

**INTERVENTIONAL ULTRASOUND:
ENDOSCOPIC ULTRASOUND GUIDED HEPATICOGASTROSTOMY**

Ph.D. Thesis

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"Let a man lift himself by his own Self, let him not lower himself; for the Self alone is the friend of oneself and this Self alone is its own enemy."

Bhagavad Gita Chapter 6 Verse 5

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1. LIST OF ABBREVIATIONS

AG: Antegrade-Stenting

CI: Confidence Intervals

CDS: Choledochoduodenostomy

cSEMS: Fully-covered Self-Expandable Metallic Stents

ERCP: Endoscopic Retrograde Cholangiopancreatography

EUS: Endoscopic Ultrasound Guided

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

HGAS: Hepaticogastrostomy with Antegrade

HGS: Hepaticogastrostomy

HR: Hazard Ratios

MBO: Malignant Biliary Obstruction

MINORS: Methodological index for non-randomized studies

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PS-SEMS: Partially-covered self-expandable Metallic Stents

RBO: Recurrent Biliary Obstruction

ROBINS-I: Risk of Bias in Non-randomized Studies - of Interventions

SAA: Surgically Altered Anatomy

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals:

Through the frictions created by action, my vision is to use the tools and knowledge available to me to better the human and my own condition. My mission includes bridging various disciplines in a way that meaningful relationships and shared goals give rise to meaningful endeavors and pleasant labor.



2.2. Scientometrics

Number of all publications:	3
Cumulative IF:	19.8
Av IF/publication:	6.6
Ranking (Sci Mago):	D1: 1 Q1: 2
Number of publications related to the subject of the thesis:	2
Cumulative IF:	6.8
Av IF/publication:	3.4
Ranking (Sci Mago):	Q1: 2
Number of citations on Google Scholar:	28
Number of citations on MTMT (independent):	23
H-index:	2

The detailed bibliography of the student can be found on pages 57-58.

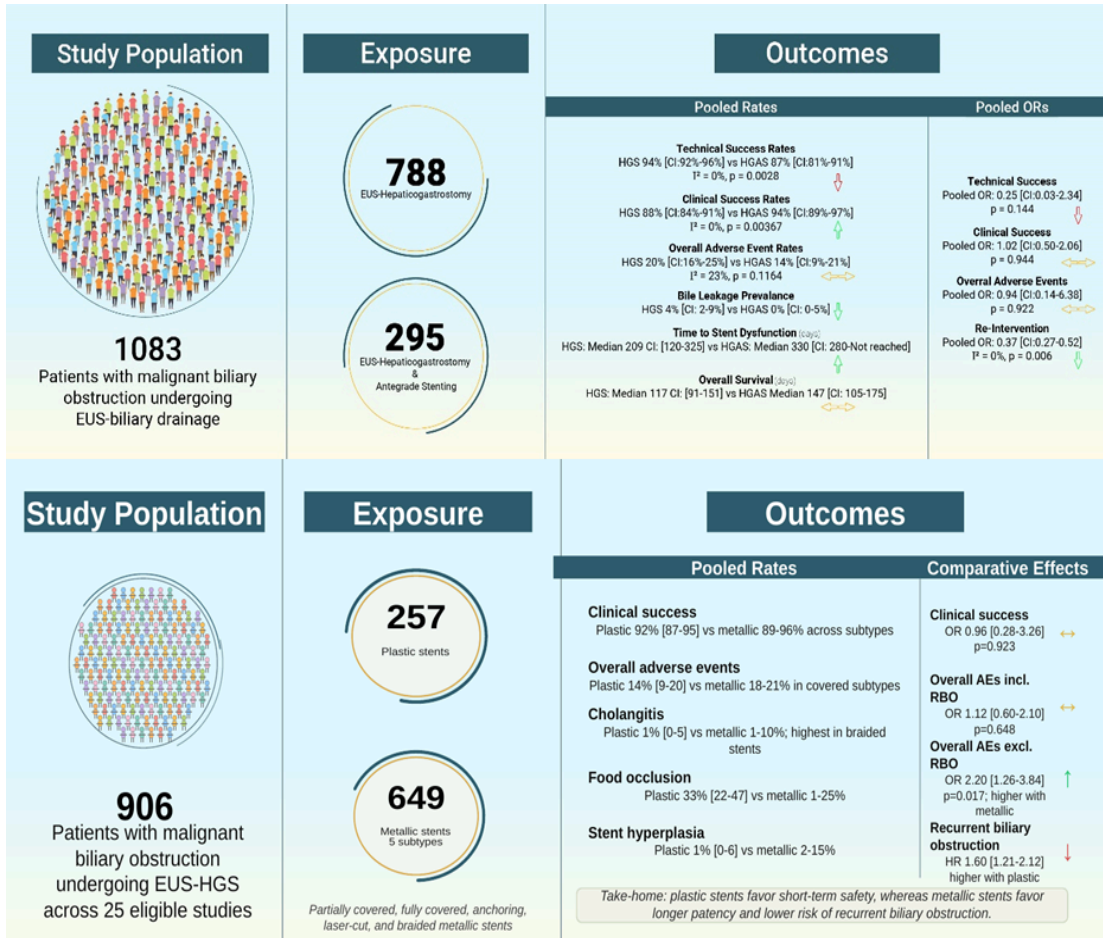
2.3. Future plans

My future plans revolve around the ups and downs of four directions. Firstly, being a knowledgeable and capable doctor in my field, as well as continuing to improve my knowledge, which should provide me with one or even two T-shaped distributions. Having a close circle that I enjoy being part of, including my family. Thirdly, continue improving on my parallel interests. Fourthly, eventually collecting the branches to converge into a thick trunk which I will be responsible of, or even if the circumstances bring it that way be an integral and part of my further future plans.

3. SUMMARY OF THE THESIS

Since the established demonstration of the piezoelectric effect by Pierre and Jacques Curie in 1880, its subsequent 30 years of lack of use due to technological constraints, as well as its consequential uptake into medical practice, ultrasound has been used in a variety of ways, from visualization of tissues to direct interventions, all the way to targeted therapy. (1) The thesis deals with one of the many ways bile can be drained from a patient in case of a lack of physiological drainage, as well as the different aspects of translational medicine. Endoscopic Ultrasound-Guided biliary drainage (EUS-biliary drainage), while it has proven itself as a non-inferior and many times superior way to drain bile, remains unknown and niche among many interventional gastroenterologists and clinicians. Our analysis sheds light on optimal ways to perform the procedure and when to use the different types of instruments available for it. At the same time, the thesis touches on technological progress, mathematical progress, and their intersection. We conclude that EUS-biliary drainage, specifically Endoscopic Ultrasound-Guided hepaticogastrostomy (EUS-HGS) has not only earned a spot in modern medical practice, but that there are optimal instruments and techniques that can be applied to extend stent patency and further alleviate re-intervention burden.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Endoscopic Ultrasound Guided Biliary Drainage

EUS-biliary drainage is an umbrella term dealing with various techniques that can be used to drain bile through non-physiological drainage routes. The concept of choledochoduodenostomy was first described by Riedel in 1888 with the first procedure being performed in 1891 by Sprengel. (2) The concept of draining intrahepatic ducts existed since 1948 with the Longmire-Dogliotti procedure (intrahepatic cholangiojejunostomy), as well as modified versions of the procedure, namely hepatogastrostomy published in 1964. (3-5) It was only until the early 2000s, with the help of ultrasound that these procedures transitioned from the dangerous open surgery, to minimally invasive ones. (6)

5.1.1. Endoscopic Ultrasound-Guided Hepaticogastrostomy: EUS-HGS

EUS-HGS is mainly used in patients with Surgically Altered Anatomy (SAA), for whom conventional endoscopic access to the papilla has been proven to be troublesome. With the use of ultrasound as guidance for proper puncture and fistula formation, an alternative route for bile drainage can be established. Although there is evidence supporting superior alternatives in patients with normal anatomy, EUS-HGS can be used not only for patients with altered anatomy but also in patients in whom cannulation has proven difficult due to ampullary tumors or invading pancreatic head tumors, hilar obstruction or in whom the bile duct is not sufficiently dilated for Endoscopic Ultrasound-Guided choledochoduodenostomy (EUS-CDS) to be a better fit.

5.1.2. What is the problem to solve?

Although EUS-HGS has established itself as a useful procedure, the bibliography is fragmented regarding the different ways to approach the procedure, as well as the individual stent types and other devices that affect patient outcomes. Therefore, the aim was to consolidate the available knowledge through the framework of meta-analytic approaches to compare the individual papers, locate areas of common and differing views, as well as summarize the quantitative and qualitative results.

5.1.3. What is the importance of the topic?

Traditionally, gastroenterology focuses on Endoscopic Retrograde Cholangiopancreatography (ERCP), with the bulk of unsuccessful cases being directed to a percutaneous approach, which is not only painful and uncomfortable for the patient but also carries a higher risk of infection. As with every new technology or procedure, a number of people need to be (re)trained to carry out the said task, which not only proves cumbersome for the doctors but for policymakers alike. Following 20 years of using the techniques, EUS-biliary drainage has already established itself as a suitable successor or complement to ERCP.

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

The results offer a guide, as well as direction for future research for those interventionists dealing with such procedures.

6. OBJECTIVES

6.1. Study I. – Hepaticogastrostomy versus hepaticogastrostomy with antegrade stenting for malignant biliary obstruction: a systematic review and meta-analysis

This study aimed to compare the effects of the addition of antegrade stenting (modified ERCP with stent insertion through the intrahepatic bile ducts instead of the Vater's papilla) on pure hepaticogastrostomy. The null hypothesis was that there is no difference in primary outcomes between the two procedures. The alternative hypothesis was that the combination of the two procedures offers better clinical outcomes.

6.2. Study II. – Plastic versus metallic stents for endoscopic ultrasound-guided hepaticogastrostomy in malignant biliary obstruction: a systematic review and meta-analysis

This study aimed to compare how outcomes such as stent dysfunction and adverse events are influenced by the different stent types used in EUS-HGS. The null hypothesis was that there is no difference in primary outcomes between the two stent types. The alternative hypothesis was that metallic stents offer higher patency with no difference in clinical outcomes.

7. METHODS

Our systematic reviews and meta-analyses are reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement (7). The Cochrane Handbook's recommendations for Systematic Reviews of Interventions Version 6.1.0 (8) and Cochrane Prognosis Methods Group (9) were followed and the review protocols were registered on PROSPERO (Study I.: *CRD42024509412*; Study II.: *CRD42024509412*;))

7.1. Literature search and eligibility criteria

We performed a systematic literature search in four databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase and Web of Science for Study I, and three medical databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, for Study II. The dates of the searches and the queries used are detailed in the original publications. (10, 11)

For Study I, patients with malignant biliary obstruction (MBO) who underwent EUS biliary drainage with HGS with or without the AGS procedure were included. Randomized controlled trials (RCTs), cohort studies, or case series with more than five patients were analyzed. Study II included patients (MBO) who underwent EUS biliary drainage with HGS with plastic or metallic stents. Randomized controlled trials (RCTs), cohort studies, or case series with more than five patients were included.

7.2. Study selection and data collection

EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) was used for the articles' selection. Two independent authors screened the publications separately for the title, abstract, and full text, and disagreements were resolved by a third author.

Two authors independently extracted data into a predefined Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA), and a third reviewer resolved the discrepancies.

The following data were collected from each eligible article: data regarding the article (first author, year of publication, DOI, country, study design, study duration, original study/data source), data regarding participants (demographics and subject

characteristics: age, sex, treatment applied, subgroups examined), data regarding outcomes for studies I and II were focused on technical success, clinical success, overall adverse events rates, re-intervention rates, time to stent dysfunction, and overall survival. As well as, clinical success, overall adverse events with and without biliary obstruction, and recurrent biliary obstruction. Secondary outcomes were cholangitis, stent occlusion, stent migration, and hyperplasia.

7.3. Quality assessment

The "Risk of Bias In Non-randomized Studies - of Interventions" (ROBINS-I) tool was used for both studies I and II, included in the direct comparative meta-analysis, and the "Methodological index for non-randomized studies" (MINORS) tool for the studies included in the proportional meta-analysis. We followed the recommendation of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup and used GRADEPro Guideline Development Tool for visualization (12, 13).

7.4. Data synthesis and analysis

A random-effects model was used to pool effect sizes. Pooled Odds Ratios (OR) based on raw data were calculated using the Mantel-Haenszel method with 95% confidence intervals (CI). (14) Small study publication bias was assessed by visual inspection of funnel plots and calculating modified Egger's test p-values. A possible small-study bias was assumed if the p-value was less than 10%.

Two main kinds of analyses for pooling proportions were performed. Classical two-level meta-analyses were conducted for pooling when different studies were included. If more results were available in separate categories (subgroups) in the same study, a three-level model was used. For time-to-event data, the hazard ratio (HR) was used with a 95% confidence interval (CI) as the primary measure of effect between the two groups of interest: Plastic as the experimental group and MS as the control group. The HR was calculated for the Plastic vs. MS groups. The classical random-effects meta-analysis method and the IPD-based Cox hazard model with Gaussian random effects were used to calculate the pooled HRs. Additionally, as a secondary measure, the survival probabilities at specific time points were estimated and pooled using a 3-level

model ("multilevel") to indirectly compare the survival rates in the groups. An estimation for distribution-free pooled survival curves was also performed using the method implemented by Pandey ("curve estimate"). The findings were summarized and presented in tables, on forest plots, Kaplan-Meier (KM) plots (using KM estimates), and estimated survival curves. (15)

All statistical analyses were performed using R with *the metaSchwarzer 2023, v6.2.1 package* for basic meta-analysis calculations and plots, the *metafor Viechtbauer 2023, v4.2.0 package* for three-level models, the *IPDfromKM v0.1.10* and *metaSurvival v0.1.0 packages* for summary survival curves, and the *dmetar package* for additional influential analysis calculations and plots. (16-20)

8. RESULTS

8.1. Study I. Hepaticogastrostomy versus hepaticogastrostomy with antegrade stenting for malignant biliary obstruction: a systematic review and meta-analysis

The results of our first study suggest that the combination of EUS-HGS with EUS-Antegrade Stenting (EUS-AG), named Hepaticogastrostomy with Antegrade stenting (HGAS) provides higher stent patency with fewer needs for re-intervention while maintaining similar bilirubin reduction and overall survival rates. Technical success was reduced, with no strong signs of a statistically significant effect.

8.1.1 Pooled studies that compared the two procedures directly:

Technical success between HGS and HGAS showed an OR = 0.38 (CI: 0.07–2.00), $p = 0.179$. Clinical success showed an OR = 1.02 (CI: 0.50–2.06), $p = 0.944$. The overall adverse events showed an OR = 1.09 (CI: 0.30–3.94), $p = 0.867$. For re-intervention, comparison of HGS and HGAS showed an OR = 0.37 (CI: 0.27–0.52), $p = 0.006$.

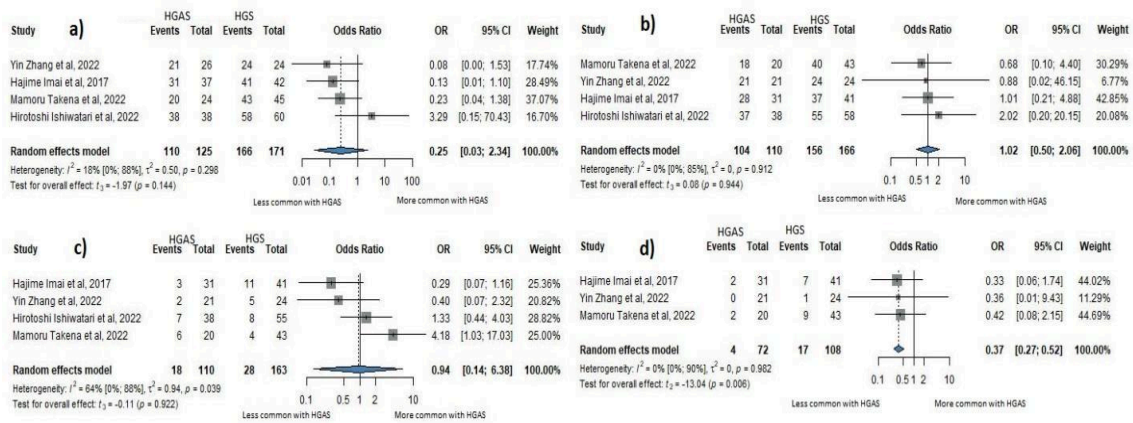


Figure 1. Summary figure for direct comparisons of HGS and HGAS: a) Technical success tends to be more common during HGS than HGAS, but not reaching significance. (21-25) b) Clinical success defined as at least 40% bilirubin decrease within 1 month of the procedure not differing between the two procedures. (21-25) c) Overall adverse events not showing difference between the two procedures. (21-25) and d) Re-intervention odds were significantly lower between the procedures, favouring HGAS. (21, 24, 25) OR: Odds Ratios, CI: Confidence Interval, HGS: Hepaticogastrostomy, HGAS: Hepaticogastrostomy with Antegrade Stent

8.1.2 Pooled studies that only had one group in each:

The pooled technical success was 94% (CI: 92%–96%) for HGS and 89% (CI: 83%–93%) for HGAS, $p=0.00273$. The pooled clinical success was 88% (CI: 84%–91%) for HGS and 94% (CI: 89%–97%) for HGAS, $p=0.0367$.

Pooled adverse events were 20% (CI: 16%–25%) for HGS and 14% (CI: 9%–20%) for HGAS, $p=0.0728$. Bile leakage in the HGS group had a 4% prevalence (CI: 2%–9%), whereas the prevalence in the HGAS group was calculated at 0% (CI: 0%–5%).

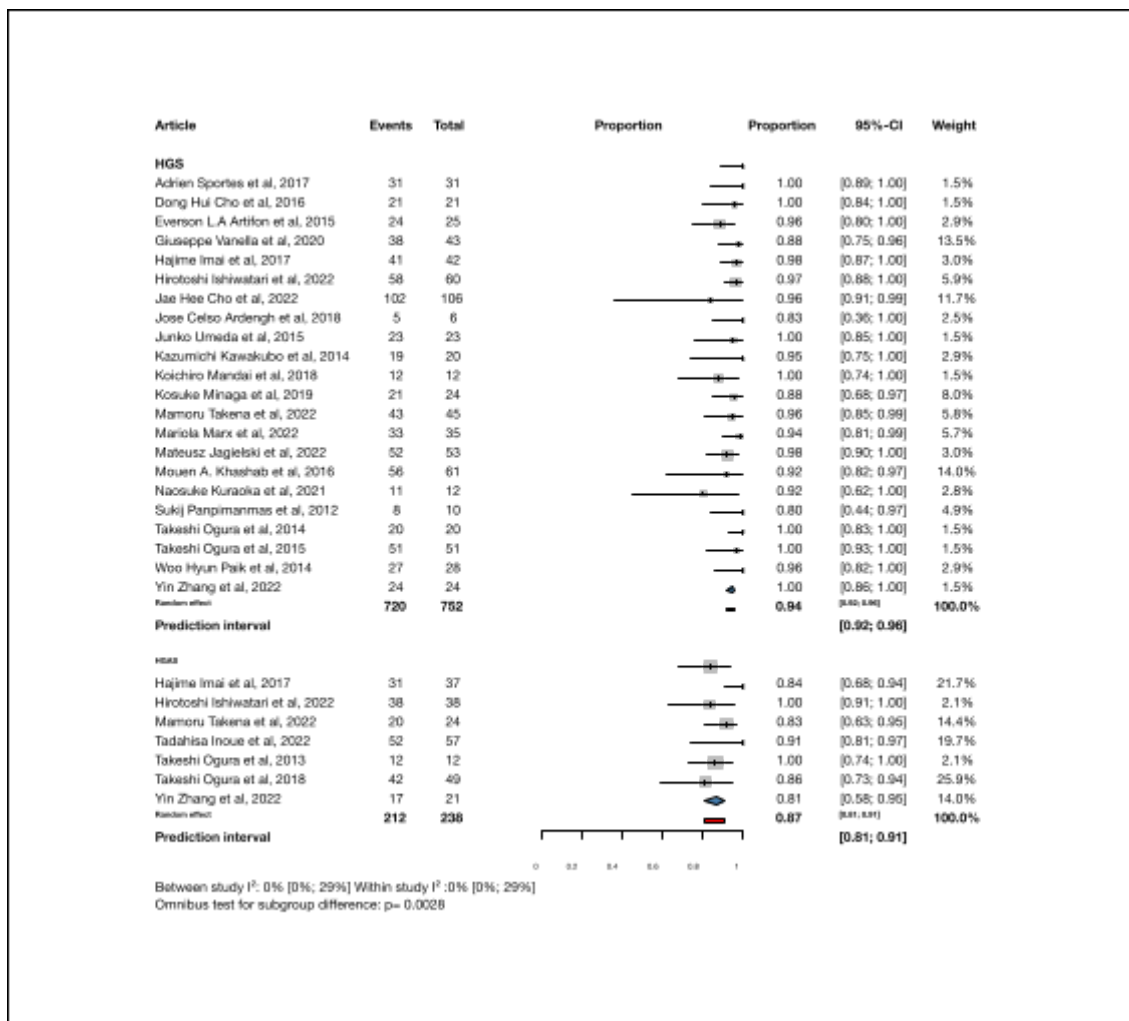


Figure 2. Pooled technical success with (HGAS) and without (HGS) antegrade stenting showing no difference between the two procedures. (21-44) CI: Confidence Interval, HGS: Hepaticogastrostomy, HGAS: Hepaticogastrostomy with Antegrade Stent

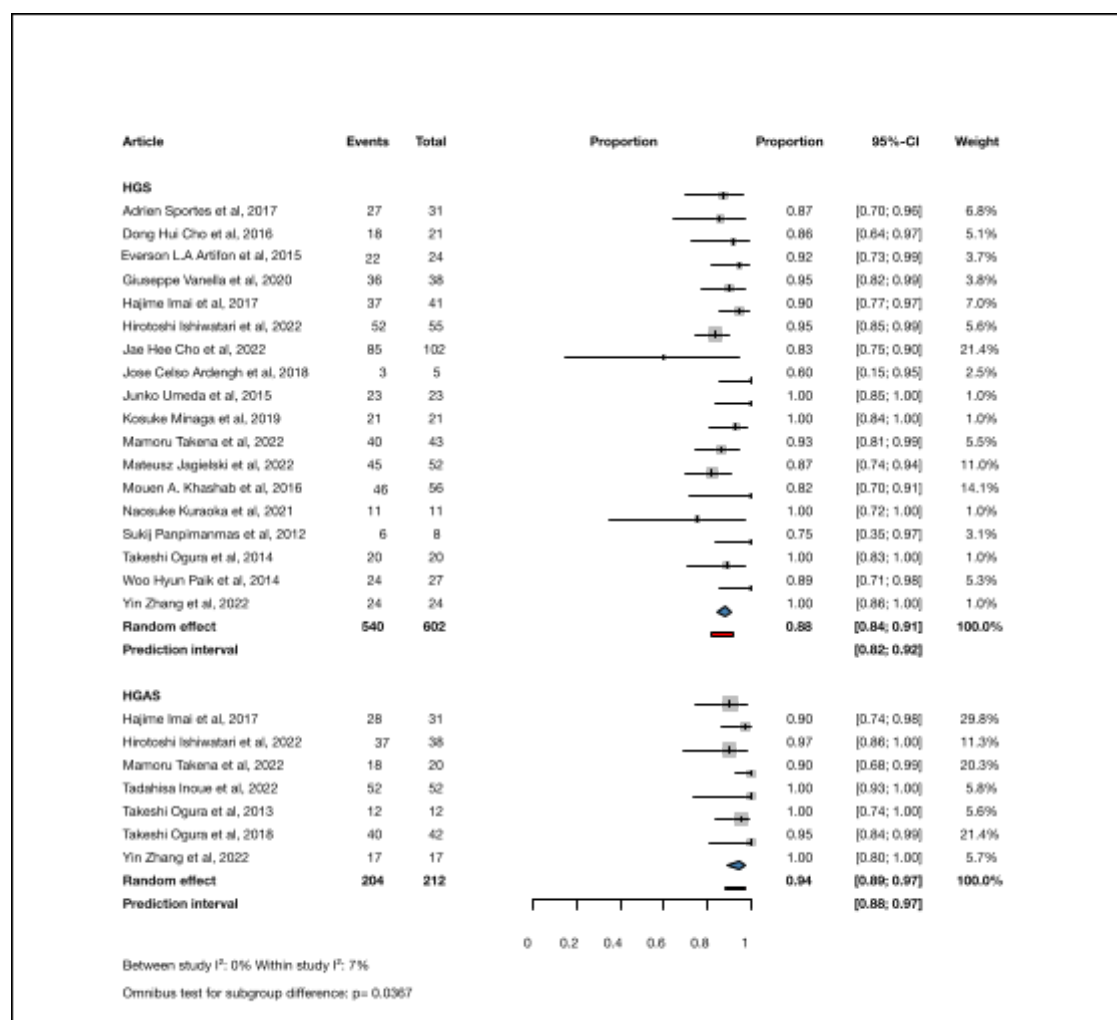


Figure 3. Pooled clinical success with (HGAS) and without (HGS) antegrade stenting showing no difference between the two procedures. (21, 23-28, 30, 32, 33, 36, 38, 40-44) CI: Confidence Interval, HGS: Hepaticogastrostomy, HGAS: Hepaticogastrostomy with Antegrade Stent

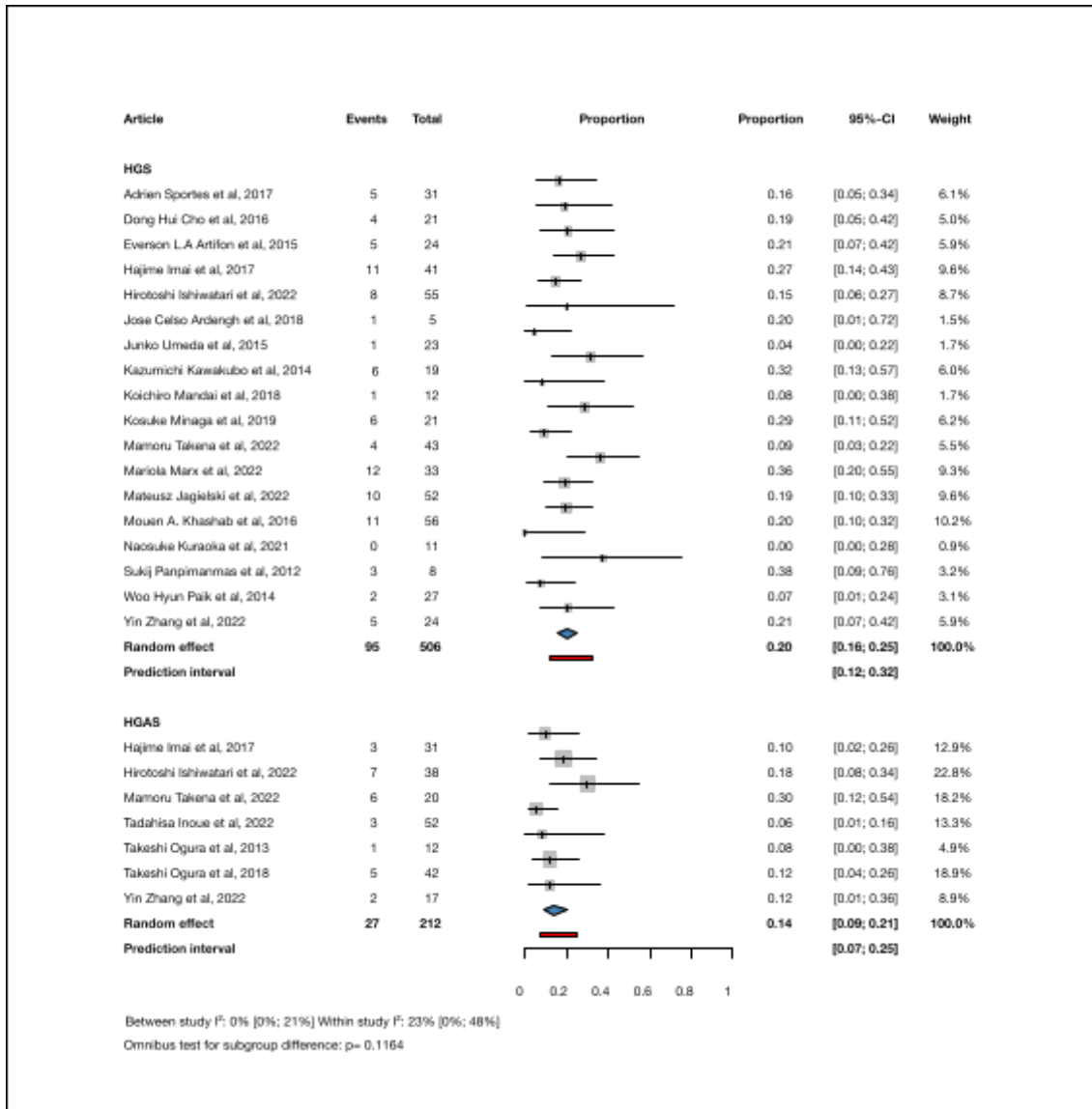


Figure 4. Pooled overall adverse events with (HGAS) and without (HGS) antegrade stenting showing no difference between the two procedures. (21-23, 25-38, 41-47) CI: Confidence Interval, HGS: Hepaticogastrostomy, HGAS: Hepaticogastrostomy with Antegrade Stent

8.1.3 Individual patient data from Kaplan-Maier plots:

Time to stent dysfunction was 217 (CI: 120–308) days for HGS and 333 (CI: 280–not reached) days for HGAS. The overall survival for HGS and HGAS was 117 (CI: 94–147) and 140 (CI: 105–170) days, respectively. The results indicate that while bile draining procedures do not increase survival, the addition of AGS to HGS leads to a significantly higher stent patency. Such effect is positive from a patient and clinician point of view since a higher stent patency directly increases quality of life, decreases re-intervention rates and allows this patient population to spend less time in the hospital due to recurrent biliary obstruction.

Figure 5. Summary figure of survival curves: a) Time to stent dysfunction was significantly higher for HGAS compared to HGS b) Overall survival did not differ between the two procedures. (21-23, 25, 37)

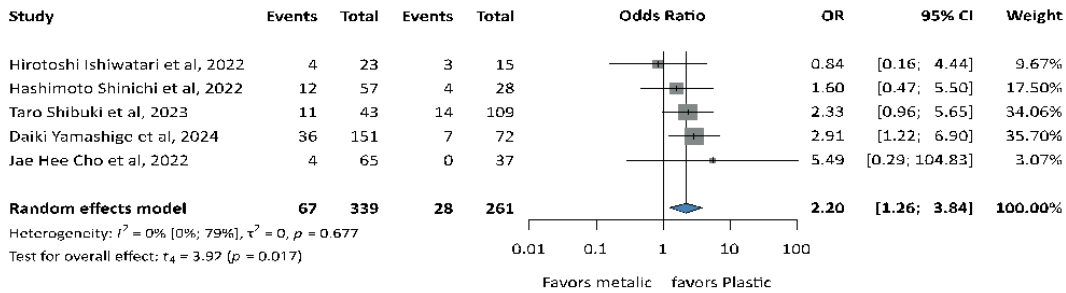
8.2. Study II. Plastic versus metallic stents for endoscopic ultrasound-guided hepaticogastrostomy in malignant biliary obstruction: a systematic review and meta-analysis

The results of the second study suggest that although adverse events are more commonly encountered in the metallic stent group than plastic ones, the time to recurrent biliary obstruction is significantly higher for metallic stents. Individual stent types appear to have different prevalence of adverse events, allowing for a path to partial population-specific care. For example, patients with previous history of cholangitis or at higher risk of it might gain from avoiding braided-metallic stents given the higher proportion of cholangitis encountered in this group.

8.2.1. Individual patient data of RBO and two-group studies:

The overall adverse events without RBO showed a significant difference favoring plastic stents (OR: 2.20, CI: 1.26–3.84, $p = 0.017$, I^2 : 0%, CI: 0%–79%). However, plastic stents showed a higher hazard of RBO (HR: 1.603, CI: 1.211–2.122, $p = 0.001$).

a)



b)

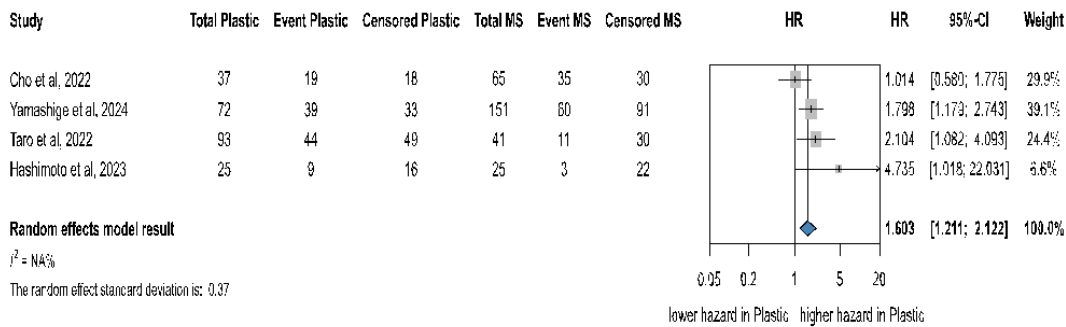


Figure 6. Summary figure: a) Overall adverse events without recurrent biliary obstruction favored plastic stents over metallic stents in HGS. (23, 28, 48-50) b) Individual patient data for recurrent biliary obstruction showing that metallic stents have a higher patency than plastic. (23, 28, 48, 49) OR: odds ratio, HR: hazard ratio, CI: confidence interval, MS: Metallic Stents

8.2.2. Pooled results from two- and one-group studies:

From seven studies, the pooled overall adverse event proportion without biliary obstruction was 12% (CI: 7%–19%) for plastic stents. From six studies, 15% (CI: 8%–24%) for PCSEMS (partially covered self-expandable metallic stents). Three studies showed 20% (CI: 10%–37%) for cSEMS (covered self-expandable metallic stents). From seven studies for PCSEMS with anchoring, the pooled adverse proportion was 12% (CI: 7%–21%). The rates were 8% (CI: 1%–27%) for metallic laser-cut stents and 10% (CI: 5%–17%) for metallic-braided stents; however, only one study was included for each.

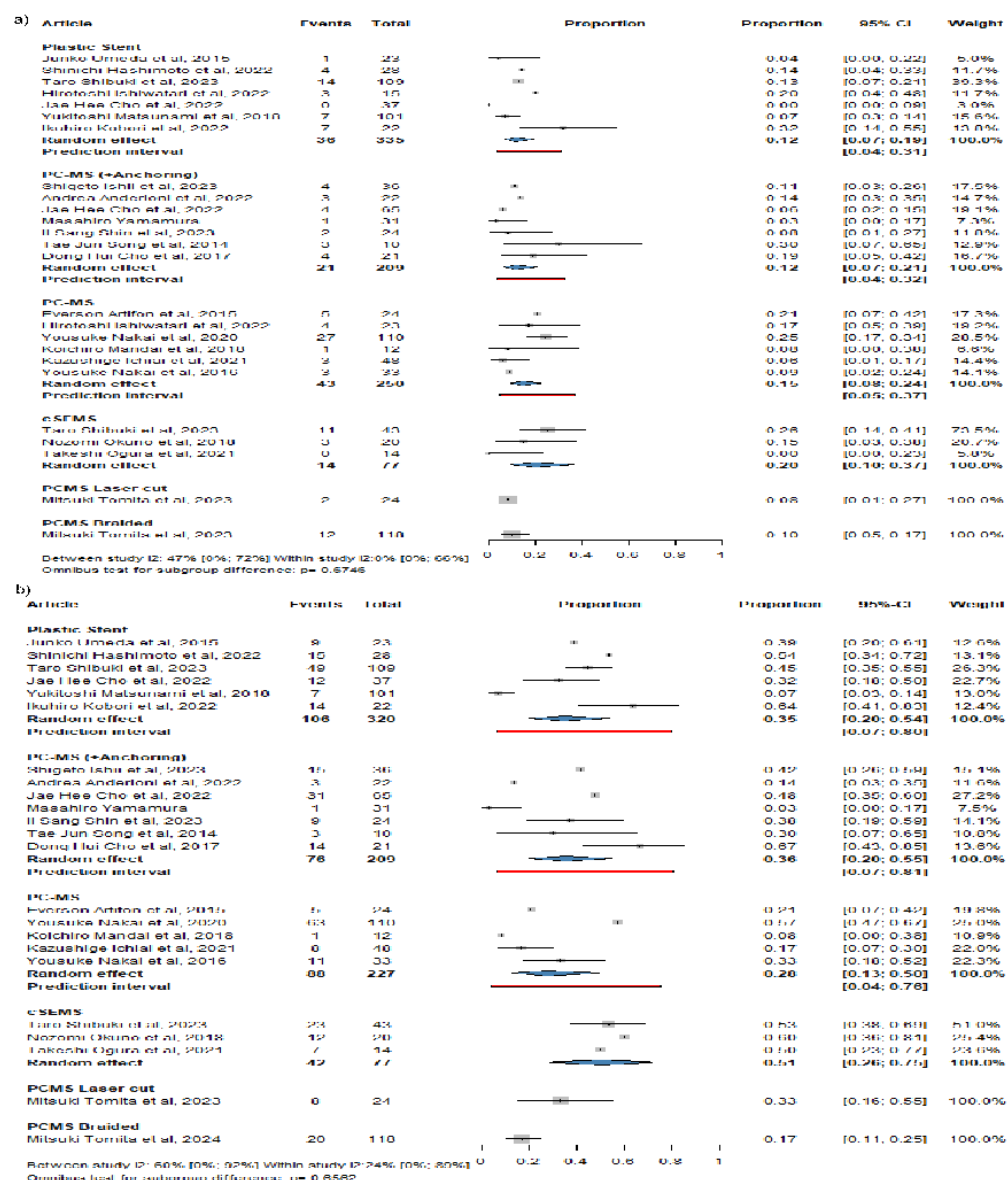


Figure 7. Summary figure of pooled overall adverse events: **a)** Without recurrent biliary obstruction showed no difference between individual stent types. **b)** with recurrent biliary obstruction showed no difference between plastic and different metallic stent types. (23, 27, 28, 34, 43, 45, 46, 48, 49, 51-59) PCSEMS: partially covered self-expandable metal stents, cSEMS: fully-covered self-expandable metal stents CI: confidence interval

8.2.3. Pooled results of outcomes leading to RBO:

Plastic stents had zero events for cholangitis in 257 cases, with a pooled proportion of 1% (CI: 0%–5%). PCSEMS with anchoring also had zero events in 60 cases, yielding a proportion of 3% (CI: 0%–16%). For cSEMS, zero events were reported in 69 cases, with a proportion of 2% (CI: 0%–14%). One event was observed in 192 cases among PCSEMS, resulting in a proportion of 1% (CI: 0%–5%). Two events were reported in 39 instances for metallic laser-cut stents, 5% (CI: 1%–23%), and 19 events in 197 cases for metallic-braided stents (10%, CI: 5%–19%).

Stent occlusion was observed in 75 of 257 cases with plastic stents, yielding a pooled proportion of 31% (CI: 23%–40%). For cSEMS, 17 events were reported in 69 cases, corresponding to 25% (CI: 14%–40%). For PCSEMS with anchoring, 7 events occurred in 60 cases, resulting in a proportion of 12% (CI: 5%–27%). In PCSEMS, 11 events were noted among 192 cases, 6% (CI: 3%–11%). No events were reported with metallic laser-cut or metallic-braided stents, with a pooled proportion of 2% (CI: 0%–20%) and 1% (CI: 0%–5%), respectively.

For stent migration, 5 events were reported in 257 cases with plastic stents, yielding a pooled proportion of 2% (CI: 1%–6%). PCSEMS with anchoring had 0 events in 60 cases, with a proportion of 2% (CI: 0%–14%). For cSEMS, 6 events were observed in 69 cases, corresponding to a proportion of 17% (CI: 7%–35%). Among PCSEMS, 2 events occurred in 192 cases, 2% (CI: 1%–8%). No events were reported for metallic laser-cut (39 cases) and metallic-braided stents (197 cases), with pooled 2% (CI: 0%–20%) and 1% (CI: 0%–5%), respectively.

For plastic stents, hyperplasia was not observed in any of the 257 cases, with a pooled proportion of 1% (CI: 0%–5%). In PCSEMS with anchoring, 9 events were reported in 60 cases 16% (CI: 7%–31%), while PCSEMS had 31 events in 192 cases (19%, CI: 12%–31%). For cSEMS, 3 events were observed in 69 cases, 6% (CI: 2%–18%). PCSEMS had 31 events in 192 cases, 19% (CI: 12%–31%). Among metallic stents, 5 events were reported in 39 cases with laser-cut stents, 16% (CI: 6%–38%), and 4 events in 197 cases with braided stents, 3% (CI: 1%–8%).

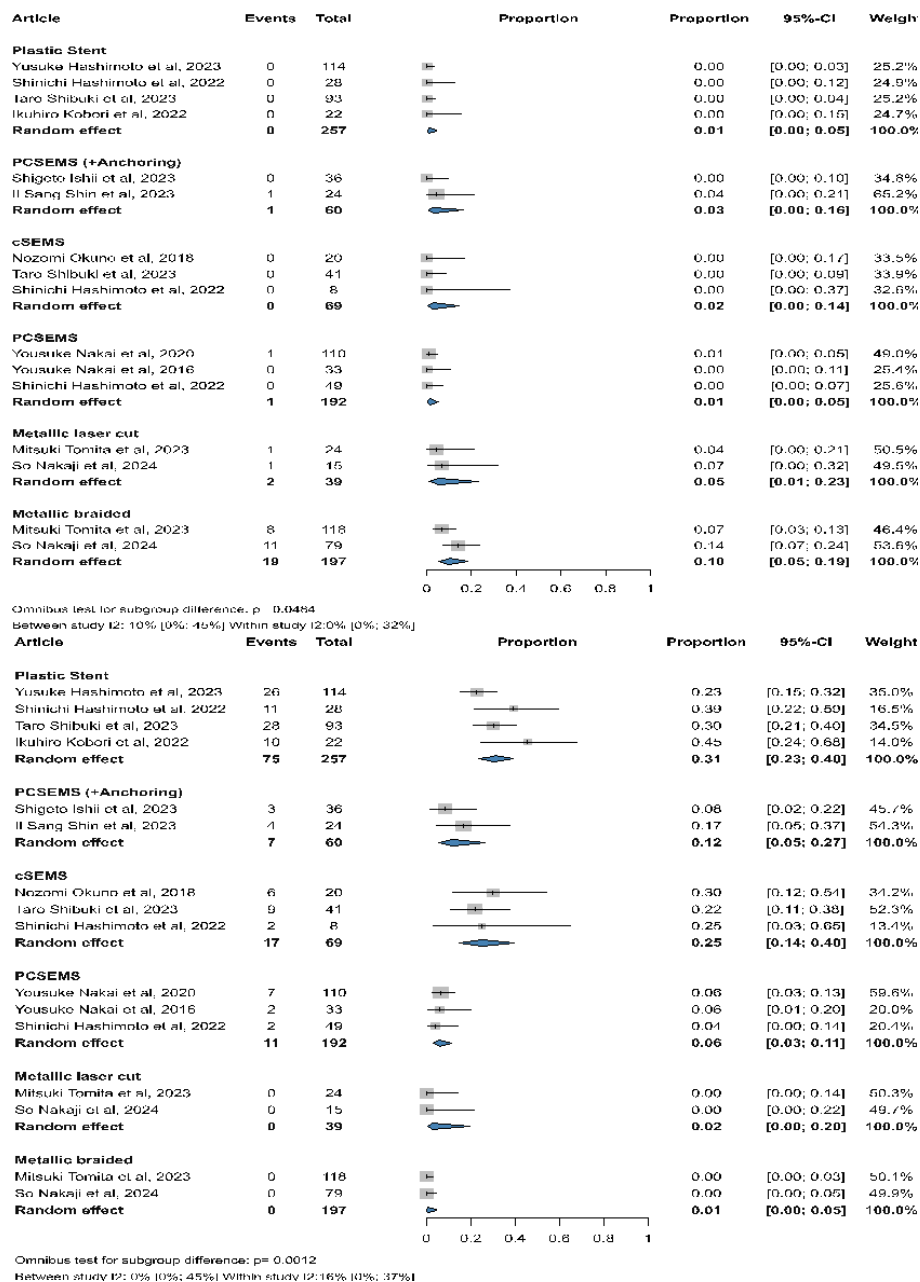


Figure 8. Summary figure of a) RBO caused by Cholangitis showed that people with braided-metallic stents are more prone to developing such infection compared to other stent types. b) RBO caused by stent occlusion showed plastic stents being more prone compared to other stent types. CI: confidence interval, PCSEMS: partially-covered self-expandable metal stents, cSEMS: fully-covered self-expandable metal stents (48, 49, 52, 55, 58, 60)

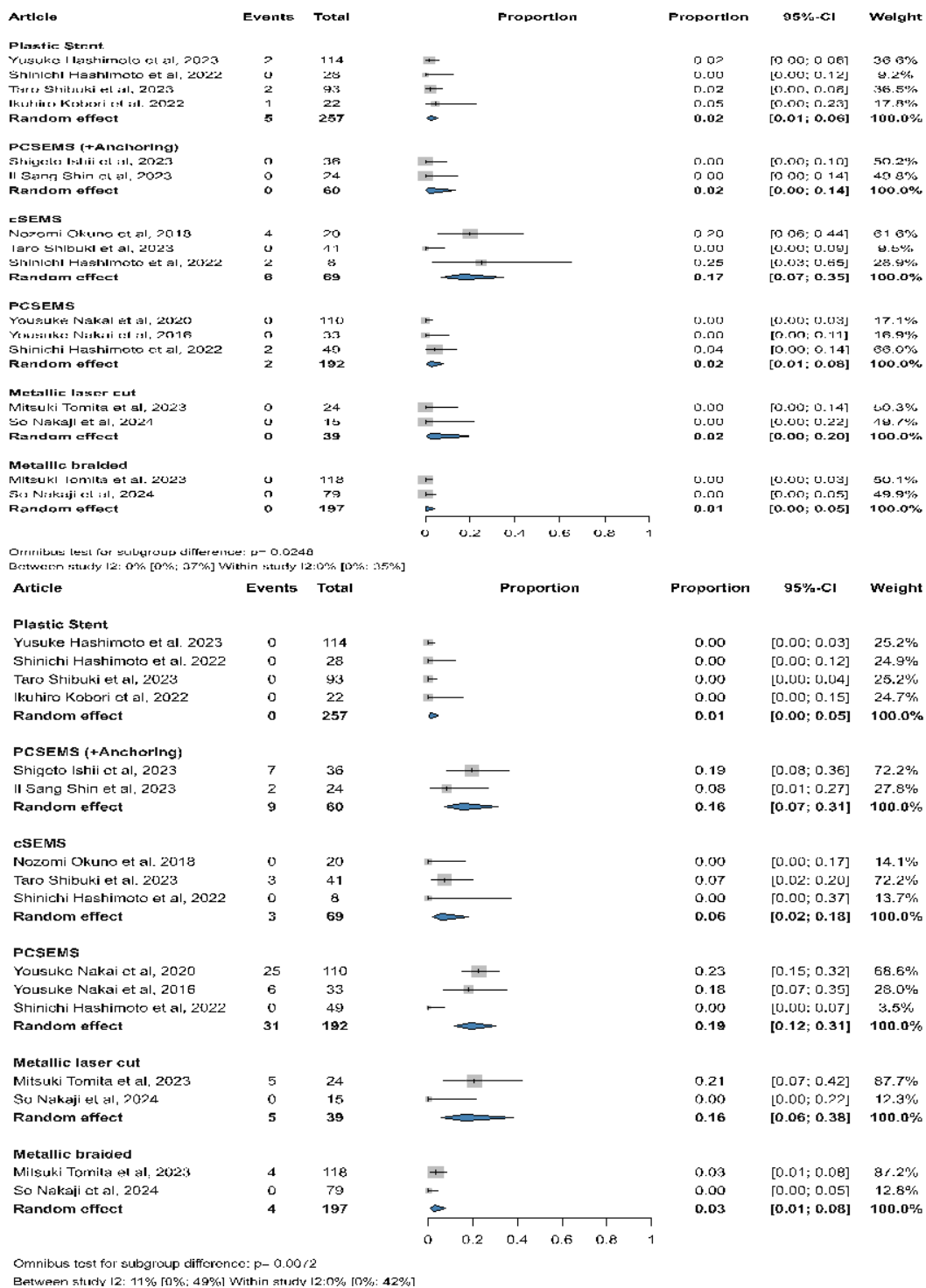


Figure 9. Summary figure: **a)** RBO caused by stent migration was more prominent in cSEMS compared to other stent types. **b)** RBO caused by stent hyperplasia was less prominent in the metallic braided and plastic stent groups compared to other stent types.

(48, 49, 52, 53, 55, 58, 61-64) CI: confidence interval, PCSEMS: partially-covered self-expandable metal stents, cSEMS: fully-covered self-expandable metal stents

8.3. Results of the qualitative analysis

Due to the inclusion of non-comparative studies, the quality of evidence of the assessed outcomes strength of evidence, namely clinical success, overall adverse events and recurrent biliary obstruction, was considered low for both studies. The strength of evidence for technical success was considered high for the first study.

8.3.1. Study I. Hepaticogastrostomy versus hepaticogastrostomy with antegrade stenting for malignant biliary obstruction: a systematic review and meta-analysis

Table 1: *Risk of bias assessment, MINORS* (methodological index for non-randomized studies)

Author (Year)	Point 1	Point 2	Point 3	Point 4	Point 5	Point 6	Point 7	Point 8	Point 9	Point 10	Point 11	Point 12	Sum
Sukij Panpimanmas et al, 2012	2	0	0	2	2	2	2						10
Adrien Sportes et al, 2017	2	2	2	2	2	2	2						14
Koichiro Mandaia et al, 2018	2	0	0	2	2	2	2						10
José Celso Ardengh et al, 2018	2	0	2	2	2	2	0						10
Takeshi Ogura et al, 2018	2		1	2	2	2	2						11
Mariola Marx et al, 2022	2		0	1	2	2	2						9
Hirotoishi Ishiwatari et al, 2022	1	2	2	1	2	1	0	0	2	0	0	2	13
Hajime Imai et al, 2017	2	1	2	1	2	1	0	0	0	0	0	2	11
Everson L.A. Artifon et al, 2015	2	0	1	1	2	2	0						8

Author (Year)	Point 1	Point 2	Point 3	Point 4	Point 5	Point 6	Point 7	Point 8	Point 9	Point 10	Point 11	Point 12	Sum
Junko Umeda et al, 2015	2	2	1	2	2	2	0						11
Dong Hui Cho et al, 2016	0	2	0	2	2	2	0						8
Mateusz Jagielski et al, 2021	0	2	0	2	2	2	0						8
Naosuke Kuraoka et al, 2021	0	2	0	2	2	2	0						8
Kazumichi Kawakubo et al, 2014	2	0	0	2	2	2	0						8
Mouen A. Khashab et al, 2016	2	2	0	2	2	2	1						11
Kosuke Minaga et al, 2019	2	0	0	2	2	2	0						8
Takeshi Ogura et al, 2013	2	2	0	2	2	2	0						10
Yin Zhang et al, 2021	2	0	1	2	2	2	0	0	0	2	0	2	13
Jae Hee Cho et al, 2022	0	0	1	2	2	2	0						7
Tadahisa Inoue et al, 2022	2	2	1	0	2	0	0						7
Mamoru Takenaka et al, 2022	2	2	1	2	2	2	0	0	2	0	0	2	13
Giuseppe Vanella et al, 2020	2	2	1	2	2	2	2						13
Woo Hyun Paik et al, 2014	2	0	2	2	2	2	2						12

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Hajime Imai et al, 2017	+	+	+	+	+	+	+	+
Hirotooshi Ishiwatari et al, 2022	+	+	+	+	+	+	+	+
Mamoru Takeda et al, 2022	+	+	+	+	×	×	×	×
Yin Zhang et al, 2022	+	+	+	+	+	+	+	+

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
× Serious
+ Low

Figure 10: *Risk of bias assessment, ROBINS-I (Risk of bias in non-randomized studies of Interventions)*

8.3.2. Study II. Plastic versus metallic stents for endoscopic ultrasound-guided hepaticogastrostomy in malignant biliary obstruction: a systematic review and meta-analysis

Table 2: Risk of bias assessment, MINORS (methodological index for non-randomized studies)

Author (Year)	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Sum
Yousuke Nakai et al, 2016	2	2	0	2	1	2	1	0					10
Yukitoshi Matsunami et al, 2018	2	2	0	2	1	2	1	0					10
Taro Shibuki et al, 2022	2	2	0	2	1	2	1	0	2	2	2	2	16
Yusuke Hashimoto et al, 2023	2	2	0	2	1	2	1	0					10
Tae Jun Song et al, 2014	2	2	2	2	1	2	1	0					12
Dong Hui Cho et al, 2017	2	2	2	2	1	2	1	0					12
Hirotoishi Ishiwatari et al, 2022	2	2	2	2	1	2	1	0	1	2	2	2	17
Everson L.A Artifon et al, 2015	2	2	2	2	1	2	1	2					14
Jae Hee Cho et al, 2022	2	2	2	2	1	2	1	2	2	2	2	2	22
Mitsuki Tomita et al, 2023	2	2	0	2	1	2	1	0					10
Yousuke Nakai et al, 2020	2	2	0	2	1	2	1	0					10
Junko Umeda et al, 2015	2	2	2	2	1	2	1	0					12

Author (Year)	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Sum
Masahiro Yamamura et al, 2021	2	2	2	2	1	2	1	0					12
Nozomi Okuno et al, 2018	2	2	2	2	1	2	1	2					14
Koichiro Mandai et al, 2018	2	2	0	2	1	2	1	0					10
Shigeto Ishii et al, 2023	2	2	0	2	1	2	1	0					10
Shinichi Hashimoto et al, 2022	2	2	0	2	1	2	1	0	1	0	0	2	11
James Emmanuel et al, 2020	2	2	0	2	1	2	1	0					10
Takeshi Ogura et al, 2021	2	2	0	2	1	2	1	0					10
Yuki Fujii et al, 2022	2	2	0	2	1	2	1	0					10
Andrea Anderloni et al, 2022	2	2	2	2	1	2	1	0					12
Ikuhiro Kobori et al, 2022	2	2	0	2	1	2	1	0					10
Kazushige Ochiai et al, 2021	2	2	1	2	1	2	1	0					11
Kazushige Ochiai et al, 2021	2	2	0	2	1	2	1	0					10

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Hirotoishi Ishiwatari et al, 2022	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Taro Shibuki et al, 2023	⊖	⊖	⊖	⊕	⊖	⊕	⊖	⊖
	Shinichi Hashimoto et al, 2022	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Jae Hee Cho et al, 2022	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
	Daiki Yamashige et al, 2024	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
		Domains: D1: Bias due to confounding. D2: Bias due to selection of participants. D3: Bias in classification of interventions. D4: Bias due to deviations from intended interventions. D5: Bias due to missing data. D6: Bias in measurement of outcomes. D7: Bias in selection of the reported result.							Judgement ⊖ Moderate ⊕ Low

Figure 11: Risk of bias assessment, ROBINS-I (Risk of bias in non-randomized studies of Interventions).

9. DISCUSSION

9.1. Summary of findings

For our analysis, we focused on the outcomes of EUS-HGS in case of the addition of AGS or different metallic and plastic stent types. Studies were separated based on two-groups (direct comparisons), one-group (indirect comparisons), as well as individual patient data extracted from relevant plots, namely for outcomes relating to stent patency and overall survival.

For study I, the main finding suggests that the combination of hepaticogastrostomy with antegrade stenting is better than hepaticogastrostomy alone for extending the time to stent dysfunction but not the overall survival, with a complementary decrease in re-intervention odds with no additional burden in terms of post-procedural adverse events. Even though such procedures are mostly palliative, or bridges to definitive treatment, the ability of a patient to acquire the stents within a single procedure, without having to deal with re-hospitalizations or increased adverse events associated with said procedures offers a complementary increase in quality of life, which, especially for terminally ill patients such as those with pancreatic cancer, is important not only for the patients but also for their relatives and close-circle as well.

For study II, the main findings imply that different subtypes of metallic stents, as well as plastic stents, have a plethora of ways to be used for different patient populations to fit the individual profile of patients, from those that get the stent before definitive treatment, to those that can extract more value from different stent types associated with their own needs, such as avoiding the use of braided-metallic stents to those patient populations susceptible to cholangitis.

9.2. Strengths

These meta-analyses were the first to be performed in the field; the patient population is well defined and can be regarded as homogeneous to a high degree, since most of the patients suffered from untreatable, distal malignant biliary obstruction, giving the opportunity for low to moderate heterogeneity. Moreover, the ability to use individual patient data with a high number of patients for outcomes such as time to stent

dysfunction and overall survival allows for the opportunity of having a clear picture of the effects of the different stents used and techniques performed and their effects of the above-mentioned population. Our results are indicative of clear effects as well as a clear direction for future research.

9.3. Limitations

The limitations of our study revolve but are not limited to those common to every meta-analytical calculation, mainly having to use aggregated data to draw conclusions, no additional analyses were performed to extract more detailed information from the available dataset. Given that a large number of studies were not direct group comparisons, spill-over heterogeneity from inter-procedural variabilities such as operators' skills, different procedure protocols and device used appeared as the moderate heterogeneity of some of the outcomes explored. At the same time, most of the studies used were cohort studies with very few randomized controlled trials available on the topic thus limiting the strength of evidence.

10. CONCLUSION

The thesis explores the way technologies which initially are used for military purposes penetrate into everyday life, mainly, but not limited, due to their medical applications. The progression of the presentation of a technique until its full acceptance by the professional (and general) audience is a long process that can last anywhere from 30 to 100 years. The idea to connect different bilio-enteric segments to allow for bile-load alleviation in patient populations where proper physiological bile discharge has been compromised dates to the end of the 19th century. At a similar time, Jacques and Pierre Curie provided the pure mathematics to describe the piezoelectric effect which finally led to its military uses, such as SONAR during WWI, an environment where costs are less of a concern than performance. Finally, with the uptake of ultrasound for medical applications, the same procedures, changed from open-surgeries to truly minimally invasive ones. From the time any pure theoretical concept moves to a product, later branching from military applications to civilian ones, a plethora of use cases arise.

Furthermore, the thesis implicitly contains different aspects of translational medicine, from pure theory, to research, to product launch, ultrasound might be the pinnacle everyday example of translational medicine. Moreover, since the formal inclusion of statistics as a mathematical branch, its consequential uptake by Economics and later its penetration into the medical sphere, medicine underwent a major transformation from authoritative, anecdotal evidence to more rigorous, statistics-based approaches. Thus, with the advent of this new era, together with the growing number of published studies, the need to analyze data not as solitary studies but as the whole available literature arose. Through the lens of meta-analysis, medical professionals can consolidate the literature and gather available data to create, confirm, or even discover new information which can later prove important for patient care. The introduction of statistics into medical practice can still be considered in its early phase of penetrance. The new paradigm of always-available-intelligence is bound to push the field further both in terms of work created and the ways analyses can be performed, the same way Economics has underwent a significant shift, providing more and more precision and value, the same standards need to start being applied for medical research. Thus, through the historical progress of ultrasound from fundamental mathematics to concrete

applications, and through the historical transformation both Economics and Medicine undertook with the advent of modern statistical analyses, our thesis explores some of the threads spanning the network of how modern medicine and medical doctors operate. It is difficult to envision which exact direction the world is going to take in relation to which industry and which tools will be necessary to sustain one of these many directions. At the same time, it is of utmost importance for the medical practitioners of the future, be they nurses or doctors, to be provided with the proper knowledge of these future tools, so that they can themselves expand their own cognitive light-cones, as well as those of their community and beyond. With the advent of factory-driven intelligence overtaking human-driven one, the possibilities of creation, be they mathematical concepts or engineering feats, appear more approachable than ever, and healthcare personnel must be ready to create the next ultrasound, the next application for the next ultrasound, or even expand the statistical analyses and ways bedside medical research is realized.

In conclusion, A combination of unawareness, lack of education and training, as well as habitual inertia, can lead to the slow or complete lack of uptake from interventionists to clinicians. At the same time, the diffusion of statistical analyses from economics to the concomitant uptake by the medical community allowed for a more systematized analyses of available data, for which meta-analysis has for better or for worse been an integral part of modern medical practice given its high strength of evidence when performed properly. EUS-biliary drainage has not only proven itself over the course of the last few decades but still appears underutilized. Our results offer recommendations and guidance on how to approach such procedures, which techniques and stents to prefer and when, as well as identifying research gaps and outlining future research paths. For modern healthcare to move in faster rhythms, a combination of education, cooperation, and communication between front-line physicians and policymakers is of utmost importance.

Our results have a direct effect on how interventional gastroenterologists approach performing such procedures, what to avoid, and which stents to use in different situations and for individual patient needs.

11. IMPLICATIONS FOR PRACTICE

Our findings act as a guidance for gastroenterologists that specialize in interventional ultrasound and more specifically in EUS-biliary drainage procedures. Although, at times the strength of our evidence and the moderate heterogeneity of some results could hinder a clear view, our results, through the lens of meta-analyses can provide the necessary information to take informed decisions before EUS-HGS procedures are performed, namely, which method and which stents should be considered. Patients gain by decreased re-intervention odds when AGS is combined with HGS, as well as the choice between plastic or metallic stents, given the patient's own individual profile (bridge-to-surgery, consideration of higher patency or even cholangitis risk).

12. IMPLICATIONS FOR RESEARCH

Further studies need to be conducted comparing different metallic stents with each other, the biggest gap and source of heterogeneity identified in our research is the often lack of separation between HGS and HGAS. More specifically, research articles can be encountered where no clear separation between the two techniques exist, thus reporting HGAS as HGS. Attention needs to be drawn to such cases, and better reporting needs to be performed. Furthermore, our studies noted that metallic stents had not been properly compared with each other, different hospitals might use different devices for the same procedure which can act as a source of heterogeneity.

13. IMPLICATIONS FOR POLICYMAKERS

Our results can be used to inform international guidelines and strengthen the evidence base for EUS-HGS procedures.

14. FUTURE PERSPECTIVES

In connection to the topic, more research can be conducted in the form of outcomes from specific devices and track dilation techniques, as well as a more thorough analysis on the factors that influence adverse events, especially bile leakage, which is the one adverse event that people performing such procedures should take extra caution minimizing. The acceptance of discussed procedures and their penetrance into more gastroenterologists' everyday work.

The further, deeper penetrance of statistical analyses into everyday medical practice requires many more years to manifest itself in full, which consequentially requires another full-scale shift of the thinking of medical professionals towards how their work can realize more of its potential.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

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Hepaticogastrostomy versus hepaticogastrostomy with antegrade stenting for malignant biliary obstruction: a systematic review and meta-analysis

THERAPEUTIC ADVANCES IN GASTROENTEROLOGY (1756-283X 1756-2848):
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Citing papers: 4 | Independent citation: 4 | Self citation: 0 | Unknown citation: 0 |
Number of citations in WoS: 4 | Number of citations in Scopus: 2 | WoS/Scopus
assigned: 4 | Number of citations with DOI: 4

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Number of cited publications: 1

16.2. Publications not related to the thesis

Bednárík Dániel Steve, Földvári-Nagy Kincső Csepke, Simon Viktor, Rancz Anett, Gede Noémi, Veres Dániel Sándor, Paraskevopoulos Panagiotis, Schnabel Tamás, Erőss Bálint, Hegyi Péter, Lenti Katalin, Földvári-Nagy László

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Journal subject: Scopus - Health Policy Rank: D1

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Journal subject: Scopus - Oncology Rank: D1

Journal subject: Scopus - Public Health, Environmental and Occupational Health Rank: D1

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