Protocol

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Endoscopy for acute upper gastrointestinal bleeding: a protocol for systematic review and network meta-analysis of randomized controlled trials

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Background: Previous studies have reached mixed conclusions regarding the timing of endoscopic approaches for managing individuals with acute upper gastrointestinal bleeding (AUGIB). Therefore, the authors performed a protocol for systematic review and meta-analysis to assess the efficacy of various timing endoscopic approaches in managing individuals with AUGIB.

Methods: The authors will search multiple databases, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure, VIP Database, Wanfang Database, WHO International Clinical Trials Registry Platform, and Chinese Clinical Trial Register. The search will cover the entire duration, starting from the establishment of these databases until July 2023. The selection criteria will focus on randomized controlled trials that assess the efficacy of endoscopy with varying timing in managing patients with AUGIB. The primary outcomes will include primary hemostasis and inpatient death. The secondary outcomes will include recurrent bleeding, need for surgical intervention, admission to the ICU, blood transfusion needs, and duration of hospitalization. Two reviewers will select the studies, extract data, and assess the risk of bias. A Bayesian approach will be used to conduct a network meta-analysis.

Results: The results of this systematic review and meta-analysis will be published in peer-reviewed journals.

Conclusion: This network meta-analysis provides comprehensive evidence of different timing endoscopic approaches for managing individuals with AUGIB.

Keywords: acute upper gastrointestinal bleeding, network meta-analysis, systematic review, timing of endoscopy

Introduction

Prompt and effective management is necessary for acute upper gastrointestinal bleeding (AUGIB), a common medical emergency that poses a substantial risk to patient health[1–3]. It is associated with significant death rates and healthcare costs[4,5]. The use of endoscopic procedures has become a crucial element in the treatment of AUGIB, allowing both diagnosis and treatment[6–8]. Timely recognition and suitable intervention have been associated with improved results, including reduced death rates, reoccurrence of bleeding, requirement for blood transfusion, and the need for surgical procedures[9,10].

HIGHLIGHTS

- Endoscopy is known as the preferred method for managing acute upper gastrointestinal bleeding (AUGIB), however, the best timing endoscopic approach is not clear.
- This study will be the first Bayesian network meta-analysis evaluating effectiveness of different timing endoscopic strategies in the treatment of patients with AUGIB.
- We will exclusively consider randomized controlled trials for inclusion, as they are generally regarded as a more reliable source of unbiased information compared to other study designs.

The advantages of endoscopic intervention for AUGIB have been widely acknowledged. However, meta-analyses[11–13] published to date have not reached consistent conclusions regarding the timing of endoscopic approaches in managing individuals with AUGIB. Meanwhile, these previous meta-analyses had the following shortcomings: (a) There was very high heterogeneity between studies[12,13]. (b) The number of included studies was very small[11]. (c) The definitions of 'very early' endoscopy and 'early' endoscopy were inconsistent[11]. (d) The included studies were published over a 35-years period[11,12]. During this time, endoscopic devices improved, and guidelines changed, which may represent a further limitation of these meta-analyses.

The differences in practice guidelines and recommendations emphasize the need for a thorough assessment of existing evidence to guide clinical decision-making and enhance patient outcomes. Network meta-analysis (NMA) provides a powerful

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method for synthesizing data from numerous studies and comparing the effectiveness of endoscopic interventions across various timing strategies. The primary objective of this NMA is to compare the effectiveness of various timing approaches for endoscopic treatment of AUGIB. Our focus will be on primary hemostasis and inpatient mortality, utilizing both direct and indirect evidence from randomized controlled trials (RCTs). We will also compare rebleeding, surgical necessity, admission to the ICU, blood transfusion, and hospitalization duration. The results of this study will provide comprehensive and robust insights into AUGIB management.

Methods

The protocol strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[14]. The results of NMA will be presented following the guidelines of the PRISMA statement and the PRISMA-NMA extension[15], which is specifically tailored for NMA. This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO)[16]. Our objective is to guarantee transparency, consistency, and methodological rigor in the communication of our research results by adhering to these well-established reporting principles. The utilization of these guidelines enhances the credibility and interpretability of the research outcomes.

Eligibility criteria

Any RCT comparing the results of endoscopy at different times for AUGIB patients meets the eligibility criteria for inclusion in the NMA. Participants will include patients admitted for endoscopic evaluation of AUGIB, regardless of variceal bleeding.

Categorization of studies

To improve comprehensibility and offer better assistance in making decisions, the intervention arms within the endoscopy group will be classified into the following categories: (a) very early endoscopy, which pertains to conducting the procedure with utmost promptness, ideally within a time frame of 12 h from initial presentation. (b) Early endoscopy: in this classification, the procedure is performed within 12–24 h after the initial appearance. (c) Late endoscopy: this classification includes instances where endoscopy is conducted more than 24 h after the initial presentation. By categorizing the timing of endoscopy in this manner, we aim to provide a clearer understanding of the impact of endoscopy at different times on the outcomes. This classification system will facilitate meaningful comparisons and assist in effectively guiding clinical decisions.

Data sources and search strategy

To identify relevant RCTs, we will conduct searches in PubMed, Embase, Web of Science, Wanfang Database, VIP Database, and China National Knowledge Infrastructure for peer-reviewed articles. Additionally, we will search medRxiv for preprint papers. The search will span from July 2020 to July 2023. To ensure a thorough search, a combination of medical subject heading (MeSH) and free-text terms will be employed. These terms can be divided into three primary categories: clinical conditions (such as upper gastrointestinal, upper gastrointestinal, stomach, esophagus, bleeding, or hemorrhage), interventions (very early endoscopy, early endoscopy, emergency endoscopy, late endoscopy, or delayed endoscopy), and study design (including RCT, controlled trials, or randomized controlled trials). Search terms will be adjusted according to the specific requirements of each database. In addition, the reference lists of the included studies will undergo a thorough manual search to ensure that no potentially missed eligible studies are identified in the initial database search. The search strategy for PubMed is presented in Table 1.

Study selection

The search results from each database, along with any additional records, will be gathered and imported into EndNote X9. After eliminating duplicate records through deduplication, two separate reviewers (L.X.L. and X.Y.W.) will assess the titles and abstracts of the identified studies to exclude any irrelevant ones. The remaining studies will be subjected to a comprehensive evaluation of their complete texts according to the pre-established criteria for inclusion. The discussion will be used to resolve any differences in the study selection among the reviewers. Detailed records will be maintained for the excluded studies, documenting the reasons for exclusion. Figure 1 displays a PRISMA flowchart that visually demonstrates the study selection process, presenting a concise depiction of the screening, and selection procedures.

Data extraction

A predesigned form will be used by two separate reviewers (L.X.L. and X.Y.W.) to extract pertinent data from the included studies. The gathered information will include details about the publication (first author, year of publication, and country), characteristics of the population (age, sex, risk of bleeding, and sample size), intervention (time period for early endoscopy), and outcomes of interest. If the required data are not provided, efforts will be made to reach out to the authors of the original study to acquire the missing information. In case of any discrepancies or disagreements, consensus will be reached through discussion.

Table 1

Search strategy in PubMed.

Order	Search items
#1	MeSH terms: 'Upper Gastrointestinal Tract'
#2	Title/abstract: 'Gastrointestinal Tract, Upper' OR 'Upper GI Tract' OR 'GI Tract, Upper'
#3	#1 OR #2
#4	MeSH terms: 'Hemorrhage'
#5	Title/abstract: 'Hemorrhages' OR 'Bleeding'
#6	#4 OR #5
#7	MeSH terms: 'endoscopy'
#8	Title/abstract: 'Surgical Procedures, Endoscopic' OR 'Procedure, Endoscopic Surgical' OR 'Procedures, Endoscopic Surgical' OR 'Surgical Procedure, Endoscopic' OR 'Endoscopy, Surgical' OR 'Surgical Endoscopy' OR 'Endoscopic Surgical Procedure' OR 'Endoscopic Surgical Procedures'
#9	#7 OR #9
#10	MeSH terms: Randomized Controlled Trials as Topic
#11	Title/abstract: 'Clinical Trials, Randomized' OR 'Trials, Randomized Clinical' OR 'Controlled Clinical Trials, Randomized'
#12	#10 OR #11
#13	#3 AND #6 AND #9 AND #12

MeSH, medical subject headings.

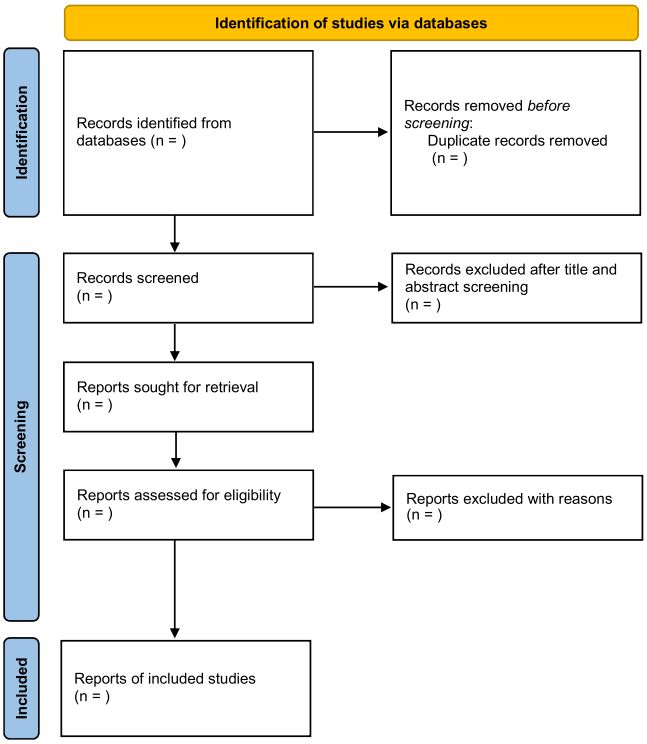

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases.

Outcome measurements

The primary outcome measures for this study are hemostasis and inpatient mortality. Secondary outcome measures include recurrent bleeding, necessity for surgical intervention, ICU admission, necessity of blood transfusion, and length of hospitalization. Comprehensive insights into the effectiveness of various timing strategies for endoscopic therapy in managing AUGIB will be obtained through careful assessment and analysis of these outcomes.

Risk of bias assessment

The Cochrane tool, Risk of Bias 2, will be utilized[17]. The tool detects possible biases in the randomization process, deviations from intended interventions, absence of outcome data, outcome measurements, and selection of reported results. Two independent reviewers (L.X.L. and X.Y.W.) will assess the risk of bias. The final determination of 'low risk of bias', 'some concerns', or 'high risk of bias' will be reached depending on the answers provided to these inquiries. Reviewers will discuss and resolve any discrepancies that occur during the assessment process. A thorough evaluation of the risk of bias intend to guarantee the reliability and validity of the included studies, thereby enhancing the overall credibility of the evidence in the analysis.

Data synthesis

The characteristics of the included trials will be summarized and presented in a tabular format. This summary provides a comprehensive overview of key details such as study design, sample size, participant demographics, and intervention characteristics. To compare the effects of different timing endoscopic interventions on outcomes in patients with AUGIB, a Bayesian NMA will be conducted using the 'netmeta' package available in the R software[18]. This package provides the necessary tools and algorithms to perform a NMA and derive meaningful conclusions from combined evidence. The analysis will include both direct and indirect comparisons of the interventions, enabling a comprehensive understanding of their relative effectiveness. The results of these comparisons are presented in the form of a network diagram that visually depicts the relationships between different interventions and their respective outcomes. Each node in the diagram represents an intervention category specified by the inclusion criteria. The size of each node is directly related to the number of patients receiving specific treatment. The effects of pairwise comparisons between the two interventions are depicted as edges that connect the respective nodes. The thickness of the edge lines corresponds to the weight assigned to pairwise comparison. A contribution matrix will be generated to assess the impact of individual comparisons and the influence of both direct and indirect evidence on the overall summary effects. This matrix will provide insights into the relative contributions of different comparisons and the strength of the evidence derived from direct and indirect sources. In cases where quantitative synthesis is not feasible or deemed inappropriate, narrative synthesis will be conducted[19]. This narrative synthesis will involve a descriptive summary and interpretation of the findings, allowing for qualitative understanding of the evidence obtained from the included trials.

Assessment of transitivity and meta-biases

Based on the preliminary search findings, it is anticipated that endoscopy interventions for AUGIB identified will be amenable to joint randomization, thus satisfying the transitivity assumption. Consequently, inferences regarding comparisons between interventions in the network will be drawn from a combination of direct evidence (i.e. pairwise RCTs) and indirect evidence (i.e. deriving the effect of B–C from A–B and A–C comparisons). Both direct and indirect evidence will be utilized or a combination of both to inform the analysis and make informed assessments of the relative effectiveness of interventions within the network.

NMA

Assuming the similarity of the effect-modifier distribution across studies, a frequentist NMA will be conducted, taking into account the proposed closed network geometry. By incorporating all available evidence within the network, pairwise effect sizes will be computed to assess relative treatment effects. In situations where a direct comparison between the two interventions is lacking, indirect comparisons can be made using a common comparator. Various graphical tools will be employed to facilitate the ranking of mixed (direct and indirect) effect sizes, as well as to present the corresponding 95% CI for all treatment combinations within the network. These include network forest plots, interval plots, and league tables. These visual aids will provide a comprehensive overview of the treatment effects and aid in the interpretation and comparison of different interventions in the network.

Detection of heterogeneity

Our meta-analysis aims to combine the results of the included studies if they exhibit sufficient homogeneity in terms of participants, interventions, and outcomes. To assess the degree of heterogeneity among the individual studies, we will employ both the χ^2 test and inconsistency index (I^2)[20]. If the I^2 value is greater than 50%, indicating substantial heterogeneity, we will utilize a random-effects model for the meta-analysis to account for this variability among the studies. On the other hand, if the I^2 value is 50% or lower, indicating low-to-moderate heterogeneity, we will proceed with a fixed-effect model to combine the effect sizes.

Additional analyses

To investigate the potential effect modifiers and their impact on the primary outcome, network meta-regression will be conducted using a random-effects model whenever adequate data and information are available within the included studies. Effect modifiers of interest may include factors such as the average age of participants, sex distribution, etiology of bleeding, severity of illness, and study quality. Subgroup analyses will also be performed based on specific cutoff times for very early endoscopy, age categories, study quality, publication time, sex, etiology, severity of illness, and bleeding risks. These subgroup analyses will focus on studies that specifically assess the clinical outcomes of very early endoscopy. To ensure the robustness of the primary findings, sensitivity analysis will be conducted by systematically excluding one study at a time. This analysis will help to assess the impact of individual studies on the overall results and provide insights into the stability and reliability of the findings. Furthermore, potential publication bias will be assessed by inspecting a comparison-adjusted funnel plot[21]. This graphical tool will help to identify any potential asymmetry in the distribution of study effects, which could suggest the presence of publication bias.

Credibility of the evidence

We will utilize the Confidence in Network Meta-Analysis (CINeMA) approach to evaluate the credibility of the data obtained from NMA[22]. Two independent reviewers (L.X.L. and X.Y.W.) will assess the following six domains: within-study bias, cross-study bias, indirectness, imprecision, heterogeneity, and incoherence. In cases where disagreements arise, a discussion between the reviewers is initiated to reach a consensus. The confidence in the results will be graded using the following categories: 'high', 'moderate', 'low', and 'very low'. This grading system reflects the level of confidence in the quality and reliability of the evidence generated by the NMA. By employing this rigorous assessment process, we aimed to evaluate the credibility of the evidence obtained from the NMA, allowing us to make informed conclusions and recommendations based on the quality of the available evidence.

Discussion

AUGIB is a common surgical emergency requiring hospital admission and associated with high morbidity and mortality. Early diagnosis and intervention can minimize mortality. Endoscopy has been recognized as the most important method for managing AUGIB. Although several studies, including meta-analyses, have explored the timing of endoscopic treatment of AUGIB, there is still controversy on the timing of endoscopy. The present study will utilize NMA to explore the optimal timing of endoscopic treatment of AUGIB, and the results of the study will provide high-quality evidence-based medical evidence for the endoscopic management of AUGIB.

The present systematic review will have several notable strengths. Firstly, to our best knowledge, this study will be the first Bayesian NMA evaluating effectiveness of different timing endoscopic strategies in the treatment of patients with AUGIB. Secondly, we will only consider RCTs for inclusion, as they are generally regarded as a more reliable source of unbiased information compared to other study designs. Nevertheless, it is important to acknowledge several possible limitations inherent to the intended systematic review. Firstly, the number of included studies may be limited, because we will only consider RCTs for inclusion. Secondly, there may be considerable heterogeneity between studies.

We are confident that the present systematic review and NMA will be an exceptional contribution to the field of AUGIB. Whether the results will allow the generation of specific guidelines and recommendations for timing endoscopic strategies in the treatment of patients with AUGIB, or identify the particular fields where more quality studies are required, this effort will be a critical contribution to evidence-based care of patients with AUGIB.

Ethical approval

Ethical approval was not obtained because we conducted systematic reviews that did not collect personal information from patients.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

X.F.T.: designed the study; L.X.L. and X.Y.W.: developed the search strategy and risk of bias assessment; X.F.T.: wrote the manuscript; Y.W.Z.: revised the protocol. The authors have thoroughly reviewed the protocol and provided consent for publication.

Conflicts of interest disclosure

There are no conflicts of interest to disclose.

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Guarantor

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Data availability statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Provenance and peer review

None.

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