

UNDERRECOGNIZED RISK FACTORS IN ACUTE GASTROENTEROLOGICAL CONDITIONS REQUIRING ENDOSCOPIC INTERVENTION

Ph.D. Thesis Booklet

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1. Introduction

1.1. Overview of the topic

Acute gastrointestinal conditions often require urgent endoscopic intervention, where outcomes are strongly influenced by patient-related and anatomical risk factors. Endoscopic retrograde cholangiopancreatography (ERCP) and acute gastrointestinal bleeding (GIB) represent high-risk clinical settings in which early recognition of such factors is essential for optimizing endoscopic decision-making.

1.2. What is the problem to solve?

Although parameters such as papilla morphology and hemodynamic instability (HI) are readily assessable factors, they are rarely integrated into structured risk stratification or procedural planning. Consequently, their prognostic and procedural relevance is often not fully incorporated into clinical decision-making.

1.3. What is the importance of the topic?

Both ERCP and acute GIB carry substantial risks of adverse outcomes, and insufficient early risk stratification

may contribute to treatment failure or procedure-related complications. Identifying and standardizing simple, clinically meaningful risk factors may support safer and more individualized endoscopic care.

1.4. What would be the impact of our research results?

By synthesizing evidence on papilla morphology in ERCP and HI in GIB, this work aims to clarify their relevance as clinically applicable risk factors in acute endoscopic settings. The results may contribute to a more structured, evidence-based approach to risk stratification and procedural planning, with the potential to improve patient outcomes and enhance procedural safety.

2. Objectives

2.1. Study I. – Morphology of the papilla can predict procedural safety and efficacy of ERCP: a systematic review and meta-analysis

We assessed the clinical relevance of papilla morphology in ERCP by examining its association with procedural difficulty and post-ERCP adverse events. We examined whether specific papilla types serve as anatomical risk factors predisposing to less favorable ERCP outcomes.

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

We evaluated the prognostic role of HI at presentation in acute GIB by examining its association with key clinical outcomes. We specifically assessed whether HI is associated with increased risks of mortality, rebleeding, and other adverse events, indicating worse short- and medium-term prognosis.

3. Methods

Two independent systematic reviews and meta-analyses were conducted in accordance with the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.

The protocols were prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifiers CRD42021285727 and CRD42022360894.

3.1. Search strategy

MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched from inception to the latest available date without restrictions. Search terms were tailored to each study, focusing on papilla morphology and ERCP in Study I, and on gastrointestinal bleeding and HI in Study II. Additional relevant records were identified through reference and citation screening.

3.2. Eligibility criteria

3.2.1. Study I

Eligibility was defined using the condition–context–population (CoCoPop) framework and included adult patients undergoing ERCP with a native papilla. Studies reporting outcomes related to cannulation performance and post-ERCP adverse events across different papilla morphologies were eligible.

3.2.2. Study II

Eligibility was defined using the population–exposure–outcome (PEO) framework and included adult patients with gastrointestinal bleeding, comparing outcomes in those with and without HI at presentation. Clinically relevant outcomes such as mortality and rebleeding were evaluated across different bleeding locations.

3.3. Study selection and data extraction

3.3.1. Study I

Records identified through the systematic search were screened at title–abstract and full-text level, and data were extracted on study characteristics, papilla morphology categories, and ERCP-related outcomes. Papilla

morphology was classified primarily according to the Haraldsson system.

3.3.2. Study II

Records were screened using the same procedure, and data were extracted on study and patient characteristics, bleeding source, hemodynamic status at presentation, and reported outcomes.

3.4. Risk of bias and quality of evidence assessment

3.4.1. Study I

The risk of bias was evaluated using the Joanna Briggs Institute Critical Appraisal Checklist and the overall certainty of evidence was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

3.4.2. Study II

The risk of bias for each outcome was evaluated using the Quality in Prognostic Studies tool.

3.5. Data synthesis and analysis

3.5.1. Study I

Pooled event rates with 95% confidence intervals (CIs) were calculated using random-effects meta-analysis, and outcomes were compared across papilla morphology types, with heterogeneity assessed using the I^2 statistic.

3.5.2. Study II

Pooled odds ratios with 95% CIs were calculated using a random-effects model to compare outcomes in patients with and without HI, and subgroup analyses were performed according to the source of bleeding.

4. Results

4.1. Study I

From the 6,952 identified records, 17 studies were included in the review and 14 in the meta-analysis.

4.1.1. Quantitative synthesis

4.1.1.1. Difficult cannulation

Nine studies reported difficult cannulation, of which eight were included in the meta-analysis. In analyses using the Haraldsson classification, type I papillae showed a lower rate (26%) compared with other types, with a trend toward significance ($p = 0.075$). When all classifications were pooled, the difference became statistically significant ($p = 0.019$).

4.1.1.2. Cannulation failure

Eight studies reported cannulation failure. Using the Haraldsson classification, no significant differences were detected ($p = 0.262$). When all studies were pooled, the difference became significant ($p = 0.047$), with the highest rate in type II (8%) and the lowest in type I (3%).

4.1.1.3. Post-ERCP pancreatitis

Across nine studies (eight in the meta-analysis), type II papillae showed a higher rate of post-ERCP pancreatitis (11%) in Haraldsson-based analyses ($p = 0.044$), while pooled analyses using other systems showed a similar, but non-significant trend ($p = 0.103$).

4.1.1.4. Post-ERCP bleeding

Six studies reported bleeding outcomes, and no significant differences were observed between papilla types in any model ($p = 0.859$ and $p = 0.808$).

4.1.2. Qualitative synthesis

Type I papillae were consistently associated with shorter cannulation time and fewer cannulation attempts, whereas longer cannulation time and a higher number of cannulation attempts were more frequently reported in type II and type IV papillae. Evidence on perforation and infection was limited.

4.1.3. Risk of bias and certainty of evidence

Most studies showed a low risk of bias, and no publication bias was detected. However, the overall certainty of

evidence was low to very low due to the observational study designs.

4.2. Study II

From 11,583 screened records, 62 studies were included in the qualitative synthesis and 39 in the meta-analysis.

4.2.1. Mortality

4.2.1.1. In-hospital mortality

A total of 27 studies assessed the association between HI and in-hospital mortality in upper gastrointestinal bleeding (UGIB), of which 22 were included in the meta-analysis. Patients presenting with HI had markedly increased odds of in-hospital mortality (OR 5.48; CI 3.99–7.52; $I^2 = 74\%$). This association remained significant in studies defining HI as systolic blood pressure (SBP) ≤ 100 mmHg and/or pulse rate ≥ 100 /min (OR 4.14; CI 2.47–6.94; $I^2 = 67\%$). Findings from additional non-pooled studies were consistent with these results.

4.2.1.2. Follow-up mortality (30–42 days)

Follow-up mortality was evaluated in 19 studies, of which 10 were included in the meta-analysis. HI was associated with increased 30–42-day mortality (OR: 4.15; CI: 3.18–5.42; $I^2 = 68\%$), and this association remained significant in studies defining HI as SBP ≤ 100 mmHg and/or pulse rate ≥ 100 /min (OR 4.03; CI 2.68–6.05; $I^2 = 58\%$).

4.2.2. Rebleeding

4.2.2.1. In-hospital rebleeding

In-hospital rebleeding was investigated in 17 studies, of which 11 UGIB studies were included in the meta-analysis. These analyses demonstrated higher odds of rebleeding in patients with HI (OR 3.68; CI 2.24–6.50; $I^2 = 91\%$). In studies applying the SBP ≤ 100 mmHg and/or pulse rate ≥ 100 /min definition of HI, the association remained significant (OR 3.92; CI 1.80–8.55; $I^2 = 94\%$).

4.2.2.2. Follow-up rebleeding (30–42 days)

Eight studies assessed 30–42-day rebleeding, of which four UGIB studies were included in the meta-analysis, showing an increased odds of rebleeding in hemodynamically unstable patients (OR 4.12; CI 1.83–

9.31; $I^2 = 39\%$). Comparable estimates were observed in studies using the same $SBP \leq 100$ mmHg and/or pulse rate ≥ 100 /min definition of HI (OR 4.13; CI 1.11–15.37; $I^2 = 0\%$).

4.2.3. Other outcomes

Across five studies, HI was associated with a higher need for surgical intervention in UGIB (OR 3.65; CI 2.17–6.14), with similar trends observed in lower GIB. Two studies reported a greater need for transfusion in unstable UGIB patients (OR 3.57; CI 2.60–5.00 and OR 3.42; CI 2.73–4.28). Evidence regarding the length of hospital stay was limited and inconsistent, and no studies reported the use of endoscopic rescue therapy in hemodynamically unstable patients.

4.2.4. Risk of bias

Across outcomes, the risk of bias was predominantly low to moderate, with only a minority of studies judged to be at high risk. No consistent indication of publication bias was identified.

5. Conclusions

5.1. Study I.

Our findings indicate that the morphology of the major papilla is associated with ERCP outcomes and procedure-related adverse events. The rate of difficult cannulation was lower in type I papillae, whereas post-ERCP pancreatitis was more frequently observed in type II papillae. In contrast, cannulation failure rates did not differ significantly between papilla types when the Haraldsson classification was applied.

5.2. Study II.

Overall, HI is strongly associated with worse clinical outcomes in acute GIB. It is linked to a higher risk of in-hospital and short-term mortality and rebleeding, as well as an increased likelihood of requiring surgical intervention.

6. Bibliography

6.1. Publications related to the thesis:

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

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Publication: 34763940

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IF: 3.9

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Publication: 34123722

Journal subject: Scopus - Gastroenterology Rank: Q1

IF: 3.9

6.2. Publications not related to the thesis:

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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