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Over-the-scope clips vs standard endoscopic interventions for first-line treatment of NVUGI bleeding: Meta-analysis of randomized trials

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ABSTRACT

Background and study aims Recently, over-the-scope clips (OTSCs) have been extensively studied for hemostasis of nonvariceal upper gastrointestinal bleeding (NVUGIB). Our goal was to compare the efficacy of OTSCs with standard endoscopic interventions (SEIs) as first-line treatments.

Patients and methods A comprehensive search of electronic databases was performed to identify randomized clinical trials (RCTs) comparing OTSCs with SEIs as first-line therapy for NVUGIB. This search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Results Of 819 reviewed studies, five RCTs comprising 555 patients (277 OTSCs vs. 278 SEIs) were included. The OTSC group had a lower 30-day rebleeding rate (risk ratio [RR] 0.43; 95% confidence interval [CI] 0.24–0.77; $I^2 = 0\%$; $P = 0.004$) and a higher clinical success rate (RR 1.19; 95% CI 1.11–1.28; $I^2 = 0\%$; $P < 0.00001$). There was no significant difference in technical success (RR 1.06; 95% CI 0.98–1.14; $I^2 = 73\%$; $P = 0.13$), 30-day all-cause mortality (RR 0.50; 95% CI 0.22–1.14; $I^2 = 0\%$; $P = 0.10$), need for further intervention (RR 1.22; 95% CI 0.43–3.47; $I^2 = 0\%$; $P = 0.71$), or length of hospital stay (mean difference 0.31; 95% CI: -1.08- 1.70; $I^2 = 0\%$; $P = 0.66$). Risk of bias, which was assessed using the Cochrane Risk of Bias 2.0 tool, indicated some concerns about bias.

Conclusions OTSCs are more efficient than SEIs as first-line treatment in terms of rebleeding within 30 days and clinical success rates.

Introduction

Incidence of nonvariceal upper gastrointestinal bleeding (NVUGIB) has substantially declined in recent years [1,2]; however, NVUGIB still accounts for a significant proportion of hospital admissions [3]. Furthermore, with aging of the population, there has been an increase in comorbidities, thereby leading to a steady mortality rate of NVUGIB [4] and indicating the substantial relevance of this condition [5]. Standard endoscopic interventions (SEIs), including methods such as epinephrine in-

jection, thermal therapy, and through-the-scope clipping (TTSC), exhibit a high rate of initial hemostasis, and they fail in approximately 15% of cases [6]. Furthermore, the rebleeding rate of SEIs is approximately 17% [7].

Over-the-scope clipping (OTSC) was initially designed for closing wall defects, such as iatrogenic perforations and fistulas [8]. However, its ease of handling and gripping strength have also proven to be effective in managing NVUGIB, and it is recommended as a first-line treatment option for high-risk bleeding ulcers and persistent or recurrent bleeding according to several guidelines [9].

There is a growing interest in the study of OTSCs, and their comparison with SEI for treatment of NVUGIB is a recurring theme in research. Previous meta-analyses [10, 11] have yet to include the most recent studies, which encompass a significant number of patients and would yield more precise conclusions regarding the methods. Therefore, an updated meta-analysis is warranted to gain a comprehensive understanding of the current status of NVUGIB and to make an informed choice regarding the optimal first-line therapeutic approach in daily practice.

Patients and methods

Protocol and registration

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [12] guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/prospero) under the file number CRD42023469944. Approval for the study was granted by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo.

Eligibility criteria

A search for randomized controlled trials (RCTs) comparing OTSCs with SEIs for NVUGIB without prior endoscopic hemostatic therapy among adults (aged 18 years or older) was conducted. There were no restrictions on language or publication date. Non-human studies were excluded.

Search strategy

We searched the MEDLINE and Embase electronic databases and gray literature from inception to June 2024. The search strategy for the MEDLINE and Embase databases and the gray literature was as follows: [(OTSC OR Over-the-Scope) AND (Nonvariceal OR Non-variceal OR NVUGIB OR Gastrointestinal bleeding)].

Study selection and data collection process

Two independent authors reviewed all records from the sources previously mentioned based on their titles. Abstracts of the potentially relevant studies were then evaluated for eligibility. If an abstract met the eligibility criteria or if there was uncertainty, the full text of the study was examined. Duplicate records were eliminated. Any discrepancies were resolved through consensus and consultation with a third reviewer. The data were entered into an Excel table.

Data items

After determining which studies would be analyzed, the following data were extracted: participant characteristics, such as the etiology of bleeding, use of anticoagulants/antiplatelet agents, size, location of the lesion, and Forrest classification in case of ulcers; interventions (OTSC or SEI); and outcomes (technical success, clinical success, rebleeding within 30 days, 30-day all-cause mortality, further interventions, and hospital stay). A subgroup analysis for clinical success was performed, including only patients with peptic ulcer lesions, to mitigate potential bias arising from diversity of bleeding etiologies. For extraction of data not available in the studies, the respective authors were contacted to obtain the necessary data.

"Technical success" was defined as cessation of bleeding through the hemostatic method assigned by randomization during the index upper gastrointestinal endoscopy.

"Clinical success" was defined as hemostasis at the index upper gastrointestinal endoscopy site associated with absence of rebleeding evidence within 30 days.

Risk of bias and quality of evidence

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool (RoB-2) [13]. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for each outcome using the GRADEpro – Guideline Development tool software [14].

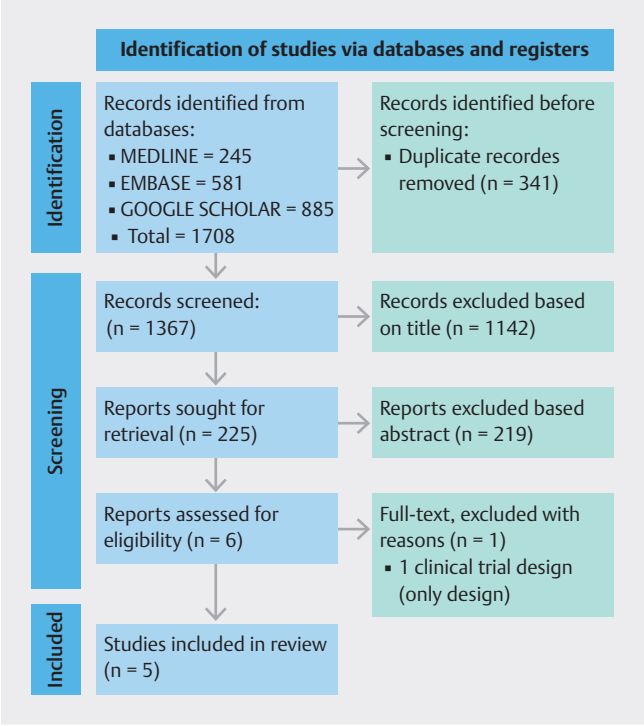
Statistical analysis

The software Review Manager (RevMan) version 5.4.1 was used for meta-analysis of data derived from the studies. Dichotomous endpoints were assessed using the risk ratio (RR) with a 95% confidence interval (CI). The mean difference (MD) and standard deviation (SD) were used for continuous variables with 95% CIs. In studies where continuous variables were described as medians and interquartile ranges, the McGrath method was used to obtain the MD and SD. $P \leq 0.05$ was considered to indicate statistical significance for the RR and MD. Heterogeneity was analyzed using the Higgins method (I^2) [15]. Heterogeneity (I^2) > 50% was considered high, and in such cases, the random effects model was employed in these cases; otherwise, the fixed effects model was used.

Results

Study selection

The initial search strategy yielded a total of 1708 articles, including 245 from the MEDLINE database, 581 from Embase, and 882 from Google Scholar. Six studies were chosen for a thorough review of the full text after applying eligibility criteria and eliminating duplicate studies. One study was excluded because it exclusively constituted a clinical trial design. Therefore, five studies were included in both the quantitative and qualitative analyses [16, 17, 18, 19, 20] (▶ **Fig. 1**).



▶ **Fig. 1** PRISMA flow diagram. Moher D, Shamseer L, Clarke M et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4:1

Study characteristics

The five included studies were RCTs involving 555 patients: 277 in the OTSC group and 278 in the SEI group. The main outcomes of the studies are shown in ▶ **Table 1**.

Risk of bias and quality of evidence

Overall risk of bias of the studies was assessed by the RoB 2 tool. Risk of bias was low for four of the five studies, except for the studies by Lau et al., which had some concerns about bias (▶ **Fig. 2**). The study by Lau et al. had some concerns due to exclusion of patients with bleeding from sites unfavorable for OTSC placement before randomization.

Quality of evidence was evaluated using the GRADE approach. Quality of evidence was judged as moderate for rebleeding within 30 days and hospital stay; low for clinical success, all-cause mortality, and further interventions; and very low for technical success (▶ **Table 2**).

Meta-analysis

Technical success

Five studies [16, 17, 18, 19, 20] were included in this analysis, totaling 555 patients (277 in the OTSC group and 278 in the SEI group). There was no significant difference in technical success between OTSCs and SEIs (RR: 1.06; 95% CI: 0.98, 1.14; I^2 = 73%; P = 0.13) (▶ **Fig. 3**). A leave-one-out sensitivity analysis was performed. However, heterogeneity remained above 50% even after the individual exclusion of all studies included in this outcome.

Clinical success

All the studies [16, 17, 18, 19, 20] were utilized in this analysis, comprising 555 patients (277 in the OTSC group and 278 in the SEI group). Clinical success was significantly higher in the OTSC group (RR: 1.19; 95% CI: 1.11, 1.28; I^2: 0%; P < 0.00001) (▶ **Fig. 3**). Furthermore, four studies [16, 17, 19, 20] including a total of 413 patients (220 in the OTSC group and 213 in the SEI group) were included in the analysis of clinical success, considering that only PU lesions were significantly more common in patients who underwent OTSC (RR: 1.19; 95% CI: 1.10, 1.28; I^2: 17%; P < 0.00001) (▶ **Fig. 3**).

Rebleeding within 30 days

A total of 555 patients (277 in the OTSC group and 278 in the SEI group) across the five studies [16, 17, 18, 19, 20] were included in this analysis. Incidence of rebleeding within 30 days was higher in the SEI group (RR: 0.43; 95% CI: 0.24, 0.77; I^2: 0%; P = 0.004) (▶ **Fig. 3**).

All-cause mortality within 30 days

This analysis included 555 (277 in the OTSC group and 278 in the SEI group) of the patients from the five studies [16, 17, 18, 19, 20]. Rates of 30-day all-cause mortality were not significantly different between OTSCs and SEIs (RR: 0.50; 95% CI: 0.22, 1.14; I^2: 0%; P = 0.10) (▶ **Fig. 4**). For obtaining the data from Soriani et al. for analysis of this outcome, the respective authors were contacted.

Further interventions

Five studies [16, 17, 18, 19, 20] were used in this analysis, including 555 patients (277 in the OTSC group and 278 in the SEI group). There was no significant difference between the groups in terms of further interventions (RR: 1.22; 95% CI: 0.43, 3.47; I^2: 0%; P = 0.71) (▶ **Fig. 4**). The authors of Soriani et al. were contacted to obtain the necessary data for analysis of this outcome.

Length of hospital stay

All 555 patients (277 in the OTSC group and 278 in the SEI group) from the five studies [16, 17, 18, 19, 20] were utilized in this analysis. The difference in the mean length of hospital stay was not statistically significant between the OTSC group and the SEI group (MD: 0.31; 95% CI: -1.08, 1.70; I^2: 0%; P = 0.66) (▶ **Fig. 4**).

Discussion

To the best of our knowledge, this is the largest meta-analysis to date comparing OTSCs vs. SEIs for first-line treatment of NVUGIB. This analysis enabled more definitive conclusions and expanded the number of studies and patients compared with previous research. Moreover, this study holds a significant advantage because it included the most recently published RCT [16], which had a substantial sample size. Our subgroup analy-

▶ **Table 1** Study characteristics

Study	Study design	Patients (OTSC/SEI)	Mean age (years, OTSC/SEI)	Sex (% male, OTSC SEI)	ASA, n (OTSC/SEI)	Use of anticoagulants and/or antiplatelet agents, n (OTSC/SEI)	Baseline hemoglobin, mean (SD), g/dL	SEI	Etiology	Outcomes
Soriani et al. 2023 Italy	RCT	61 / 51	62 / 72	72 / 65	1: 3/3 2: 13/15 3: 39/23 4: 6/10	32/14	8.6 (2)/8.7 (2.3)	TTSC	PU	TS, CS, R30 d, FI, HS, M30d
Lau et al. 2023 Hong Kong	RCT	93 / 97	62 / 64	80 / 77	NM	19/22	8.4 (2.5)/8.1 (2.4)	TTSC Thermal methods ± epinephrine	PU Dieulafoy's lesion Angiodysplasia Duodenal diverticulum Gastrointestinal stromal tumor Mallory-Weiss tear	TS, CS, R30 d, FI, HS, M30d
Meier et al. 2022 Germany	RCT	48 / 52	70 /75	69/71	1: 15/22 2: 22/16 3: 13/10 4: 0/2	7/3	7.09 (2.29) /7.57 (1.89)	TTSC Thermal methods	PU Anastomotic ulcer Dieulafoy's lesion Esophagitis Mallory-Weiss tear	TS, CS, R30 d, FI, HS, M30d
Chan et al. 2022 Hong Kong	RCT	50 / 50	72/71	68/66	1: 0/0 2: 9/7 3: 12/14 4: 4/7	21/22	NM	TTSC Thermal methods + epinephrine	PU	TS, CS, R30 d, FI, HS, M30d
Jensen et al. 2020 USA	RCT	25 / 28	68/66	77/86	NM	16/26	7.1 (1.5)/7.7 (2.3)	TTSC Multipolar probe thermal coagulation + epinephrine	PU Anastomotic ulcer Dieulafoy's lesion	TS, CS, R30 d, FI, HS, M30d

CS, clinical success; FI, further intervention; HS, hospital stay; M30 d, mortality all-cause in 30 days; NM, not mentioned; OTSC, over-the-scope clip; PU, peptic ulcer; RCT, randomized clinical trial; R30 d, rebleeding within 30 days; SD, standard deviation; SEI, standard endoscopic interventions; TS, technical success; TTSC, through-the-scope clip.

sis was reinforced by explicitly concentrating on patients with NVUGIB due to PUs, thus highlighting a substantial difference in one of the outcomes. This differentiation was not attainable in previous meta-analyses [11], nor did this study include RCTs whose inclusion criteria consisted of patients with recurrent NVUGIB, as He et al.[21] which included Schmidt et al.[22].

Analysis of the results revealed that OTSCs were associated with a higher rate of clinical success, both in the overall population and in subgroup analysis for PUs. This composite outcome, defined as absence of persistent bleeding and rebleeding, is the opposite of the "further bleeding" endpoint recommended in assessment of NVUGIB treatment by the International Consensus Conference [23]. This outcome has considerable relevance, because it impacts complications related to patient condition, need for reintervention, hospitalization, additional expenses, and other factors that affect the patient and burden the health care system.

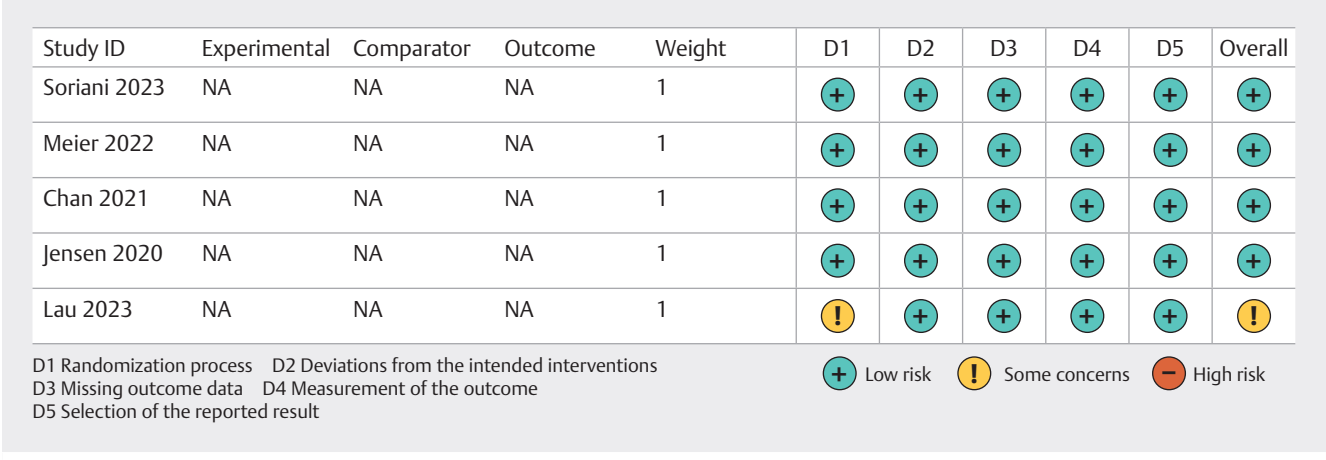
There was no difference in technical success rate, and there was no significant difference between the interventions. However, there was a lower rate of rebleeding in patients treated with OTSCs. This is a highly relevant finding and may constitute a paradigm shift, considering that the main guidelines [23, 24] do not recommend or cite weak evidence for use of OTSCs as a first-line approach in management of NVUGIB. Furthermore, OTSCs were associated with lower rates of rebleeding within 30 days. This occurs due to a combination of factors: 1) greater tensile strength; 2) grasping a larger coverage area; and 3) full-thickness grasping [8, 25]. Thus, OTSCs should be considered an alternative to improve rebleeding rates that remain high despite advances in use of SEIs [7]. The significant difference in rebleeding within 30 days was possibly one of the major contributors to the significant difference in clinical success, given that the former is one of the components of this composite outcome.

In contrast to a previous meta-analysis [11], where no difference in clinical success was found between the groups of patients with bleeding secondary to peptic ulcers, this meta-analysis demonstrated the superiority of OTSCs for outcomes, with statistical significance. A combination of factors can explain this finding. First, OTSCs have a higher clinical success rate as a first-line treatment for NVUGIB [10, 11], and PU represents its leading etiology [2]. The second confusion factor is caused by studies including several etiologies of NVUGIB in the inclusion criteria, consequently leading to heterogeneity in the groups in the outcome analysis. Finally, our study increased the sample size, which was a decisive factor in making the difference significant.

Technical success showed similar results in the OTSC and SEI groups. This can be explained by factors associated with technical difficulty, such as OTSC and SEI. Location of bleeding on the posterior wall of the duodenum or at the transition from the first to the second portion, for example, is a factor that increases the amount of persistent bleeding in both the SEI [16] and the OTSC groups [19], although there was no subgroup analysis. Another example is significant difficulty in locating both TTSCs [16] – one of the main methods used in the SEI group – and OTSCs [19] in fibrotic ulcers due to substantial resistance to approximate their edges.

Despite the lower rebleeding rate and higher clinical success in patients with PU lesions, those who experienced rebleeding [17] or who were refractory to OTSC use [19] had a potential risk of experiencing higher rates of transarterial embolization, although the difference was not significant. This potential risk may be explained by greater difficulty in achieving hemostasis in the presence of OTSCs. This device likely prevents placement of a TTSC or increases risk of transmural thermal injury from contact between the heat probe or argon plasma coagulation and the metal clip, in addition to potential tissue damage caused by this device. In addition, there is selection bias, because patients who experienced rebleeding or persistent bleeding with OTSCs may have had more severe lesions, and those outcomes might have likely occurred with SEI as well. Thus, studies with a larger sample size may achieve a more definitive statistical response.

No statistically significant differences were observed regarding rates of 30-day all-cause mortality or hospital stays. This analysis may have been compromised by two studies [18, 19] that incorporated crossovers after rebleeding occurred, despite

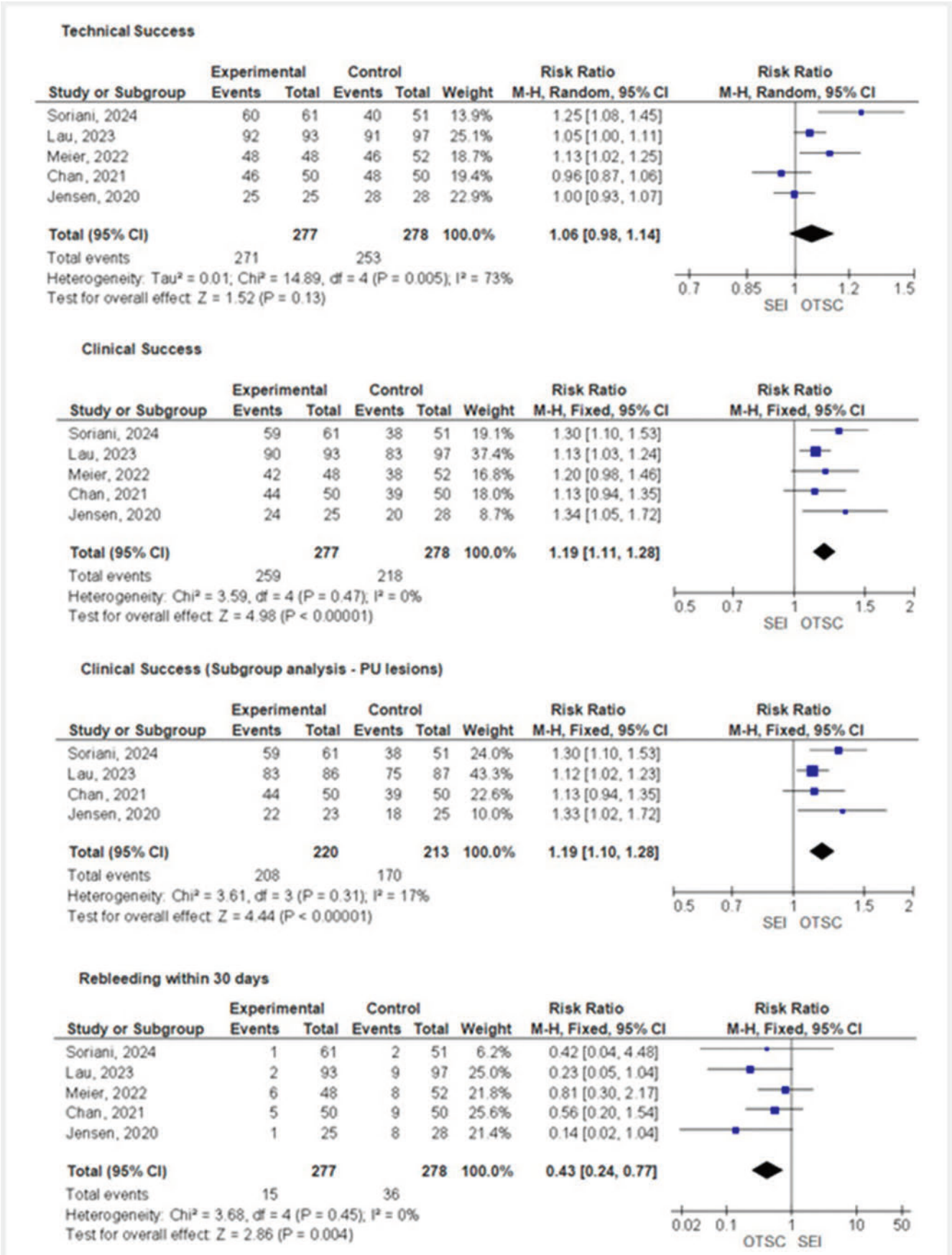


▶ **Fig. 2** Risk of bias 2 tool (RoB2). NA, not available.

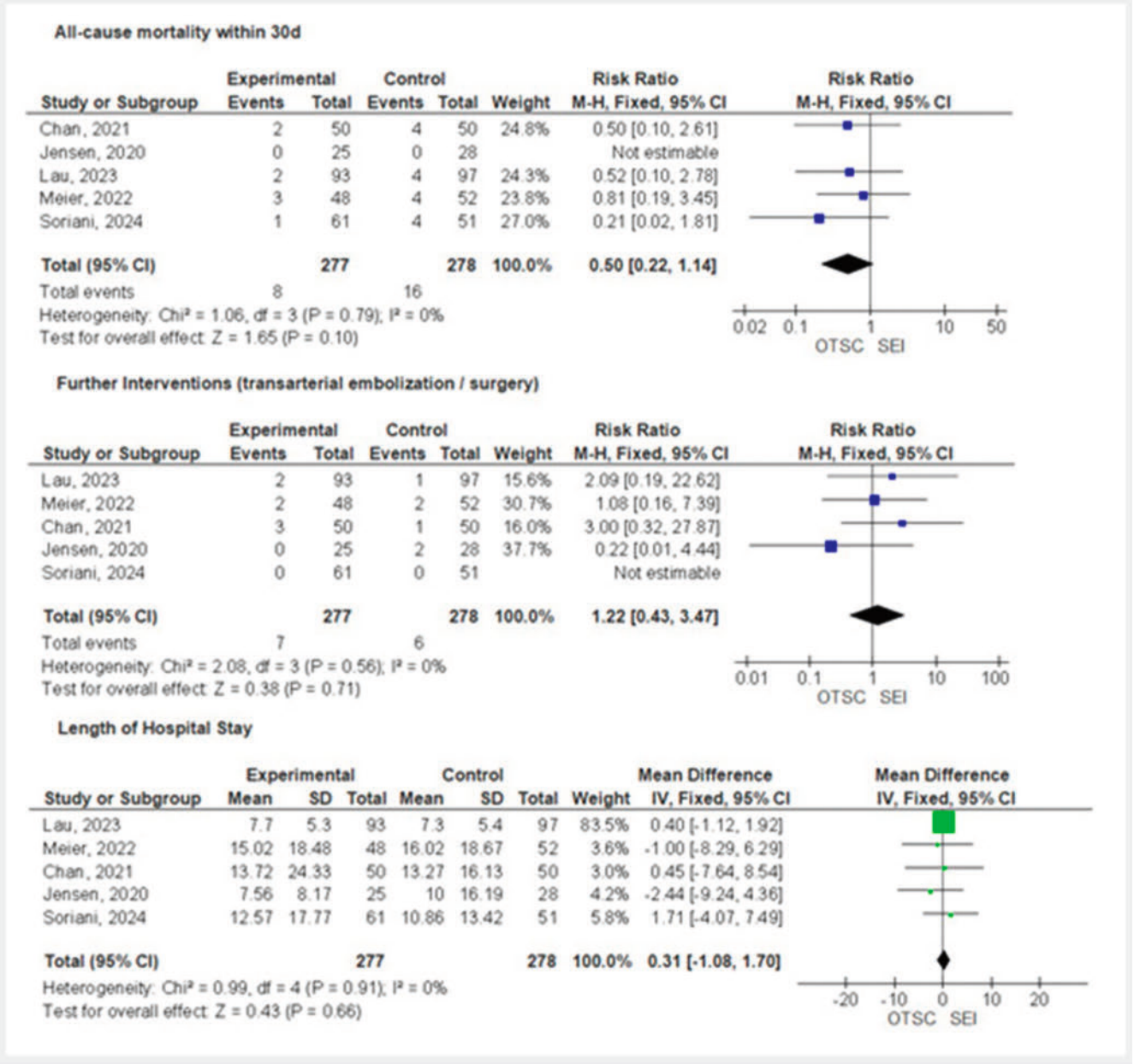
▶ **Table 2** Quality (certainty) of evidence of studies selected, as determined by GRADE criteria.

Certainty assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[control]	Relative (95% CI)	Absolute (95% CI)	
5	Randomized trials	Serious*	Serious†	Serious‡	Serious§	All plausible residual confounding would suggest spurious effect, while no effect was observed	271/277 (97.8%)	253/278 (91.0%)	Not estimable	**60 fewer per 1.000** (from 130 fewer to 10 more)	●○○○ Very low
5	Randomized trials	Serious*	Not serious	Serious‡	Not serious	None	259/277 (93.5%)	218/278 (78.4%)	Not estimable	**150 fewer per 1.000** (from 210 fewer to 90 fewer)	●●○○ Low
5	Randomized trials	Serious*	Not serious	Serious‡	Serious§	All plausible residual confounding would suggest spurious effect, while no effect was observed	7/216 (3.2%)	12/227 (5.3%)	Not estimable	**20 more per 1.000** (from 20 fewer to 60 more)	●●○○ Low
5	Randomized trials	Serious*	Not serious	Serious‡	Serious§	All plausible residual confounding would suggest spurious effect, while no effect was observed	7/216 (3.2%)	6/227 (2.6%)	Not estimable	**10 fewer per 1.000** (from 40 fewer to 30 more)	●●○○ Low
5	Randomized trials	Serious*	Not serious	Serious‡	Serious§	Strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	201	212	–	MD **0.23 higher** (1.21 lower to 1.66 higher)	●●●○ Moderate
5	Randomized trials	Very serious*,¶	Not serious	Serious‡	Not serious	Strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	15/277 (5.4%)	36/278 (12.9%)	Not estimable	**70 more per 1.000** (from 30 more to 120 more)	●●●○ Moderate

CI, confidence interval; MD, mean difference.
*This outcome included the study by Lau et al., which presented a selection bias as demonstrated by the Cochrane Risk of Bias 2.0 tool.
†Heterogeneity >50% and ≤75%.
‡The included studies differed in relation to bleeding etiologies and methods used as standard endoscopic interventions.
§No significant difference was found.
¶Studies showed heterogeneity related to performing a second-look upper gastrointestinal endoscopy



▶ **Fig. 3** Forest plot of technical success, clinical success, clinical success in subgroup analysis of PU lesions, and rebleeding within 30 days. OTSC, over-the-scope clip; PU, peptic ulcer; SEI, standard endoscopic intervention.



▶ **Fig. 4** Forest plot of all-cause mortality at 30 days, further interventions, and length of hospital stay. OTSC, over-the-scope clipping; SEI, standard endoscopic intervention.

being ethically and clinically appropriate. Consequently, patients with a higher probability of requiring additional interventions and facing mortality underwent both types of treatment, introducing a confounding bias that could have compromised statistical analysis of these two outcomes.

This systematic review and meta-analysis has several limitations. One of them is performance of a second-look endoscopy in only one study [18]. This approach could decrease the real rebleeding rate because high-risk lesions are identified and treated, preventing further bleeding, unlike in situations where second-look endoscopy is not routinely conducted. In addition, it was not possible to perform a meta-analysis of subgroups that would provide detailed information about the types of lesions, allowing the distinction of characteristics favoring or disfavoring use of OTSCs or SEIs. Another limitation is that only a few studies [18, 19] mentioned implementation of crossover after rebleeding, which may have compromised analysis of further interventions, hospital stays, and 30-day all-cause mortality. Furthermore, it was not possible to extract information such as management of patients with persistent and recurrent bleeding from one of the studies [16].

Another point that should be highlighted is the fact that the endoscopists who performed the OTSC applications in most of the RCTs [16, 17, 19, 20] included in this systematic review had received previous adequate training. Thus, as discussed by Pittayanon et al.[26], our results and conclusions should be lim-

ited to cases performed by endoscopists experienced in use of OTSC. Furthermore, this point should also be considered by the European Society of Gastrointestinal Endoscopy (ESGE), which did not mention it in its most recent recommendations [9].

Conclusions

In conclusion, this meta-analysis demonstrated that OTSCs were associated with lower rebleeding rates and greater clinical success than SEIs. In addition, despite not considering the costs of OTSCs, because only high-impact evidence studies were included, with the majority exhibiting a low risk of bias, this systematic review adds a higher quality of evidence that provides a basis for introducing OTSCs into guidelines as a new alternative for first-line treatment NVUGIB for experienced endoscopists.

Conflict of Interest

Dr. Eduardo Guimaraes Hourneaux De Moura: Olympus - Consultant (Consulting fees) and Boston Scientific - Consultant (Consulting fees). These were not relevant to this study. Dr. Marcos Eduardo Lera dos Santos: Olympus - Consultant (Consulting fees) and Boston Scientific - Consultant (Consulting fees). These were not relevant to this study. Dr. Vitor Ottoboni Brunaldi: received honoraria for lectures from Erbe Elektromidizin GHMB. These were not relevant to this study. Dr. Paulo Ferreira Mega, Dr. Alexandre Moraes Bestetti. Dr. Angelo So Taa Kum and Dr. Igor Valdeir Gomes de Sousa do not have any conflicts of interest to declare.

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