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Lactate level as a predictor of outcomes in patients with acute upper gastrointestinal bleeding: A systematic review and meta-analysis

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Abstract. There remains no consensus on the prognostic value of lactate in predicting adverse outcomes such as mortality, rebleeding and higher intensive care unit (ICU) admission rates in patients with upper gastrointestinal bleeding (UGIB). The present study aimed to determine the prognostic accuracy of lactate level in predicting adverse clinical outcomes in patients with acute UGIB. Systematic literature search was conducted in PubMed Central, SCOPUS, EMBASE, MEDLINE, Google Scholar and ScienceDirect databases for studies published up to February 2023. Random-effects model was used for the meta-analysis and the results were presented as pooled standardized mean differences or odds ratio (OR) with 95% confidence interval (CIs). A total of 11 studies were included in the present review. Most of the studies had a high risk of bias. Pooled OR were as follows: 1.39 (95% CI: 1.29-1.51; I^2=85%) for the prediction of mortality; 1.29 (95% CI: 1.17-1.42; I^2=85.9%) for prediction of ICU admission, 1.14 (95% CI: 1.06-1.23; I^2=42.4%) for rebleeding and 2.84 (95% CI: 2.14-3.77; I^2=8.1%) for the need of packed red blood cell (pRBC) transfusion. Sensitivity and specificity for the mortality prediction were 72% (95% CI: 57-83%) and 75% (95% CI: 61-85%), respectively, with the area under the curve of 0.79 (95% CI: 0.72-0.85). In conclusion, the results showed that lactate level is a moderately accurate early prediction marker of most adverse clinical outcomes such as mortality, rebleeding, ICU admission and the need for pRBC transfusion in acute UGIB patients.

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Introduction

Upper gastrointestinal bleeding (UGIB) is a frequent medical emergency (1) that may arise from peptic ulcers, oesophageal varices, Mallory-Weiss tears and malignancies and is associated with high mortality and morbidity rates (2). Therefore, early detection and prompt management are essential to improve patient outcomes. However, predicting outcomes in patients with acute UGIB is still challenging. Traditional prognostic markers such as age, comorbidities and bleeding intensity are not necessarily accurate indicators of how a patient will fare (3). Therefore, identifying accurate indicators of prognosis in patients with acute UGIB is crucial.

Prognostic value of lactate levels as predictor of outcomes in acute UGIB has drawn more attention in recent years (4-6). Lactate is a by-product of an anaerobic metabolism and builds up in hypoxic tissues (7). Measuring lactate levels is an easy, affordable and accessible test (8). Recent studies show that increased lactate levels are associated with a number of unfavourable outcomes, such as mortality, extended hospital stays and requirement for ICU admission (4,6,9). Increased lactate levels in critically ill patients have been linked to poor outcomes in cases of sepsis, trauma and cardiac arrest (9).

However, it is still debatable whether lactate levels play a role in predicting outcomes in UGIB. While some studies have found no significant correlation, others have established a relationship between elevated lactate levels and poorer outcomes in UGIB patients (4-6). The main goal of the current systematic literature review was to assess the evidence, summarize available findings on the association of lactate levels with outcomes in acute UGIB and evaluate whether the lactate levels can act as predictor for adverse outcomes in patients with UGIB.

Materials and methods

Inclusion criteria

Study design. Observational studies, including cohort (prospective/retrospective), case-control and cross-sectional studies, were considered for inclusion. Full-text studies that met the eligibility criteria were included, while case reports/series and unpublished grey literature were excluded from the analysis. The study was registered at PROSPERO; no. CRD42023406493.

Study participants. Studies performed in patients with acute UGIB who underwent lactate tests were included.

Index test and reference standard. Studies comparing the prognostic role of lactate levels with the real-time occurrence of adverse outcomes through the follow-up of patients either through records or in-person were included.

Outcomes. Mortality, need for packed red blood cell (pRBC) transfusion, rebleeding and ICU admissions.

Search strategy. Search was conducted in multiple databases, including PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/), SCOPUS (https://www.scopus.com/search/form.uri?display=basic#basic), EMBASE (https://www.embase.com/login), MEDLINE (https://pubmed.ncbi.nlm.nih.gov), Google Scholar (https://scholar.google.com) and ScienceDirect (https://www.sciencedirect.com) using medical subject headings (MeSH) and free-text terms with the appropriate Boolean operators ('AND,' 'OR,' and 'NOT') to combine predefined search terms. The search period ranged between January 1964 and February 2023, without any language restrictions (Appendix S1).

Study selection. The initial stage of the study selection process was conducted independently by two researchers, who examined the titles, keywords and abstracts of the identified studies. For the second phase of screening, full texts of the selected studies were retrieved by both investigators. Studies that met eligibility criteria were ultimately included for further analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020 was used to report the present study (10).

Data extraction. For data extraction, two researchers participated in the manual data extraction procedure using a predefined semi-structured data collection form. A third researcher was involved in resolving any conflict arising out of data extraction process.

Risk of bias assessment. Quality of the included studies was assessed by two investigators using the Newcastle Ottawa Scale for observational studies (11). The scale encompasses selection, comparability and outcome domains. Based on the responses, each study was categorized as having good/poor quality.

Statistical analysis. The pooled effect was calculated as standardized mean difference (SMD)/odds ratio (OR) with 95% confidence interval (CI) depending on the type of outcome. Using the inverse variance technique, a random effects model was applied (12). Predictive accuracy was evaluated by calculating the combined values of sensitivity, specificity, likelihood ratios for positive and negative outcomes as well as the overall diagnostic OR for lactate levels. Area under the Receiver Operator Characteristic (AUROC) was used to produce Summary Receiver Operator Characteristic curves (SROC) (13).

Heterogeneity was measured by I^2 statistics and the χ^2 of heterogeneity. The effect of a single study on the pooled estimates was determined by sensitivity analysis. Publication bias assessment and meta-regression could not be performed as none of the outcomes had at ≥10 studies. STATA version 14.2 (StataCorp LLC) was used for the analysis.

Results

Search results. A total of 1,489 citations were identified across the databases. Following duplicates removal, 91 full-text articles were retrieved and underwent secondary screening. Finally, a total of 11 studies that satisfied the eligibility criteria were included (Fig. 1) (4-6,14-21).

Characteristics of the included studies. The majority of the studies were conducted in the United States of America (four studies) and Korea (three studies). Most studies were retrospective (six out of 11 studies). Sample size in the included studies varied between 104 and 1,644. The mean age of the participants varied from 55.4-72.9 years. The cut-off for the lactate levels to predict adverse outcomes ranged from 1.85 to 4.3 mmol/l. Of the studies, >50% (six out of 11 studies) had a higher risk of bias (Table I).

Mortality. A total of nine studies reported the utility of lactate levels for prediction of mortality in patients with acute UGIB. Of them, six studies reported the outcomes in terms of OR, with the pooled OR of 1.39 (95% CI: 1.29-1.51; I^2=85%), indicating that in patients with acute UGIB higher lactate level are significantly associated with increased mortality compared with normal lactate levels ($P<0.001$; Fig. 2).

The predictive accuracy of lactate for mortality in patients with acute UGIB is shown in Fig. 3. The diagnostic OR was 7 (95% CI: 5-12), the sensitivity and specificity were 72% (95% CI: 57-83%) and 75% (95% CI: 61-85%), respectively and the positive and negative likelihood ratios were 2.8 (95% CI: 2-4.1) and 0.38, respectively (95% CI: 0.27-0.54). The AUROC was 0.79 (95% CI: 0.72-0.85) (Fig. 4).

Differences in the mean values of lactate in survivors and non-survivors were reported in five studies. The pooled SMD was 1.83 (95% CI: 0.56-3.09; I^2=96.2%), indicating that the non-survivors had significantly higher values of lactate when compared with survivors ($P<0.001$; Fig. 5).

ICU admission. A total of three studies reported the value of lactate levels for prediction of ICU admission in patients with acute UGIB with the pooled OR of 1.29 (95% CI: 1.17-1.42; I^2=85.9%), indicating that higher lactate levels associated with increased odds of acute UGIB patients being admitted to ICU compared with normal lactate levels ($P<0.001$; Fig. 6). Small number of studies, reporting this outcome did not allow to assess the predictive accuracy and mean values.

Rebleeding. A total of four studies reported the utility of lactate levels for prediction of rebleeding in patients with acute UGIB. Of them, three studies reported the outcomes in terms of OR. The pooled OR was 1.14 (95% CI: 1.06-1.23; I^2=42.4%) indicating that higher lactate levels are associated with significantly higher ($P<0.001$) odds of rebleeding

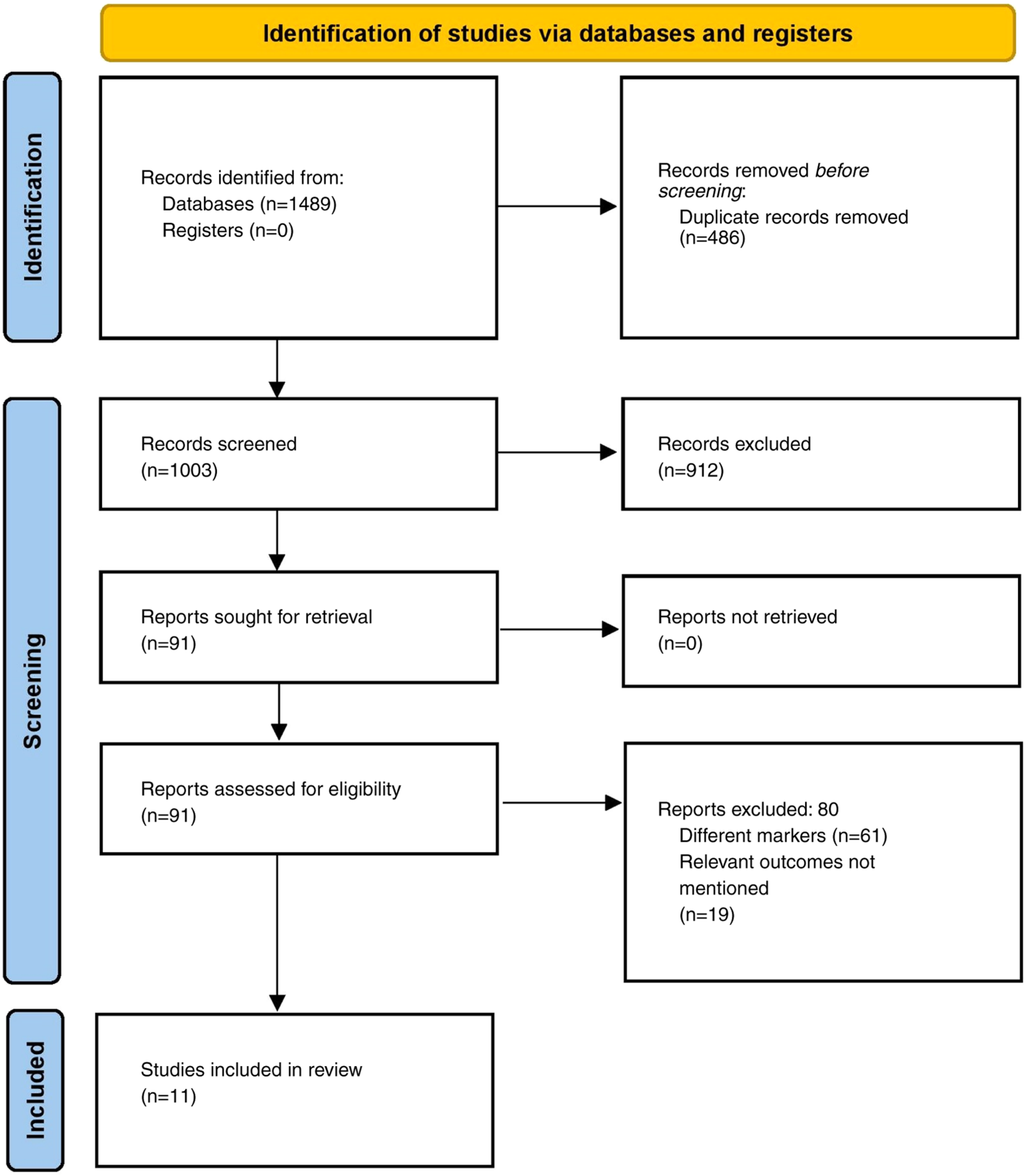

Figure 1. Search strategy.

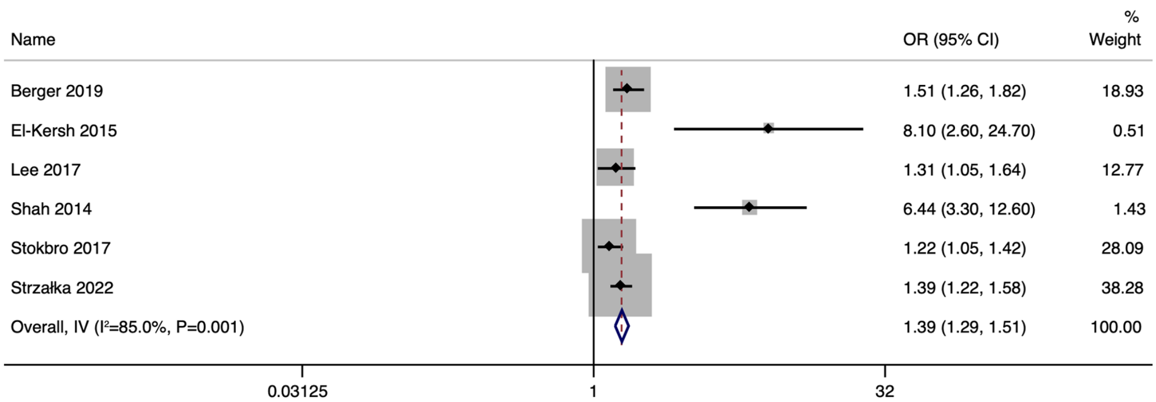

Figure 2. Forest plot showing the difference in lactate levels (in terms of odds ratio) between survivors and non-survivors of acute upper gastrointestinal bleeding patients. OR, odds ratio; CI, confidence interval.

Table I. Characteristics of the included studies.

First author, year	Study design	Country	Inclusion criteria	Sample size	Cut-off for lactate levels	Mean age, years	Sex distribution, male:female	Outcomes reported	Risk of bias	(Refs.)
Berger et al, 2019	Retrospective	USA	Consecutive patients presenting to the ED of a tertiary care medical center between January 2014 and December 2015 with a charted diagnosis of acute gastrointestinal bleeding	366	2.75	70.9	204:162	Mortality	High	(17)
El-Kersh *et al*, 2015	Retrospective cohort	USA	Consecutive patients with acute UGIB admitted to university hospital ICU between 2010 and 2013	133	2.1	55.4	86:47	Mortality	High	(19)
Gulen *et al*, 2019	Prospective	Turkey	Patients with UGIB who were admitted to the emergency department between 1 June 2018 and 31 May 2019	139	2.32	63.34	100:39	Mortality, need for packed red blood cell transfusion	Low	(15)
Kim *et al*, 2022	Retrospective	Korea	Patients aged ≥18 years who visited the ED, complaining of any GI bleeding symptoms (melena, hematemesis and/or hematochezia), serum lactate levels measured initially in the ED and then measured for follow-up after 3 h.	104	3.4	64.6	74:30	Mortality	High	(6)
Ko *et al*, 2015	Retrospective	Korea	Consecutive adult (>18 years) patients with UGIB who were hemodynamically stable (defined as an SBP of ≥90 mm Hg) at presentation in the ED of Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, Sichuan) between January 2010 and December 2014	1,003	2.5	61.8	732:271	Mortality, ICU admission, need for packed red blood cell transfusion	High	(18)
Lee *et al*, 2017	Retrospective	Korea	Adult patients (>18 years old) with UGIB who underwent endoscopic hemostasis at the Samsung Medical Center between January 2006 and August 2016	114	NR	65.1	86:28	Mortality, ICU admission, Rebleeding	Low	(16)

Table I. Continued.

First author, year	Study design	Country	Inclusion criteria	Sample size	Cut-off for lactate levels	Mean age, years	Sex distribution, male:female	Outcomes reported	Risk of bias	(Refs.)
Shah *et al*, 2014	Retrospective cohort	USA	Medical records of patients having acute gastrointestinal bleeding between January 1, 2004 and December 31, 2009	1,644	4	56.8	869:775	Mortality	Low	(20)
Shrestha *et al*, 2018	Retrospective	USA	Patients ≥18 years old presenting to emergency with acute GIB between January 2014 and December 2014	468	2	59.5	250:218	ICU admission, need for packed red blood cell transfusion	High	(14)
Stokbro *et al*, 2017	Retrospective cohort	Denmark	Patients admitted with UGIB to Odense University Hospital in the one-year period between March 1 2014 and February 28 2015	331	1.85	72.9	183:148	Mortality, Rebleeding	Low	(4)
Strzalka *et al*, 2022	Prospective	Poland	Adult patients with symptoms of acute UGIB admitted to hospital between 1st January 2018 and 31st December 2019	221	4.3	63.5	151:70	Mortality, ICU admission, rebleeding	Low	(21)
Wada *et al*, 2016	Retrospective	Japan	Patients who were admitted to hospital with a primary diagnosis of UGIB	154	NR	60	115:39	Rebleeding	High	(5)

NR, not reported; ICU, intensive care unit; UGIB, upper gastrointestinal bleeding; ED, emergency department; GI, gastrointestinal.

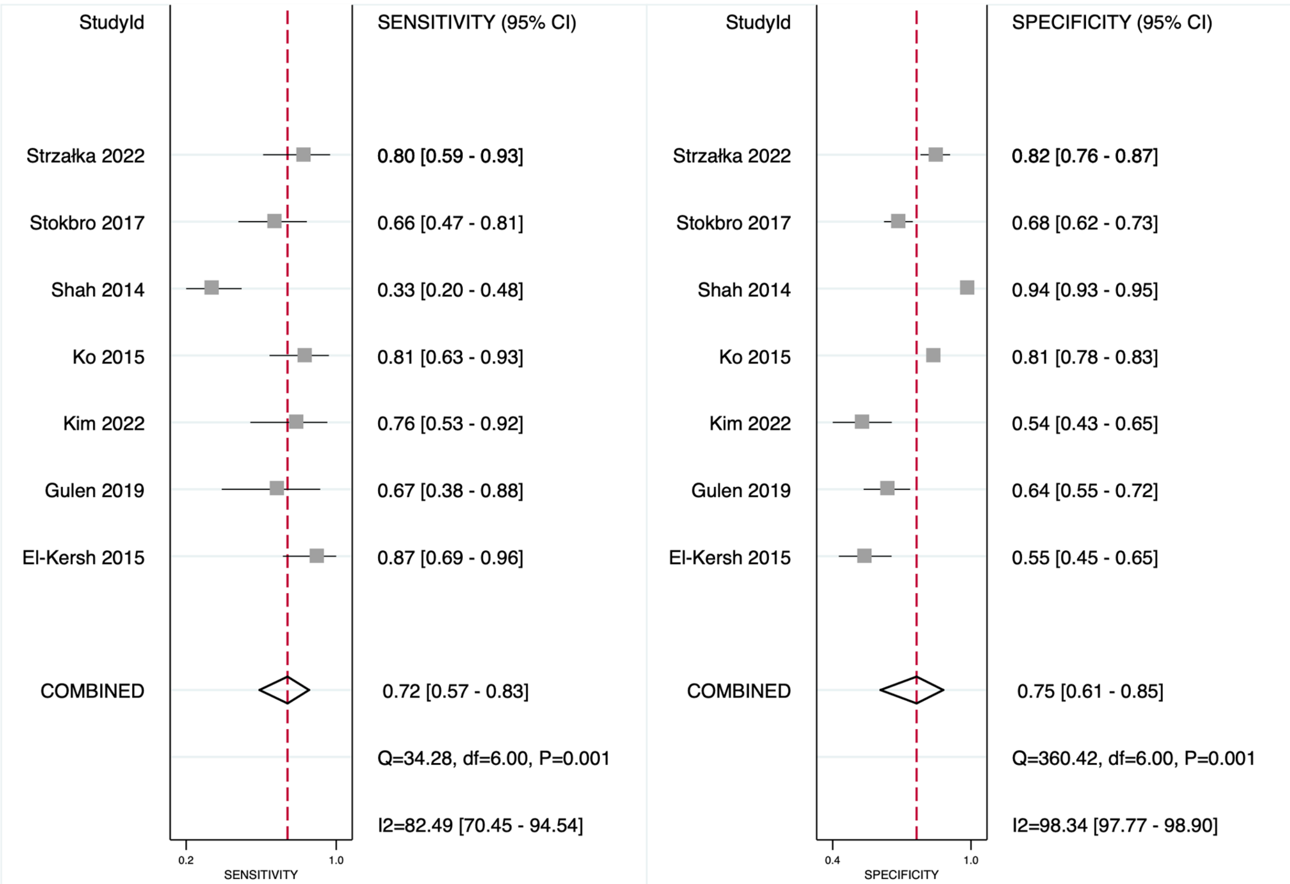

Figure 3. Forest plot showing the predictive accuracy of lactate levels for mortality of acute upper gastrointestinal bleeding patients. CI, confidence interval.

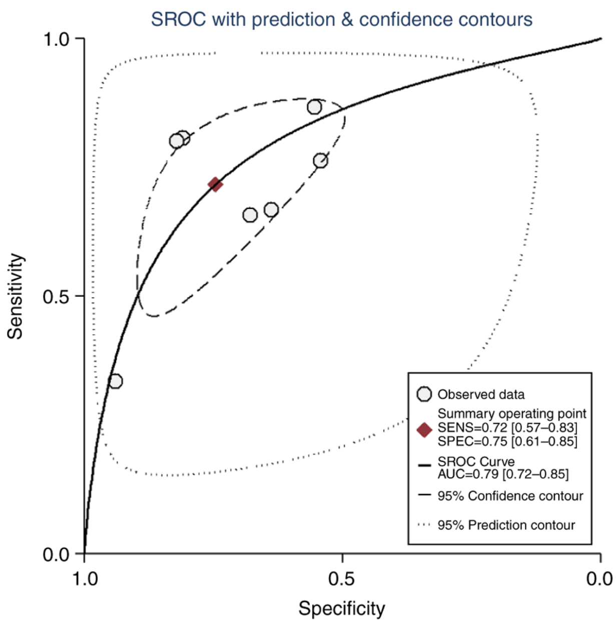

Figure 4. Summary Receiver Operative Characteristic plot showing the predictive accuracy of lactate levels for mortality of acute upper gastrointestinal bleeding patients. SROC, Summary Receiver Operative Characteristic; AUC, area under the curve.

compared with normal lactate levels (Fig. 7). The difference in mean values of lactate between acute UGIB patients with and without rebleeding were reported in two studies. Pooled SMD was -0.29 (95% CI: -0.94 to 0.37; I^2=71.1%; p=0.39; Fig. 8).

Need for pRBC transfusion. A total of three studies reported the prognostic value of lactate levels for prediction of the need for pRBC transfusion, with the pooled OR of 2.84 (95% CI: 2.14-3.77; I^2=8.1%). This indicated that in patients with acute UGIB, higher lactate levels are associated with higher odds of requiring pRBC transfusion compared with normal lactate levels (P<0.001; Fig. 9). The predictive accuracy and mean values are not reported due to the small number of studies.

Additional analysis. Sensitivity analysis did not show any difference for any of the above outcomes, indicating that there were no single-study effects.

Discussion

The present study aimed to investigate whether the lactate may act as a predictor for adverse clinical outcomes in patients with UGIB. The results suggested that the lactate level is a moderately accurate early marker for predicting most adverse outcomes such as mortality, rebleeding, ICU admission and a need for pRBC transfusion. Although, no previous similar reviews were conducted, these findings were consistent across almost all the included studies in the present review (4-6,14-21). Presently, commonly used prognostic markers in patients with acute UGIB include shock index (22), hemodynamic

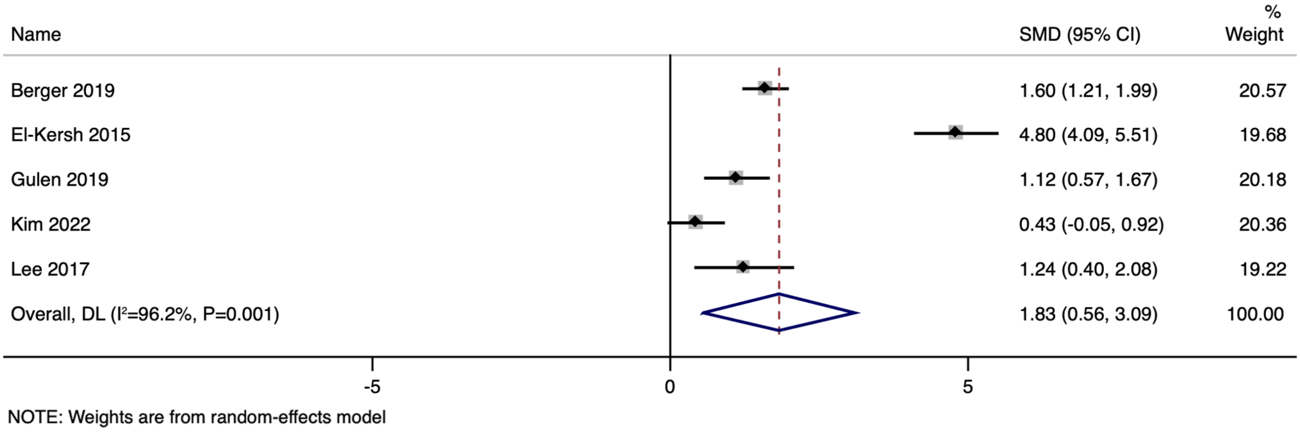

Figure 5. Forest plot showing the difference in lactate levels (in terms of mean difference) between survivors and non-survivors of acute upper gastrointestinal bleeding patients. SMD, standardized mean difference; CI, confidence interval.

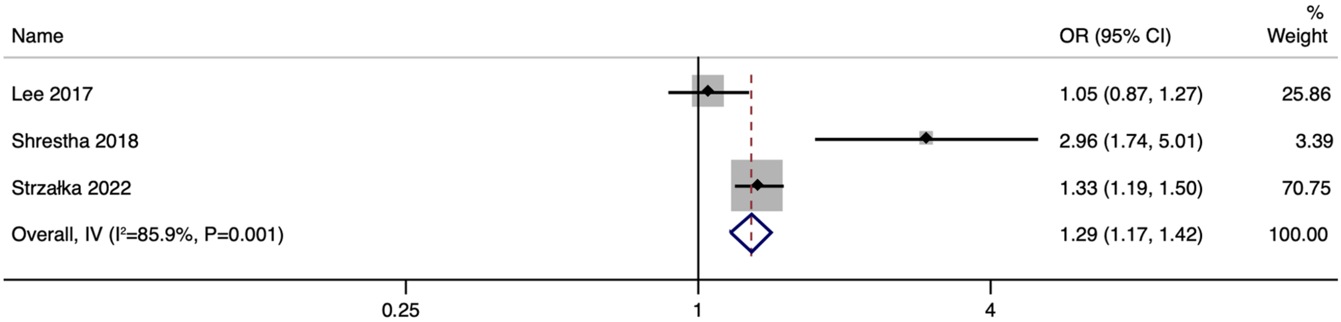

Figure 6. Forest plot showing the difference in lactate levels (in terms of OR) between patients with and without ICU admission of acute upper gastrointestinal bleeding patients. ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

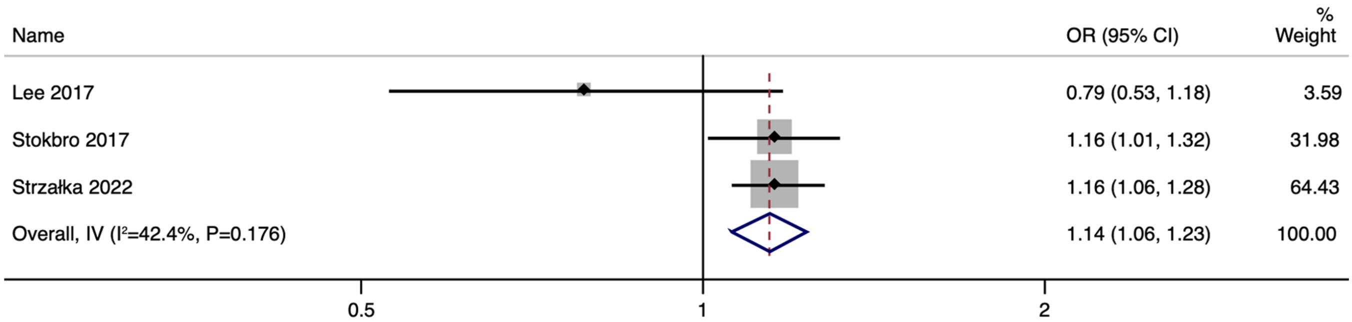

Figure 7. Forest plot showing the difference in lactate levels (in terms of OR) between patients with and without rebleeding of acute upper gastrointestinal bleeding patients. OR, odds ratio; CI, confidence interval.

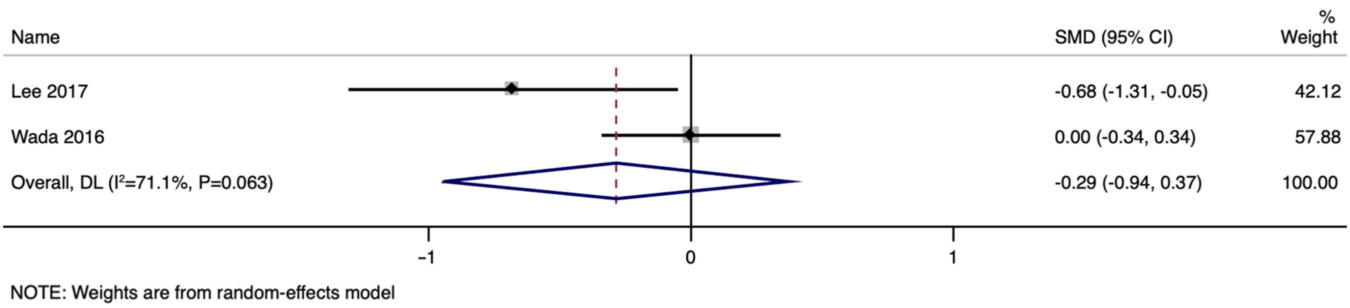

Figure 8. Forest plot showing the difference in lactate levels (in terms of mean difference) between patients with and without rebleeding of acute upper gastrointestinal bleeding patients. SMD, standardized mean difference; CI, confidence interval.

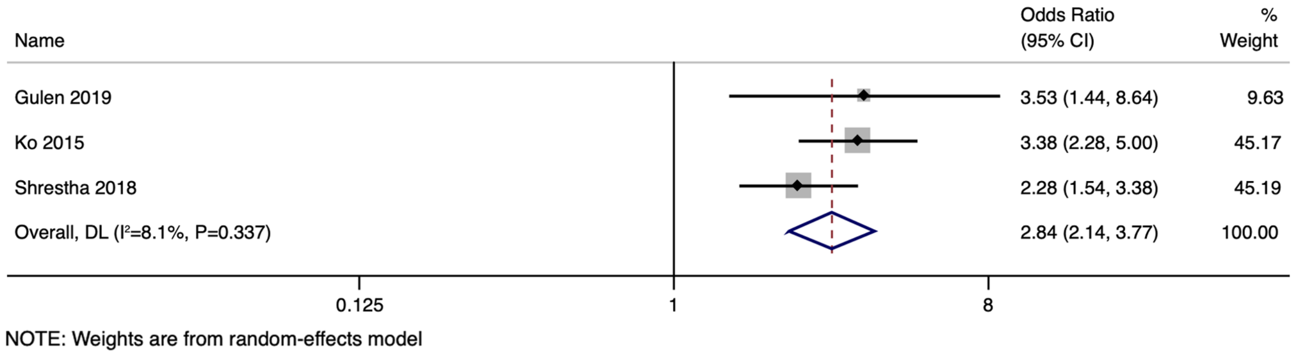

Figure 9. Forest plot showing the difference in lactate levels (in terms of odds ratio) between patients with and without need for packed red blood cell transfusion of acute upper gastrointestinal bleeding patients. CI, confidence interval.

parameters (23), Glasgow-Blatchford score (24) and Rockall score (24). However, these markers have limitations, such as low sensitivity and specificity, or a need for complex calculations. By contrast, lactate levels have been found to be more accurate than other markers such as base deficit or pH, as they rise earlier and more consistently in response to hypoperfusion and provide a more reliable marker of tissue hypoxia (25-27). Since blood loss in patients with acute UGIB can lead to a decrease in oxygen-carrying capacity, lactate levels can serve as a reliable early marker of hypoperfusion. As cells switch to anaerobic metabolism in response to hypoperfusion, lactate production is increased and it is released into the bloodstream (27), leading to adverse outcomes such as higher mortality rates, rebleeding and increase in ICU admission. Therefore, using lactate levels for early detection of hypoperfusion can help clinicians timely identify patients at risk of adverse outcomes and take appropriate action to prevent further deterioration (28).

Elevated lactate levels, a reflection of tissue hypoperfusion and oxygen supply-demand imbalance, emerged as a potent predictor in the present study. Notably, the association between higher lactate levels and the need for pRBC transfusion was more pronounced compared with other clinical outcomes. This underscores the significance of early lactate measurement, potentially guiding clinicians towards urgent interventions and potentially preventing further complications. In addition, lactate levels can be used to guide resuscitation efforts in patients with acute UGIB. Early recognition of hypoperfusion can prompt clinicians to initiate resuscitation measures such as intravenous fluids, blood transfusions, or vasopressors. Serial lactate measurements can also be used to monitor response to treatment and guide ongoing resuscitation efforts (29).

The present study had some limitations. Given the variations in methodologies and quality among the included research, its results should interpreted with caution. For some outcomes, there was significant between-study variability. Due to a restriction in the number of papers, meta-regression and publication bias evaluation were not possible. The included studies measured lactate levels at various time points (at admission, or at different time intervals after the admission). This variation in the timing of measurement could have influenced the predictive accuracy of lactate levels. Additionally, some of the included studies reported that lactate clearance, or the change in lactate levels over time, is more important than initial lactate levels in predicting outcomes. This highlights the potential importance of monitoring lactate levels serially rather than relying solely on a single measurement. The studies included in the present review used different lactate cut-off values to define elevated levels, which may have affected the results. Future studies with standardized lactate cut-off values are needed for better comparability and generalizability of results.

Nonetheless, the present study has several important implications for surgeons, clinicians and nursing care professionals. Lactate levels are an important tool for managing acute UGIB patients and should be used routinely in clinical practice. The present study also supported the need for more studies on the predictive accuracy of lactate. It is important to further evaluate and compare multiple biomarkers and decide on the best possible combination of tests for prediction of adverse clinical outcomes in patients with acute UGIB.

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Availability of data and materials

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

Authors' contributions

FZ conceived and designed the study. LD and LL collected the data and performed the literature search. FZ was involved in the writing of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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