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Endoscopic ultrasound-guided portal pressure gradient measurement: a systematic review and meta-analysis

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Abstract

Background Endoscopic ultrasound-guided portal pressure gradient measurement (EUS-PPG) is a new modality where the portal pressure is measured by directly introducing a needle into the hepatic vein and portal vein. This is the first systematic review and meta-analysis to evaluate the efficacy and safety of EUS-PPG.

Methods A comprehensive literature search was performed to identify pertinent studies. The primary outcomes assessed were the technical and clinical success of EUS-PPG. Technical success was defined as successful introduction of the needle into the desired vessel, while clinical success was defined as the correlation of the stage of fibrosis on the liver biopsy to EUS-PPG, or concordance of HVPG and EUS-PPG. The secondary outcomes were pooled rates for total and individual adverse events related to EUS-PPG. Pooled estimates were calculated using random-effects models with a 95% confidence interval (CI).

Results Eight cohort studies with a total of 178 patients were included in our analysis. The calculated pooled rates of technical success and clinical success were 94.6% (95%CI 88.5-97.6%; P=<0.001; I^2=0) and 85.4% (95%CI 51.5-97.0%; P=0.042; I^2=70), respectively. The rate of total adverse events was 10.9% (95%CI 6.5-17.7%; P=<0.001; I^2=4), and 93.7% of them were mild, as defined by the American Society for Gastrointestinal Endoscopy. Abdominal pain (11%) was the most common adverse event, followed by bleeding (3.6%). There were no cases of perforation or death reported in our study.

Conclusions EUS-PPG is a safe and effective modality for diagnosing portal hypertension. Further randomized controlled trials are needed to validate our findings.

Keywords Endoscopic ultrasound, portal pressure gradient, portal hypertension, cirrhosis

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Introduction

Cirrhosis is now the ninth leading cause of mortality in the United States (US) [1]. The economic burden of cirrhosis is substantial; the annual direct costs are estimated to be $2.5 billion, with an additional $10.6 billion in indirect costs [2]. These costs increase substantially for patients with decompensated cirrhosis, with annual costs of over $2,400 for diuretic-responsive ascites, $24,480 for diuretic-refractory ascites, $16,400 for hepatic encephalopathy treatment, and $25,600 for treatment of patients with variceal hemorrhage [3]. Portal hypertension (PH) is the major driver of these complications; therefore, the proper diagnosis and management of PH is paramount [4,5].

Conflict of Interest: None

*Both authors contributed equally to the manuscript as co-first authors

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Measurement of hepatic venous pressure gradient (HVPG) via a transjugular approach using interventional radiology (IR) is the current standard method for determining PH [4,6,7]. It is calculated by measuring the difference between the wedged (indirectly estimated pressure in the portal system) and free hepatic venous pressure, with the help of a catheter in the hepatic vein [4]. An HVPG of >5 mmHg is consistent with mild sinusoidal PH and compensated cirrhosis, while HVPG values of >10 mmHg represent clinically significant PH (CSPH) and are predictive of decompensation, and complications such as variceal hemorrhage and spontaneous bacterial peritonitis [8,9]. Measuring the HVPG by IR approaches is a technically challenging and invasive procedure that requires fluoroscopy; it is therefore rarely performed outside of tertiary centers. Additionally, HVPG cannot be used for accurate measurement in pre-hepatic or pre-sinusoidal causes of PH [10].

Direct endoscopic ultrasound-guided portal pressure gradient (EUS-PPG) measurement has emerged in recent years as a promising alternative method of evaluating PH. Lai *et al*, in 2004, first demonstrated its use in a porcine model, and in 2014 Fujii-Lau *et al* reported the first use in a single human subject [10,11]. In 2019, the US Food and Drug Administration approved a novel device called the EchoTip® Insight™ Portosystemic Pressure Gradient Measurement System (Cook Endoscopy, Bloomington, US) [12]. Under direct visualization with EUS, the portal vein and hepatic vein are identified. A 25-G needle is directly inserted into these vessels and 3 separate measurements are performed with an attached compact manometer/pressure transducer. These measurements are then averaged to determine the PPG. This is the first meta-analysis that aimed to evaluate the efficacy and safety of the use of EUS-PPG for the routine evaluation of PH.

Materials and methods

We performed an extensive literature search in several major databases—including PubMed, Medline, EMBASE, CINAHL, Cochrane, Web of Science and Google Scholar—from inception to December 2022. We used the following keywords to identify studies reporting the use of endoscopic guided ultrasound to measure portal pressure gradients: "endoscopic", "ultrasound", "portal hypertension", "pressure", "liver", "gradient", and "needle". We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [13] to identify studies that used EUS for portal pressure gradient measurements (Supplementary Fig. 1 and Supplementary Table 1).

Study selection

The titles and abstracts from each study were independently reviewed by 2 independent authors (KT and BD). A third author (SS) independently reviewed any study in instances where discrepancies occurred.

We included any study that reported outcomes on EUS-PPG measurement. We included studies irrespectively of their abstract status, manuscript status, geographical location or clinical setting, provided that they reported meaningful data that could be entered into our analysis. Our exclusion criteria were sample size <5, pregnant women, studies published in other languages without English translation, and nonhuman subjects. The data points from the most recent or comprehensive studies were included in our analysis if cohort overlap occurred.

Data abstraction and quality assessment

The Newcastle-Ottawa Scale was used to assess the risk of bias and methodological quality in cohort studies [14]. Please refer to Supplementary Table 2 for details. Two authors (SS and BD) independently performed quality appraisals. If conflict occurred, then a third author (KT) acted as the mediator.

Outcomes assessed

Primary outcomes were: (a) pooled technical success rate of EUS-PPG measurement; and (b) pooled clinical success rate of EUS-PPG measurement. Secondary outcomes were: (a) pooled rate of total adverse events (AE) of EUS-PPG measurement; and (b) pooled rate of AE subtypes of EUS-PPG measurement: abdominal pain, perforation and bleeding.

Definitions

Technical success was defined as the successful introduction of the needle into the desired vessel and measurement of portal and hepatic vein pressures. Clinical success was defined as correlation between the stage of fibrosis on liver biopsy and the PPG measurement, or concordance between HVPG and PPG. AE were defined as complications directly related to the

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procedure, and were reported as per the American Society for Gastrointestinal Endoscopy (ASGE) lexicon [15].

Statistical analysis

Pooled estimates and their corresponding 95% confidence intervals (CI) were calculated for categorical variables using the random-effects model suggested by DerSimonian and Laird [16]. A syntax was constructed to calculate the weighted mean if values of zero occurred in our data, in order to avoid introducing positive bias to the analysis. The Cochran Q statistical test and I^2 statistic were utilized to measure heterogeneity between study-specific estimates [17,18]. I^2 values of <30%, 30-60%, 61-75% and >75% were described as low, moderate, substantial and considerable heterogeneity, respectively [19]. Prediction intervals (PI) were obtained for outcomes with heterogeneity. Since the number of studies available for comparison was small, publication bias was not assessed. All pooled rates were calculated with a 95%CI and with a respective P-value, which was considered statistically significant when <0.5. The Comprehensive Meta-Analysis (CMA) software (v 3; BioStat, Englewood, New Jersey, US) was utilized in our meta-analysis.

Results

Search results and population characteristics

From an initial pool of 415 studies, 8 were included in the final analysis. A schematic diagram of the study selection according to the PRISMA guidelines is illustrated in Supplementary Fig. 1. The analysis included a total of 178 patients, the majority of whom were males (52.3%). The patients' mean age was 55.8 years (range 33.1-64). Six studies were from the US, 1 was from China, and 1 was from Australia. The etiology of liver disease was described in 5 studies. The most common etiology was nonalcoholic fatty liver disease (31.5%) followed by hepatitis C virus (14.2%). Table 1 describes the characteristics of the included studies.

Characteristics and quality of included studies

The analysis included 8 single-center studies (4 prospective and 4 retrospective). No multicenter or population-based studies were included in the final analysis. Of the studies included, 3 were published in manuscript form, 4 were published in abstract form, and 1 was published as a letter to the Editor. Two studies included more than 20 patients, 4 included more than 10 and 2 less than 10 patients. Four studies were of good quality and 4 studies were of fair quality as per the Newcastle-Ottawa scale.

Meta-analysis outcomes

Primary outcomes

The calculated pooled rate of technical success (Fig. 1) was 94.6% (95%CI 88.5-97.6%; I^2=0), while the pooled rate of clinical success (Fig. 2) was 85.4% (95%CI 51.5-97.0%; PI=2-100%; I^2=70).

Secondary outcomes

The calculated pooled rate of total AEs (Fig. 3) was 10.9% (95%CI 6.5-17.7%; PI=5-23%; I^2=4). The most common AE was abdominal pain (11.0%, 95%CI 6.4-18.3%; PI=4-25%; I^2=8.4), followed by bleeding (3.6%, 95%CI 1.4-8.8%; I^2=0). No cases of perforation or death were reported in our study. As per the ASGE Lexicon, 93.7% (95%CI 66.3-99.1%; I^2=0) of AEs were mild in nature [15].

Validation of meta-analysis

Sensitivity analysis

One study at a time was excluded to assess any dominant effect it may have had on the meta-analysis. None of

Table 1 Demographic characteristics of the included studies

Study year [ref.]	Type of study	Manuscript/ Abstract	Country	Number of patients	Mean age (years)	Male	Female
Rubin 2021 [21]	Retrospective	Letter to Editor	USA	11	61	NR	NR
Hajifathalian 2022 [22]	Prospective	Manuscript	USA	24	53	5	19
Zhang 2021 [23]	Prospective	Manuscript	China	12	63	9	3
Choi 2022 [24]	Retrospective	Manuscript	USA	83	59.4	51	32
Lim 2022 [25]	Prospective	Abstract	Australia	6	64	3	3
Radlinski 2022 [26]	Retrospective	Abstract	USA	15	57.2	8	7
Cai 2022 [27]	Retrospective	Abstract	USA	19	NR	6	13
Wang 2022 [28]	Prospective	Abstract	USA	8	33.1	6	2

USA, United States of America; NR, not reported

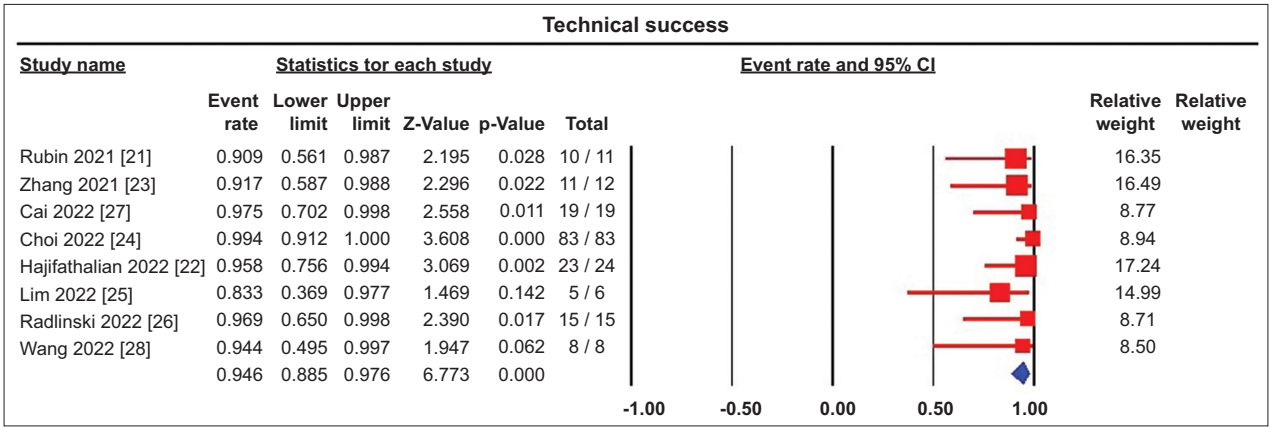

Figure 1 Forest plot showing the technical success of endoscopic ultrasound-guided portal pressure gradient measurement
CI, confidence interval

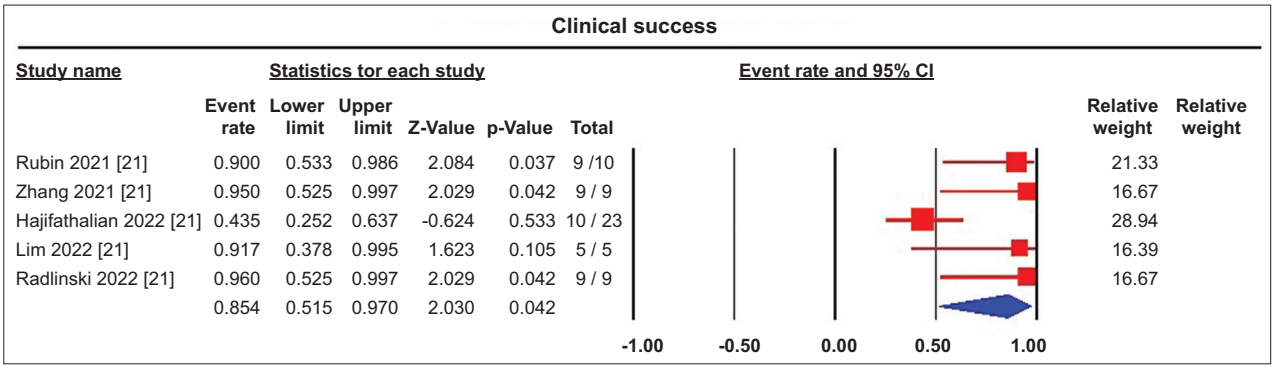

Figure 2 Forest plot showing the clinical success of endoscopic ultrasound-guided portal pressure gradient measurement
CI, confidence interval

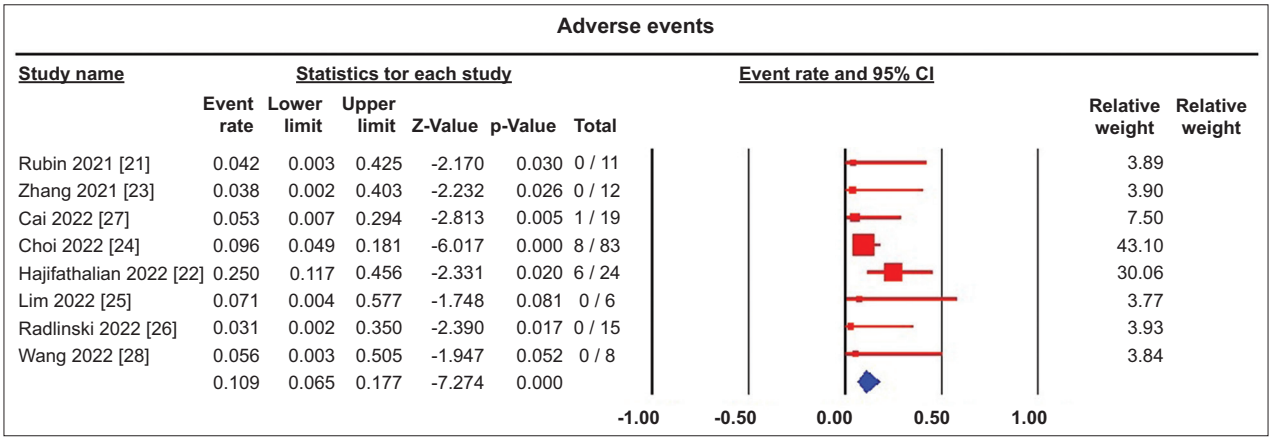

Figure 3 Forest plot showing overall adverse events associated with endoscopic ultrasound-guided portal pressure gradient measurement
CI, confidence interval

these exclusions significantly affected the outcome or the heterogeneity.

Heterogeneity

I^2 analysis and Q statistics for heterogeneity indicated low heterogeneity in the calculated rates of pooled technical success and AE, and substantial heterogeneity in the pooled clinical success of EUS-PPG.

Publication bias

As the total number of studies was less than 10, publication bias was not assessed.

Discussion

This is the first meta-analysis to investigate the EUS-guided measurement of PPG. Our analysis demonstrated high rates of clinical and technical success, with a low AE rate. The technical success rate of EUS-guided measurement of PPG was 94.6%. Since EUS has already been routinely used to identify intra-abdominal structures and vasculature, and to obtain biopsy specimens, all included studies were able to introduce the needle into the hepatic and portal veins with little difficulty [20-28]. There are certain factors that can contribute to a failure to gain access to the vessels, such as a narrow hepatic vein diameter in obese patients and sinusoidal obstruction syndrome or obstruction of a vessel in Budd-Chiari syndrome [22,23,25]. While the inferior *vena cava* could be an alternative point of entry, it too could be compressed in cases of hepatomegaly [23].

The clinical success rate of EUS-PPG was somewhat lower, at 85.4%. Variabilities in the protocol and the technical expertise of the endoscopic sonographers may have contributed to the lower clinical success rate [22]. Furthermore, the type of sedation, sedation depth, mechanical ventilation parameters, patient positioning and fluctuations in abdominal pressure can affect the accuracy of pressures measured in the hepatic and portal veins [22]. Among the 5 studies analyzed for clinical success, 4 demonstrated near-perfect clinical success rates [21,23,25,26] while the study by Hajifathalian *et al* was an extreme outlier, with a 44% success rate [22]. The pooled clinical success was 92.7% if the Hajfathalian study was removed from our analysis. In that study, there were 13 of 23 patients whose EUS-PPG results were incongruent with fibrosis on histology. The authors attributed this to Type II error secondary to a small sample size, with only a few cases having clinically significant PH, while there was also slightly greater variability in the hepatic and venous pressure measurement as compared to previous reports [22]. Zhang *et al* [23] and Lim *et al* [25] used a transjugular approach as control, while Radlinski *et al* [26] used CSPH; all 3 studies demonstrated 100% clinical success. A retrospective analysis by Choi *et al* showed a significant correlation between EUS-PPG ≥5 mmHg and histological hepatic fibrosis [29]. Although the transjugular technique has been shown to correlate well with EUS-PPG, the relationship between the 2 methods is not yet fully understood and could be influenced by patient-specific conditions such as presinusoidal PH [24].

The rate of AEs for EUS-PPG was 10.9%. Most AEs (93.7%) were considered mild as per the ASGE lexicon and were managed conservatively. The sole incidence of bleeding manifested as a hepatic hematoma and was managed conservatively [27]. In order to reduce the risk of bleeding, certain areas can be targeted for introduction of the needle, such as the trunk of the portal vein, where if bleeding occurs it can more easily be noticed and treated [23]. No incidence of perforation, infection or death related to PPG was reported. Therefore, EUS-PPG can be considered a safe procedure.

There are certain disadvantages to EUS-PPG. Given its invasiveness and cost, the widespread use of EUS-PPG may not be feasible in settings with limited resources. The accuracy of EUS-PPG also depends on the technical expertise of the clinician. Moreover, as it is an emerging technique, the relevant evidence and studies available in the literature are limited.

Nonetheless, EUS-PPG also has certain advantages. It is an excellent alternative in circumstances where the transjugular technique is not available or is inaccurate, such as thrombosis or occlusion of the hepatic vein [23]. As EUS-PPG measures portal vein pressure directly, the results will not be compromised by shunt vessels of the hepatic vein [23]. With EUS-PPG, the diagnosis and treatment of PH can be performed by and consolidated under the same gastroenterologist/endoscopist team to optimize the quality of care, with simultaneous variceal screening/surveillance/treatment and liver biopsy if needed [24].

Our study had several limitations, most of which are inherent to any systematic review and meta-analysis. First, we were not able to remove any confounding variables that may have been present in the studies. We did not use gray literature databases in our literature search, as defined by the Cochrane handbook. Second, there were no randomized controlled trials available in the literature to be included in the analysis, but only retrospective or prospective cohort studies. Third, substantial heterogeneity was noted in the pooled clinical success, probably due to different etiologies for elevated PPG and variations in operator expertise, since this is a novel technique. Last, since EUS-PPG is a new technique, the results may be less robust over time, as larger studies on this topic become available and the technique is employed more widely.

Our systematic review and meta-analysis demonstrated that EUS-PPG is a technically feasible and safe procedure for the evaluation of PH. Randomized controlled trials are needed to further evaluate its clinical efficacy. Future studies may consider comparative analyses between EUS-PPG and the transjugular approach, with biopsy as the control, to further elucidate the relationship between the 2 methods of assessing portal pressure. Trials that investigate the relationship between EUS-PPG and noninvasive tests such as fibrosis-4 index are also warranted.

Summary Box

What is already known:

- Portal hypertension (PH) is the major driver of complications in cirrhosis
- Measurement of hepatic venous pressure gradient (HVPG) via a transjugular approach during interventional radiology is the current standard method for determining PH
- HVPG cannot be used for accurate measurement in pre-hepatic or pre-sinusoidal causes of PH

What the new findings are:

- Direct endoscopic ultrasound-guided portal pressure gradient (EUS-PPG) measurement has emerged as a promising alternative method to measure PH
- EUS-PPG is a technically feasible and safe procedure to evaluate portal hypertension

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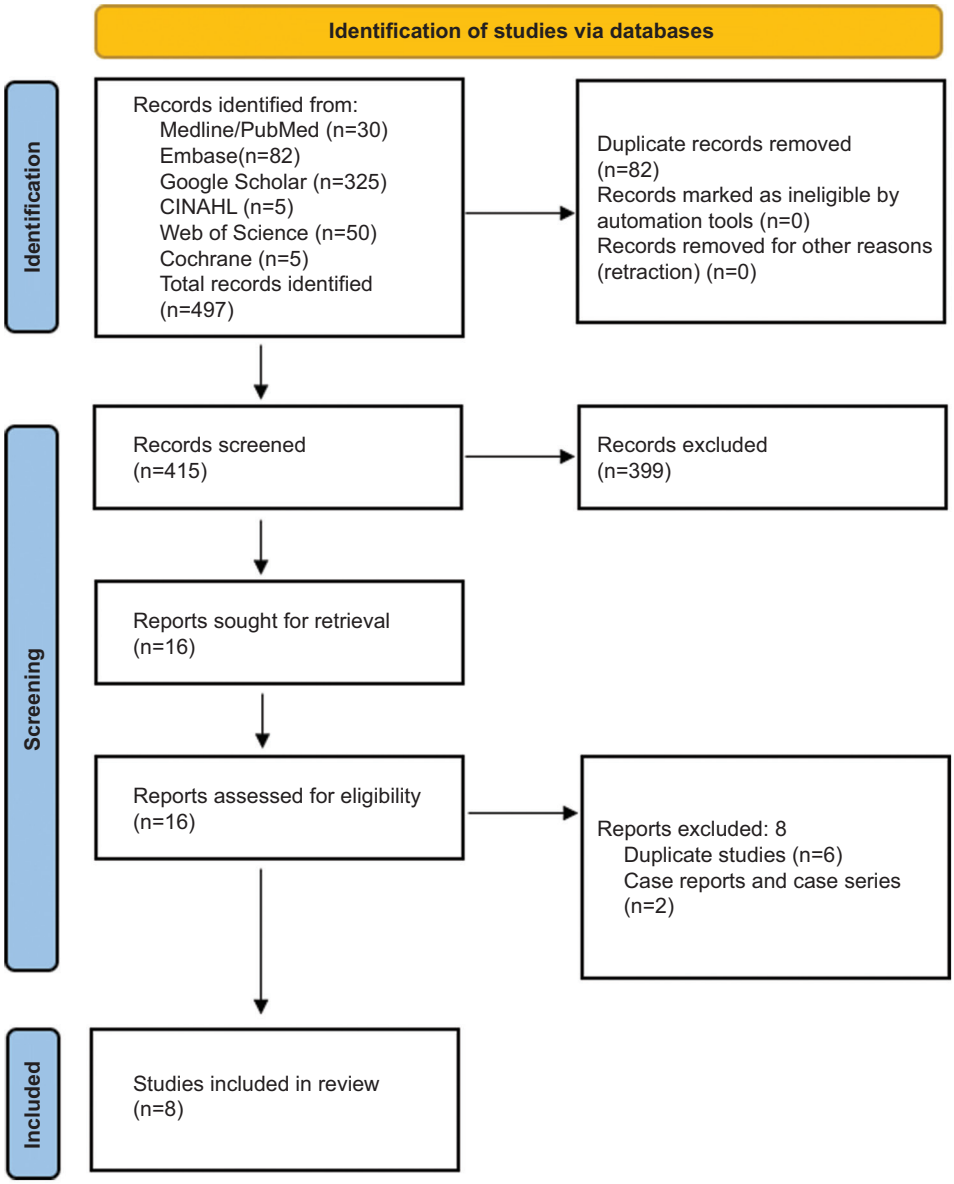
Supplementary material



Supplementary Figure 1 Preferred reporting items for systematic review and meta-analysis diagram showing the screening and study selection process

Supplementary Table 1 Preferred reporting items for systematic review and meta-analysis checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9

(Contd...)

Supplementary Table 1 *(Continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 1-3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9,10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12,13
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2 Newcastle-Ottawa scale quality assessment of studies

Study, year [ref.]	No. of patients	Newcastle-Ottawa Scale		
		Selection	Comparability	Outcome
Rubin 2021 [21]	11	**	*	**
Hajifathalian 2022 [22]	24	***	*	**
Zhang 2021 [23]	12	***	*	**
Choi 2022 [24]	83	***	*	**
Lim 2022 [25]	6	***	*	**
Radlinski 2022 [26]	15	**	*	**
Cai 2022 [27]	19	**	*	**
Wang 2022 [28]	8	**	*	**