, which were not included in the meta-analytical calculation, also suggested higher odds of in-hospital mortality in the presence of HI in UGIB.[24,35,43,52,75]

One of the identified studies detailed in-hospital mortality in a population both with UGIB and LGIB patients, also indicating increased odds among hemodynamically unstable patients (OR: 5.07; CI: 2.54–10.11).[56]

In total, 19 studies investigated follow-up mortality, all for UGIB. Among the 19 studies, 16 included information on 30- to 42-day mortality, of which 10 were included in the meta-analysis. The odds of mortality during the follow-up period were 3.99 (CI: 3.08–5.17; I^2: 52%) (see Figure 4). The influential analysis detected no outlier study (see Supplemental Figure S2).

In the analysis of studies with a definition of a blood pressure $\leqslant$100 mmHg and/or a pulse rate $\geqslant$100/min for HI, the odds of 30- to 42-day mortality were also significant (OR: 4.03; CI: 2.68–6.05; I^2: 58%) (see Supplemental Figure S3).

In addition, the other six eligible articles, five cohort studies, and one RCT suggested increased mortality in HI.[36,42,43,49,53,71] Two studies investigated 2-week mortality, one in PUB and one in VUGIB. In VUGIB patients, HI was associated with 2-week mortality (OR: 4.08; CI: 1.52–10.96), in contrast with PUB, where the results were not statistically significant (OR: 1.67; CI: 0.26–10.74). Lohse *et al.*[32] reported increased 90-day mortality in PUB (OR: 2.03; CI: 1.69–2.43).

Rebleeding

In all, 17 studies examined the association between in-hospital rebleeding and HI, 16 in UGIB, and 2 in LGIB. Of the 15 studies with UGIB as the source of bleeding, 11 were included in the meta-analysis (see Figure 5). Our results showed increased odds of in-hospital rebleeding in the presence of HI in UGIB (OR: 3.68; CI: 2.24–6.50; I^2: 91%) (see Figure 5). Subgroup analyses were made in the cases of

Table 1. Basic characteristics of included studies.

Author	Year	Country	Study type	Type of bleeding	Age	Female	No of patients	Patients with shock/HI	Outcomes	Results
Albeldawi *et al.*[38]	2014	USA	Retrospective cohort	LGIB	Mean 68 ± 12.5	49.1%	56	51.8%	In-hospital rebleeding Need for surgery Length of hospitalization	HR: 3.80 (CI: 1.06–13.70) HR: 13.5 (CI: 3.2–56.5) HR: 1.1 (CI: 1.05–1.2)
Ardevol *et al.*[18]	2017	Spain	Prospective cohort	UGIB	NA	31.9%	790	27.3%	6-week mortality	OR: 2.82 (CI: 1.94–4.09)
Bornman *et al.*[19]	1985	South Africa	Prospective cohort	PUB	Mean 51.2 ±16.5	NA	177	14.5%	In-hospital rebleeding	OR: 14.67 (CI: 5.21–41.25)
Branicki *et al.*[20]	1992	Hong Kong	Prospective cohort	PUB	Median 59 (range: 12–97)	NA	842	17.5%	In-hospital mortality In-hospital rebleeding	OR: 1.96 (CI: 0.92–4.17) OR: 1.60 (CI: 1.01–2.52)
Bratanic *et al.*[39]	2013	Croatia	Retrospective cohort	PUB	NA	30.7%	251	1.2%	In-hospital mortality In-hospital rebleeding	OR: 29.00 (CI: 2.49–337.18) OR: 13.50 (CI: 1.19–153.19)
Brullet *et al.*[21]	1996	Spain	Prospective cohort	PUB	NA	21.7%	106	23.6%	In-hospital mortality	OR: 3.34 (CI: 1.00–11.10)
Budimir *et al.*[22]	2017	Croatia	Prospective cohort	PUB	Mean 65.9	37.1%	796	9.7%	30-day mortality In-hospital rebleeding	OR: 5.56 (OR: 2.75–11.24) OR: 12.81 (CI: 7.28–22.53)
Bunchorntavakul *et al.*[40]	2017	Thailand	Retrospective cohort	NVUGIB VUGIB	Mean 54.7 ± 17 Mean 51.8 ± 11	34.4% 17.9%	180 106	8.3% 16%	30-day rebleeding	OR: 10.65 (CI: 3.57–31.78) OR: 1.99 (CI: 0.37–10.65)
Chaabane *et al.*[41]	2011	Tunisia	Retrospective cohort	UGIB	NA	42.1%	401	9.5%	In-hospital mortality	OR: 19.70 (CI: 6.43–60.32)
Chandnani *et al.*[76]	2019	India	Prospective cohort	UGIB	Mean 43.5 ± 17.2	31%	300	35.3%	30-day rebleeding	OR: 2.54 (CI: 1.37–4.71)
Charatcharoenwitthaya *et al.*[42]	2011	Taiwan	Retrospective cohort	UGIB	Mean 60 ± 15.9	30%	526	59.5%	30-day mortality	HR: 2.57 (CI: 1.05–7.76)
Cheng[9]	2014	China	Retrospective cohort	PUB	Mean 57.3 ± 4.8	47.4%	785	12.9%	In-hospital mortality	OR: 5.66 (CI: 2.86–11.21)
Chirapongsathorn *et al.*[43]	2021	Thailand	Retrospective cohort	VUGIB	Mean 53.3 ± 12.2	10.5%	713	72.5%	5-day mortality 6-week mortality 5-day rebleeding 6-week rebleeding	HR: 12.25 (CI: 7.09–21.16) HR: 12.91 (CI: 7-95–20.97) HR: 2.32 (CI: 1.30–4.15) HR: 2.14 (CI: 1.27–3.64)
Chiu *et al.*[10]	2009	Hong Kong	Prospective cohort	PUB	NA	31.6	3220	20%	In-hospital mortality	OR: 2.85 (CI: 2.15–3.77)
Clason *et al.*[23]	1986	UK	Prospective cohort	UGIB	NA	NA	326	18%	In-hospital mortality	OR: 9.33 (CI. 4.49–19-37)
Danne *et al.*[44]	1984	Australia	Retrospective cohort	UGIB	Average 56	NA	153	22.9%	Need for surgery	OR: 3.23 (CI: 1.27–8.21)

(Continued)

Table 1. (Continued)

Author	Year	Country	Study type	Type of bleeding	Age	Female	No of patients	Patients with shock/HI	Outcomes	Results
Del Piano *et al.*[24]	2013	Italy	Prospective cohort	NVUGIB	Mean 53.2 ± 10.1	33.5%	1413	9.3%	In-hospital mortality	OR. 2.89 (CI: 0.93–8.94)
Djuranovic *et al.*[25]	2007	Serbia	Prospective cohort	NVUGIB	NA	33.3%	315	21.6%	In-hospital mortality In-hospital rebleeding	OR: 18.69 (CI: 3.93–88.78) OR: 2.43 (CI: 1.28–4.61)
Elloumi *et al.*[45]	2003	Tunisia	Retrospective cohort	PUB	Average 50	18.8%	208	6.7%	In-hospital rebleeding	OR: 3.91 (CI: 1.11–13.75)
El Mekkaoui *et al.*[69]	2011	France	Ambidirectional cohort	UGIB	Mean 47.6 ± 17.7	36.5%	1303	2%	In-hospital mortality	OR: 5.60 (CI: 2.29–13.72)
Elsebaey *et al.*[26]	2018	Egypt	Prospective cohort	UGIB	Mean 68 ± 5.7	29.4%	286	56.6%	In-hospital mortality	OR: 4.47 (CI: 1.49–13.38)
Fujino *et al.*[46]	2013	Japan	Retrospective cohort	LGIB	NA	33.3%	90	41.1%	30-day rebleeding	OR: 5.56 (CI: 2.00–15.57)
Gado *et al.*[73]	2014	Egypt	Cross-sectional	PUB	mean 59 ± 7	50%	62	48.4%	2-week mortality	OR: 1.67 (CI: 0.26–10.74)
Gado *et al.*[74]	2014	Egypt	Cross-sectional	VUGIB	mean 53 ± 10	37%	224	17.4%	2-week mortality	OR: 4.08 (CI: 1.52–10.96)
Hassanien *et al.*[47]	2018	Egypt	Retrospective cohort	VUGIB	NA	30%	725	28.7%	In-hospital mortality	OR: 7.69 (CI: 5.29–11.17)
Hunt[27]	1983	Australia	Prospective cohort	PUB	NA	NA	633	29.1%	In-hospital mortality	OR: 14.96 (CI: 6.12–36.55)
Hwang *et al.*[28]	2016	Republic of Korea	Prospective cohort	NVUGIB	Mean 63 ± 16	26.4%	1584	9.8%	30-day mortality	OR: 2.75 (CI: 1.42–5.34)
Ishikawa *et al.*[48]	1995	Japan	Retrospective cohort	PUB	NA	20%	75	56%	In-hospital mortality	OR: 11.93 (OR: 0.65–219.99)
Katschinski *et al.*[29]	1994	UK	Prospective cohort	UGIB	NA	NA	2217	NA	In-hospital mortality In-hospital rebleeding	OR: 4.40 (CI: 3.06–6.33) OR: 4.60 (CI: 3.90–5.43)
Kim *et al.*[50]	2005	Korea	Retrospective cohort	M-W syndrome	NA	14%	159	22.6%	30-day rebleeding	OR: 6.37 (CI: 2.22–18.31)
Kim *et al.*[49]	2021	Korea	Retrospective cohort	VUGIB	Mean 55.5 ± 11.4	19.2%	1373	6.3%	6-week mortality	HR: 4.43 (CI: 3.19–7.60)
Kitagawa *et al.*[51]	2019	Japan	Retrospective cohort	LGIB	Mean 73.8 ± 10.5	39.6%	144	9%	90-day rebleeding	OR: 6.20 (CI: 1.75–21.97)
Koch *et al.*[52]	2013	Germany	Retrospective cohort	UGIB	Median 64 (range: 18–97)	35.9%	463	NA	In-hospital mortality	OR: 4.26 (CI: 1.11–16.3)
Lakatos *et al.*[30]	2021	Hungary	Prospective cohort	NVUGIB	Mean 68.6	38.7%	688	NA	In-hospital mortality In-hospital rebleeding Need for transfusion	OR: 1.80 (CI: 1.11–2.92) OR: 2.15 (CI: 1.33–3.47)

(Continued)

Table 1. (Continued)

Author	Year	Country	Study type	Type of bleeding	Age	Female	No of patients	Patients with shock/HI	Outcomes	Results
Lanas *et al.*[53]	2013	Spain	Retrospective cohort	PUB	NA	29.5%	539	6.7%	30-day mortality	OR: 4.36 (CI: 0.02–6.09)
Laursen *et al.*[8]	2017	Denmark	Prospective cohort	PUB	Mean 74 (range: 48–92)	45%	12,601 6643	23.3% 22.7%	In-hospital mortality In-hospital rebleeding 30-day mortality	OR: 3.60 (CI: 3.09–4.18) OR: 2.12 (CI: 1.91–2.36) OR: 2.95 (CI: 2.48–3.51)
Lausevic *et al.*[31]	2007	Serbia	Case–control	PUB	NA	NA	80	30%	In-hospital rebleeding	OR: 52.76 (CI: 6.58–423.02)
Lee *et al.*[54]	1992	Australia	Retrospective cohort	VUGIB	Mean 50 ± 13.5	38.6%	101	56.7%	In-hospital mortality	OR: 2.28 (CI: 1.01–5.16)
Liang *et al.*[72]	2012	Taiwan	Retrospective case-control	PUB	NA	29.5%	413	52.8%	30-day rebleeding	OR: 1.42 (CI: 0.88–2.28)
Lohse *et al.*[32]	2015	Denmark	Prospective cohort	PUB	NA	46%	3580	25.7%	90-day mortality	OR. 2.03 (CI: 1.69–2.43)
Mäkelä *et al.*[71]	1996	Finland	RCT	PUB	NA	65.4%	78	19.2%	30-day mortality	OR. 11. 09 (CI: 1.80–68.10)
Marmo *et al.*[33]	2014	Italy	Prospective cohort	NVUGIB	Mean 67.9 ± 16.7	34.1%	2317	7%	30-day mortality	OR: 5.52 (CI: 3.47–8.79)
Minakari *et al.*[75]	2017	Iran	Retrospective cross-sectional	UGIB	Mean 55.5 ± 22	30.8%	4747	39.8%	In-hospital mortality In-hospital rebleeding	OR: 39.84 (CI: 21.71–73.09) OR: 3.50 (CI: 2.98–4.10)
Mungan[55]	2012	Multi	Retrospective cohort	NVUGIB	Mean 57.8 ± 18.9	32.6%	423	NA	30-day mortality 30-day rebleeding	OR: 7.28 (CI: 1.81–29.24) OR: 3.49 (CI: 1.13–10.80)
Nagata *et al.*[56]	2017	Japan	Retrospective cohort	GIB	Mean 75.7 ± 10.6	38.9%	157	20.4%	90-day rebleeding	OR: 2.90 (CI: 1.10–7.70)
Nahon *et al.*[34]	2012	France	Prospective cohort	UGIB	Mean 63 ± 18	32.5%	3298	7.7%	In-hospital mortality In-hospital rebleeding	OR: 4.24 (CI: 3.07–5.85)
Nykänen *et al.*[57]	2018	Finland	Retrospective cohort	LGIB	Median 72 (range: 30–95)	30%	NA	NA	30-day rebleeding	OR 0.59 (CI: 0.17–2.06)
Ogasawara *et al.*[58]	2014	Japan	Retrospective cohort	PUB	NA	24.3%	428	10.3%	In-hospital mortality	OR: 13.98 (CI: 2.27–86.08)
Parreira *et al.*[59]	2002	Spain	Retrospective cohort	PUB	Mean 52 (SD: 18)	23.5%	200	13.5%	Need for surgery	OR: 3.86 (CI: 1.47–10.15)
Radaelli *et al.*[35]	2021	Italy	Prospective cohort	LGIB	Median 78 (range: 67–84)	47.8%	1198	9.2%	In-hospital mortality In-hospital rebleeding	OR: 5.07 (CI: 2.54–10.11) OR: 2.43 (CI: 1.41–4.18)
Restellini *et al.*[60]	2012	Canada	Retrospective cohort	NVUGIB	Mean 66.2 ± 16.8	38.3%	1677	31.9%	In-hospital rebleeding Need for transfusion	OR: 1.10 (CI: 0.80–1.50) OR: 3.42 (CI: 2.73–4.28)

(Continued)

Table 1. (Continued)

Author	Year	Country	Study type	Type of bleeding	Age	Female	No of patients	Patients with shock/HI	Outcomes	Results
Rios *et al.*[61]	2007	Spain	Retrospective cohort	LGIB	Mean 68 ± 17	46%	171	17%	Need for surgery	OR. 4.81 (CI: 1.87–12.37)
Schmulewitz *et al.*[62]	2003	USA	Retrospective cohort	LGIB	Mean 66.8 ± 15.5	49.3%	565	68.3%	Length of hospitalization	HR: 0.80 (CI: 0.70–1.00)
Sereda *et al.*[63]	1977	Australia	Retrospective cohort	UGIB	NA	26.3%	513	24.2%	In-hospital mortality	OR: 8.93 (CI: 4.57–17.46)
Shih *et al.*[64]	2018	Taiwan	Retrospective cohort	UGIB	Mean 55.7 ± 13.3	19.8%	202	22.3%	In-hospital mortality	OR: 7.60 (CI: 2.40–24.05)
Sombié *et al.*[36]	2015	Burkina Faso	Prospective cohort	UGIB	Mean 46.8 ± 17.1	29.4%	265	33.6%	30-day mortality	OR: 4.80 (CI: 1.90–11.70)
Stupin *et al.*[65]	2013	Russia	Retrospective cohort	PUB	NA	NA	895	28.4%	30-day mortality	OR: 6.80 (CI: 4.87–9.49)
Thomopoulos *et al.*[67]	2004	Greece	Retrospective cohort	PUB	Mean 58.3 ± 17.2	18.8%	191	16.8%	Need for surgery	OR: 3.85 (CI: 1.68–8.81)
Thomopoulos *et al.*[66]	2006	Greece	Retrospective cohort	VUGIB	Mean 60.5 ± 13.5	19.1%	141	18.4%	6-week mortality 1-year mortality	OR: 6.18 (CI: 2.39–16.03) OR: 1–70 (CI: 0.70–4.06)
Tsoi *et al.*[37]	2002	Hong Kong	Prospective cohort	PUB	NA	33.4%	8222	8.7%	30-day mortality	OR: 3.62 (OR: 2.77–4.70)
Vuachet *et al.*[68]	2015	France	Retrospective cohort	VUGIB	Mean 60.9 ± 10.4	22.3%	121 112	11.6% 10.7%	6-week mortality 6-month mortality 6-month rebleeding	OR: 4.60 (CI: 1.40–15.13) OR: 3.42 (CI: 1.09–10.70) OR: 3. 76 (CI: 1.09–12.86)
Wierchowski *et al.*[70]	2013	Poland	Ambidirectional cohort	NVUGIB	Mean 62.7 ± 15.6	40.9%	482	19.3%	In-hospital mortality In-hospital rebleeding	OR: 11.50 (CI: 5.43–24.36) OR: 3.30 (CI: 1.91–5.72)

HI, hemodynamic instability; HR, hazard ratio; LGIB, lower gastrointestinal bleeding; M-W, Mallory-Weiss; NA, not applicable; NVUGIB, non-variceal upper gastrointestinal bleeding; OR, odds ratio; PUB, peptic ulcer bleeding; UGIB, upper gastrointestinal bleeding; UK, United Kingdom; USA, United States of America; VUGIB, variceal upper gastrointestinal bleeding.

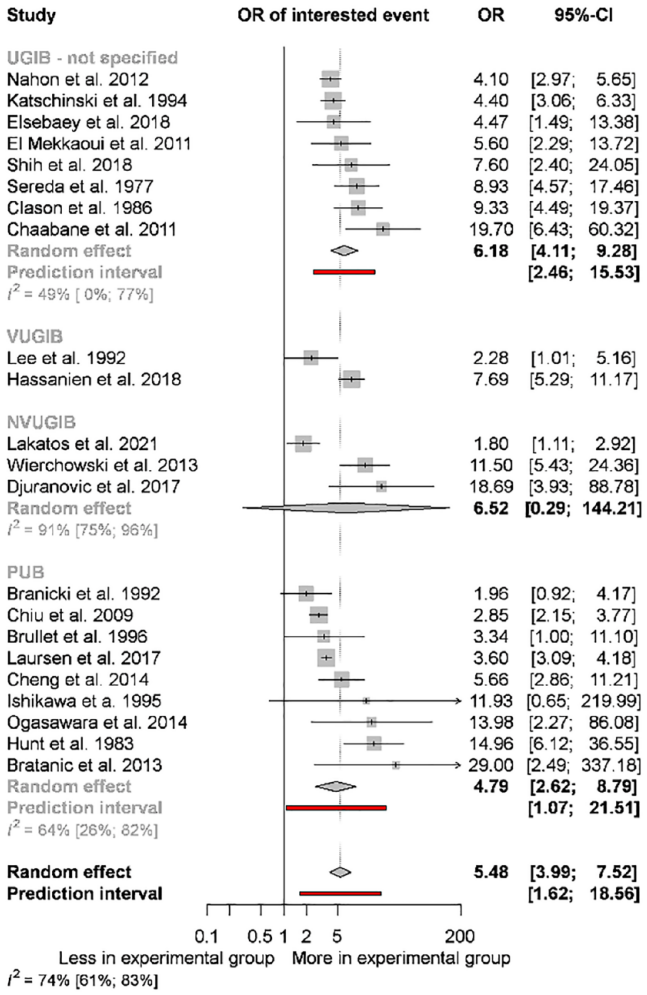

Figure 2. Forest plot representing the odds of in-hospital mortality in UGIB.
NVUGIB, non-variceal upper gastrointestinal bleeding; PUB, peptic ulcer bleeding; UGIB, upper gastrointestinal bleeding; VUGIB, variceal upper gastrointestinal bleeding.

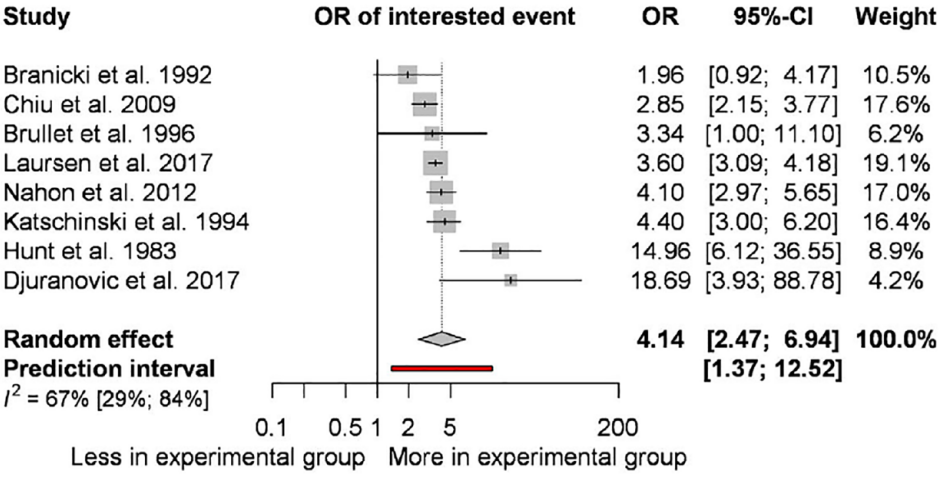

Figure 3. Forest plot representing the odds of in-hospital mortality in upper gastrointestinal bleeding in studies with a definition of a blood pressure ⩽100 mmHg and/or a pulse rate ⩾100/min for hemodynamic instability (HI).

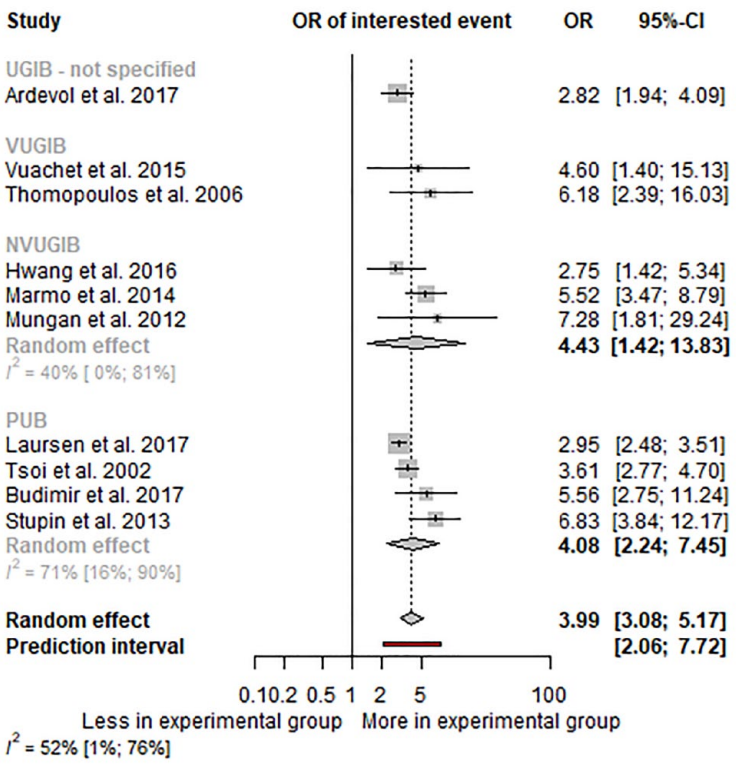

Figure 4. Forest plot representing the odds of 30- to 42-day mortality in UGIB.
NVUGIB, non-variceal upper gastrointestinal bleeding; PUB, peptic ulcer bleeding; UGIB, upper gastrointestinal bleeding; VUGIB, variceal upper gastrointestinal bleeding.

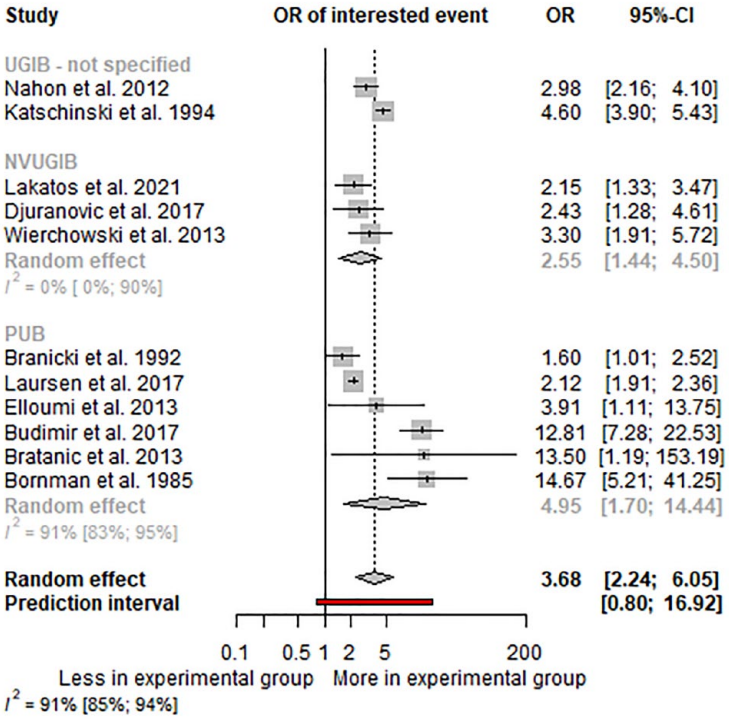

Figure 5. Forest plot representing the odds of in-hospital rebleeding in UGIB.
NVUGIB, non-variceal upper gastrointestinal bleeding; PUB, peptic ulcer bleeding; UGIB, upper gastrointestinal bleeding.

NVUGIB and PUB, where the odds were higher in the case of PUB patients, compared to NVUGIB patients (OR: 2.55; CI. 1.44–4.50 *versus* OR: 4.95; CI: 1.70–14.44). The influential analysis detected Budimir *et al.* as an outlier study; however, no clinical cause could be identified behind it.

In the analysis of studies with a definition of a blood pressure ⩽100 mmHg and/or a pulse rate ⩾100/min for HI, significant, but lower odds of in-hospital rebleeding in hemodynamically unstable patients (OR: 3.92; CI: 1.80–8.55; I^2: 94%) (see Figure 6).

Moreover, the other four studies, which were not included in the meta-analytical calculation, reported increased odds of in-hospital rebleeding.[43,60,75] Two studies investigating in-hospital rebleeding in hemodynamically unstable LGIB patients also reported increased odds (HR: 3.78; CI: 1.06–13.7; OR: 1.85; CI: 1.01–3.42).[35,38]

Nine studies detailed the odds of 30- to 42-day rebleeding in the presence of HI, eight in UGIB, and one in LGIB. Four studies of patients with UGIB were included in the meta-analysis, where the odds were 4.12 (CI: 1.83–9.31; I^2: 39%) (see Figure 7). The leave-one-out analysis was limited

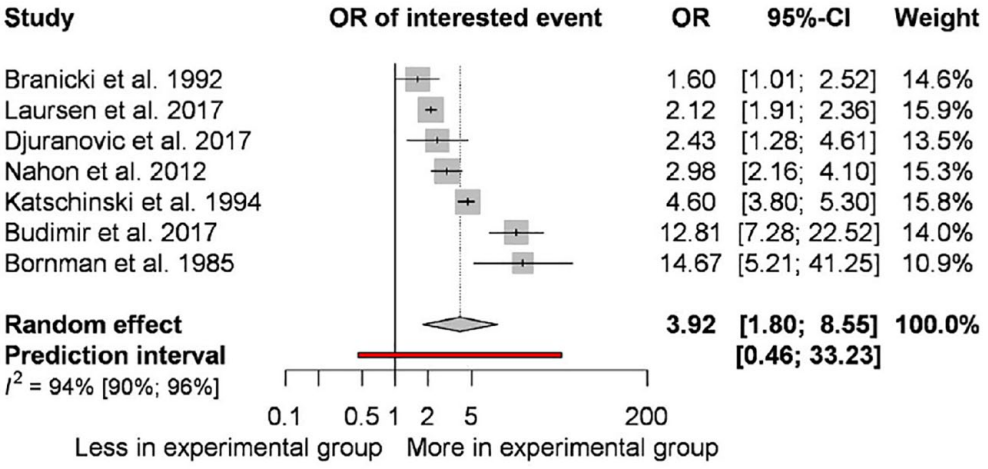

Figure 6. Forest plot representing the odds of in-hospital rebleeding in upper gastrointestinal bleeding in studies with a definition of a blood pressure ⩽100 mmHg and/or a pulse rate ⩾100/min for hemodynamic instability (HI).

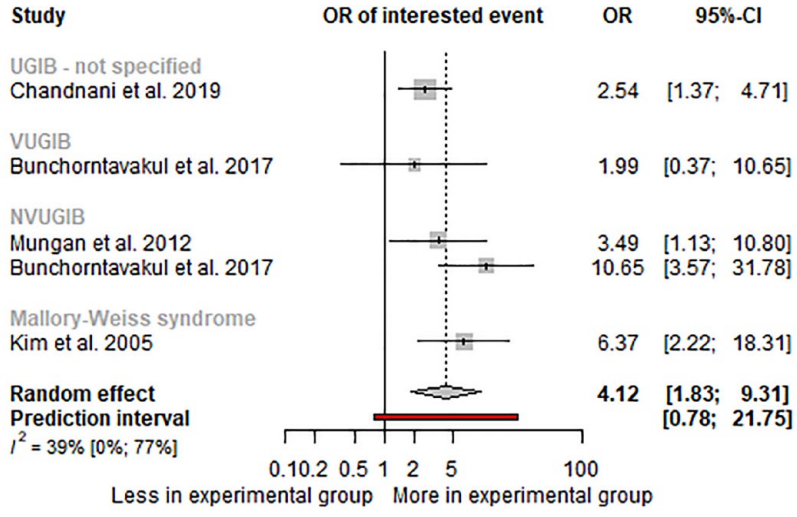

Figure 7. Forest plot representing the odds of 30- to 42-day mortality in UGIB.
NVUGIB, non-variceal upper gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding; VUGIB, variceal upper gastrointestinal bleeding.

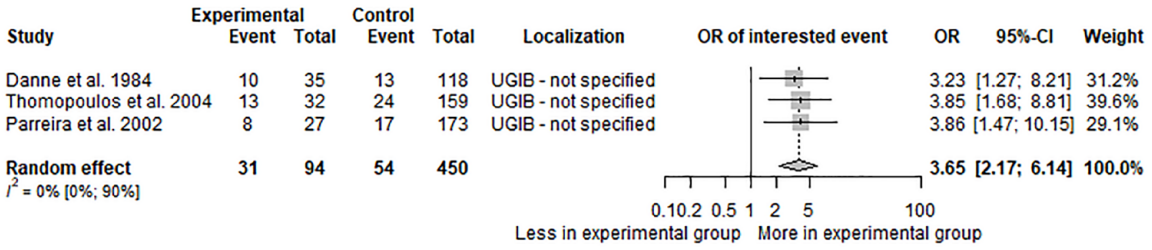

Figure 8. Forest plot representing the odds of need for surgery in upper gastrointestinal bleeding.

due to the low number of studies (see Supplemental Figure S5).

In the analyses in studies with a definition of a blood pressure ⩽100 mmHg and/or a pulse rate ⩾100/min for HI, almost similar odds were observed (OR: 4.13; CI: 1.11–15.37; I^2: 0%) (see Supplemental Figure S6).

The other five studies, four with UGIB and one with LGIB patients, also reported increased odds of 30- to 42-day rebleeding.[43,46,57,68,72] Two studies were identified investigating 90-day rebleeding, one in LGIB and one in general GIB, both reporting increased odds of rebleeding in HI (OR: 0.59; CI: 0.17–2.06; OR: 2.90; CI: 1.10–7.70).[32,51]

Need for surgery

Five studies investigated the need for surgery in the presence of HI. For UGIB, there was an increased need for surgery among hemodynamically compromised UGIB patients (OR: 3.65; CI: 2.84–4.68) (see Figure 8).

Among patients with LGIB, the two identified studies also suggested an increased need for surgery in patients with HI (HR: 13.5; CI: 3.2–5.65; OR: 4.81; CI: 1.87–12.37).[38,61]

Need for transfusion

Two studies detailed the need for transfusion. In both studies, the source of bleeding was UGIB and indicated increased odds of transfusion in the presence of HI (OR: 3.57; CI: 2.6–5.0; OR: 3.42; CI: 2.73–4.28).

Length of hospitalization

Two studies were identified for LOH, both detailing LGIB patients. Abeldawi *et al.*[38] reported increased hospital stays among hemodynamically compromised patients (HR: 1.1; CI: 1.05–1.02). In contrast, the results of Schmulewitz *et al.*[62] (HR: 0.8; CI: 0.7–1.0) indicated a trend for shorter hospital stays under the same circumstances; however, their results were not statistically significant.

Need for endoscopic rescue therapy

We could not identify any studies reporting the need for endoscopic rescue therapy in hemodynamically unstable GIB patients.

Risk of bias and publication bias assessment

Of the 27 studies detailing in-hospital mortality, one (4%) had a high, 13 (48%) had a moderate, and 13 (48%) had a low risk of bias. For follow-up mortality, of the 19 studies, 2 (11%) were found to be high-, 8 (42%) moderate-, and 9 (47%) low-risk studies. Of the 17 studies detailing in-hospital rebleeding, 7 (42%) were considered moderate- and 10 (58%) low-risk studies. In the case of follow-up rebleeding, of the 11 studies, 3 (27%) were considered moderate-risk and 7 (73%) low-risk studies. As for the need for surgery, one of the five included studies had low risk (20%) and four had moderate risk (80%). The four studies detailing the need for transfusion and the LOH were found to have moderate risk. The assessment result was graphically demonstrated, as shown in Supplemental Figures S7–S13. The results of the publication bias assessment are shown in Supplemental Figures S14–S16.

Discussion

Our meta-analysis and systematic review found that HI was associated with a fourfold increase in both in-hospital and 30- to 42-day mortality and the risk of rebleeding in UGIB. In the presence of HI, the need for surgery was also more than three

times higher. Moreover, all but one of the studies investigating the need for transfusion and LOH identified HI as a risk factor.

Hemorrhagic shock is a critical condition characterized by inadequate perfusion to vital organs leading to an imbalance in oxygen supply and demand.[77] It has several different consequences throughout various pathophysiological pathways. Hypovolemia results in decreased cardiac output, leading to reduced macro- and microcirculation, causing hypoxia. Hypoxia causes reduced oxygen delivery to vital organs to a certain point where it becomes impossible to meet the oxygen demand.[78] If there is a preexisting ischemic injury with compromised blood flow, the course and consequences of the disease can be even more severe. At a certain point in the progression of the disease, a switch from aerobic to anaerobic metabolism will occur, resulting in lactate acidosis. Moreover, current studies suggest that the initial lactate level could be associated with significantly worse patient outcomes. Shrestha *et al.* found that patients with elevated lactate levels (>2.0 mmol/l) on presentation were more likely to be admitted to ICU and receive red blood cell transfusion than patients with normal lactate levels, whereas Lee *et al.* found that at admission lactate level was associated with higher 30-day mortality.[79,80]

Many approaches are used in the literature to identify patients with HI/shock; however, almost all definitions were based on the initial low systolic blood pressure and/or high heart rate. These two parameters can be measured rapidly and noninvasively, without requiring any particular expertise or equipment. It can also be used in patients with impaired cognitive, mental, or critical status. Pre-endoscopic scoring, such as the Rockall or Glasgow-Blatchford scores, which are widely used in clinical practice to determine the severity of UGIB, also includes signs of HI, together with other risk factors.[81,82] However, based on the results of our study, only the two parameters mentioned above at presentation can predict a fourfold increase in the odds of in-hospital mortality and rebleeding in acute GIB.

Based on our result, initial resuscitation and stabilization of HI in acute GIB are crucial to prevent the development of the investigated outcomes. However, many questions about these patients' initial care still need to be clarified. There is still uncertainty regarding the optimal rate of fluid resuscitation (aggressive *versus* restrictive), the use of vasopressors, and the optimal type of fluid therapy in the guidelines. Recent meta-analyses suggest that the availability and the use of different endoscopic techniques could also impact the outcomes of the bleeding episode.[83,84] The European Society of Gastrointestinal Endoscopy (ESGE) Guideline recommends waiting at least 6 h after the development of UGIB before performing an endoscopy.[4] The recommendation is based on a prospective Danish cohort study that detected worse patient outcomes in case of too early endoscopy in hemodynamically unstable patients, such as higher in-hospital mortality rate.[8] One of the possible explanations for that could be the lack of the proper correction of the hemodynamic status in a shorter time.

All identified articles reported an increased risk for in-hospital mortality in the presence of HI. However, there were studies where the chance was extremely high. Bratanic *et al.* reported significantly higher odds of in-hospital mortality in PUB, OR: 29.00 (CI: 2.49–337.18). One of the possible explanations behind it could be that they only included patients with a high risk of bleeding, and the initial endoscopy was performed in 4 h.[39] Likewise, Chaabane *et al.* found higher odds of in-hospital mortality (OR: 19.70; CI: 6.43–60.32). Their patients also had an emergency gastroscopy, and the definition used for HI was stricter: a systolic blood pressure <90 mmHg.[41] On the other hand, Branicki *et al.*[20] and Ishikawa *et al.*[48] also reported a higher tendency for in-hospital mortality in the presence of HI (OR: 1.96; CI: 0.92–4.17 and OR: 11.93; CI: 0.65–219.99, respectively); however, their results were not significant. Branicki *et al.* used a less exact definition for GIB, that is, the presence of hematemesis or melena confirmed by the medical staff. Ishikawa *et al.* included patients only who underwent surgery for PUB, meaning a high-risk population.

Strengths of the study

This study is the first meta-analysis and systematic review quantifying HI as a risk factor for developing the most relevant adverse end points of GIB. A rigorous methodology was used to

identify all relevant studies. We also investigated the major bleeding types separately, with subgroup analyses in the case of UGIB.

Limitations of the study

Despite all the strengths, this study had some limitations too. First, in certain analyses, there was considerable statistical heterogeneity. The reason behind it could be the clinical heterogeneity across studies, for example, the difference in defining HI or the source of bleeding. Second, some of the included cohort studies were retrospective analyses. Finally, in some of the included outcomes, the risk of bias was moderate or high.

Implications for practice and research

Based on our results, patients presenting with HI should be identified and treated as proactively as possible. A unified definition of HI/shock should be integrated into clinical practice. Moreover, high-quality RCTs are needed to investigate the initial resuscitation of these patients. Finally, further prospective cohort studies should investigate the risk for initial HI, looking for modifiable factors.

Conclusion

We can conclude that hemodynamically compromised patients have increased odds of the clinically most relevant end points of GIB, including a fourfold increase in in-hospital mortality. Therefore, early resuscitation and stabilization of these patients are crucial to improve survival.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Edina Tari: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft.

Levente Frim: Conceptualization; Formal analysis; Investigation; Visualization; Writing – review & editing.

Tünde Stolcz: Conceptualization; Formal analysis; Writing – review & editing.

Brigitta Teutsch: Conceptualization; Investigation; Methodology; Validation; Writing – review & editing.

Dániel Sándor Veres: Data curation; Formal analysis; Writing – review & editing.

Péter Hegyi: Conceptualization; Writing – review & editing.

Bálint Erőss: Conceptualization; Supervision; Validation; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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