Prognostic value of the preoperative lactate dehydrogenase-to-albumin ratio in patients with gastrointestinal cancer

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Abstract. Gastrointestinal cancer (GIC) remains a major clinical burden, and readily available biomarkers are needed to improve preoperative prognostic assessment and risk stratification. The present study aimed to evaluate the prognostic significance of the preoperative lactate dehydrogenase-to-albumin ratio (LAR) in patients with GIC. A comprehensive search was performed in PubMed, Embase and the Cochrane Library to identify relevant studies published from the date of database inception to March 20, 2025. The extracted outcomes included hazard ratios (HRs) for overall survival (OS) and recurrence-free survival (RFS) and odds ratios (ORs) for major postoperative complications. A total of five independent studies involving 6,379 patients were included in the present meta-analysis. A higher preoperative LAR was significantly associated with poorer OS [HR=1.90; 95% confidence interval (CI), 1.63-2.21; P<0.001]. Subgroup analysis confirmed the robustness of this association across analytical models, cancer types, countries and LAR cut-off values. A higher LAR was also associated with poorer RFS (HR=1.83; 95% CI, 1.52-2.20; P<0.001) and a higher risk of major postoperative complications (OR=2.36; 95% CI, 1.49-3.74; P<0.001). In conclusion, preoperative LAR may serve as a useful prognostic biomarker for survival outcomes in patients with GIC. Incorporating this readily available and low-cost biomarker into routine preoperative assessment may help improve perioperative risk stratification and guide postoperative management.

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Introduction

Gastrointestinal cancers (GICs), including colorectal cancer (CRC), gastric cancer (GC) and esophageal cancer (EC), are among the most common malignancies worldwide. CRC is the third most commonly diagnosed cancer and the second leading cause of cancer-related death, whereas GC remains one of the leading causes of cancer-related death (1). Despite advances in diagnostic and therapeutic strategies, radical resection remains the cornerstone of treatment for numerous patients with GIC (2,3). However, postoperative outcomes remain unsatisfactory, and only ~50% of patients survive >5 years after surgery (4,5). Therefore, identifying sensitive and clinically accessible prognostic biomarkers is essential for improving risk stratification, guiding clinical decision-making, enabling prompt interventions, and consequently improving the survival and quality of life of patients with GIC.

Lactate dehydrogenase (LDH) is a widely used and inexpensive laboratory marker in clinical practice. As a key enzyme in glycolysis, LDH catalyzes the conversion of pyruvate to lactate under anaerobic conditions. Its expression is regulated by multiple factors, including MYC-related oncogenic signaling, hypoxia within the tumor microenvironment and cellular necrosis (6,7). Elevated LDH levels may reflect tumor burden, proliferation, invasiveness and tissue damage. LDH has been identified as a notable prognostic biomarker in several malignancies, including CRC and other GICs (8,9).

Serum albumin is another routinely measured clinical marker that reflects nutritional status and systemic inflammation. Decreased albumin levels have been associated with a poor prognosis in patients with EC, GC and CRC (10,11). Therefore, the LDH-to-albumin ratio (LAR), which integrates information on tumor metabolism, inflammation and nutritional status, may provide more comprehensive prognostic information than either marker alone. However, the prognostic value of LAR in GICs remains controversial, and to the best of our knowledge, no previous evidence-based study has systematically evaluated its clinical significance. Therefore,

the present meta-analysis aimed to synthesize evidence and clarify the prognostic role of preoperative LAR in patients with GICs. To the best of our knowledge, the present study is the first meta-analysis to comprehensively assess the value of LAR in predicting survival outcomes and postoperative complications in this patient population.

Materials and methods

Search strategy. On March 20, 2025, a systematic electronic literature search was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and the Cochrane Library (https://www.cochrane.org/). The search strategy included relevant terms such as 'lactate dehydrogenase-to-albumin ratio' and 'lactate dehydrogenase-albumin ratio' to identify eligible studies. Only human studies published in English were considered. The detailed search strategy is provided in Table SI.

Inclusion and exclusion criteria. Studies were eligible for inclusion if they met the following criteria: i) Enrolled patients with a confirmed diagnosis of GIC; ii) evaluated the prognostic significance of baseline or preoperative LAR; and iii) reported at least one relevant clinical endpoint, including overall survival (OS), recurrence-free survival (RFS) or major postoperative complications. The exclusion criteria were as follows: i) Animal studies, reviews, case reports and conference abstracts; and ii) Studies that did not provide extractable hazard ratios (HRs) or odd ratios (ORs) for outcome assessment in either the main text or supplementary materials.

Data extraction and quality evaluation. Key information was extracted from each included study, including the first author, publication year, study period, country, cancer type, treatment strategy, sample size, patient age and sex, LAR cut-off value and outcome measures. HRs and ORs derived from multivariable analyses were preferentially extracted when available. The methodological quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS). Studies with NOS scores of ≥6 were considered to be of high quality.

Statistical methods. Statistical analyses were performed using Stata version 18.0 (StataCorp LP), and pooled estimates were presented using forest plots. Between-study heterogeneity was assessed using Cochran's Q test and the I^2 statistic. For all analyses, pooled estimates were calculated using a DerSimonian-Laird random-effects model. Potential publication bias was assessed using Begg's and Egger's tests (12). Sensitivity analyses were performed by sequentially omitting each individual study to evaluate the stability of the pooled results (13). Subgroup analyses were conducted according to cancer type, country, Cox model type and LAR cut-off value. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Search results and study characteristics. The initial database search, supplemented by manual screening, identified 158 potentially relevant records. After 26 duplicate records were removed, 111 studies were excluded based on the screening of titles and abstracts because they did not meet the inclusion criteria. The full texts of the remaining 21 articles were assessed, and 12 studies were excluded for not meeting the predefined eligibility criteria. Finally, nine studies were included in quantitative analysis (Fig. 1) (14-22).

The main characteristics of the included studies are summarized in Table I. A total of 6,379 patients were included, with sample sizes ranging from 81 to 3,868. Geographically, five studies were conducted in China, three in Turkey and one in Japan. All included studies had enrolled patients who underwent surgery and were retrospective in design. NOS scores ranged from 6 to 8, indicating generally acceptable methodological quality (Table I).

Association between preoperative LAR and OS. A total of nine independent studies involving 6,379 patients were analyzed to evaluate the association between LAR and OS in patients with GIC. Among these studies, eight stratified patients into high- and low-LAR groups. The pooled results indicated that a higher LAR was significantly associated with worse OS (HR=1.90; 95% CI, 1.63-2.21; $P<0.001$; Fig. 2). Similarly, Wu *et al* (21) analyzed LAR as a continuous variable and reported that a higher LAR was associated with worse OS (HR=1.13; 95% CI, 1.02-1.45; P=0.030).

Subgroup analysis revealed that elevated LAR was consistently associated with unfavorable OS across different cancer types. Specifically, a higher LAR was associated with worse OS in patients with CRC (HR=2.06; 95% CI, 1.60-2.66; $P<0.001$), EC (HR=1.67; 95% CI, 1.26-2.23; $P<0.001$) and GC (HR=1.85; 95% CI, 1.04-3.26; P=0.035) (Fig. 3A). Similar trends were observed in country-based subgroup analysis. A higher LAR was significantly associated with worse OS in studies from China (HR=1.87; 95% CI, 1.44-2.44; $P<0.001$) and Turkey (HR=2.08; 95% CI, 1.48-2.92; $P<0.001$) (Fig. 3B). The Japanese subgroup included only one study and showed that a high LAR was associated with worse OS (HR=1.85; 95% CI, 1.22-2.80; P=0.004). However, because this subgroup was based on a single study, the result should be interpreted with caution.

Subgroup analysis based on Cox model type further supported the stability of the association between LAR and OS (Fig. 4A). In the multivariate Cox model subgroup, high LAR was significantly associated with poor OS (HR=1.86; 95% CI, 1.52-2.26; $P<0.001$), with low heterogeneity among studies ($I^2=23.9\%$; P=0.262). Similarly, in the univariate Cox model subgroup, the pooled HR remained significant (HR=2.08; 95% CI, 1.48-2.92; $P<0.001$), with no observed heterogeneity ($I^2=0.0\%$; P=0.412). No significant heterogeneity was observed between the multivariate and univariate subgroups (P=0.570).

Subgroup analysis according to the LAR cut-off value also showed broadly consistent results (Fig. 4B). In studies using a cut-off value >6, high LAR was significantly associated with worse OS (HR=1.91; 95% CI, 1.58-2.32; $P<0.001$), with no heterogeneity ($I^2=0.0\%$; P=0.859). In studies using a cut-off value of 5-6, the association remained significant (HR=1.83; 95% CI, 1.41-2.39; $P<0.001$), with low heterogeneity ($I^2=3.5\%$; P=0.375). In the subgroup with a cut-off

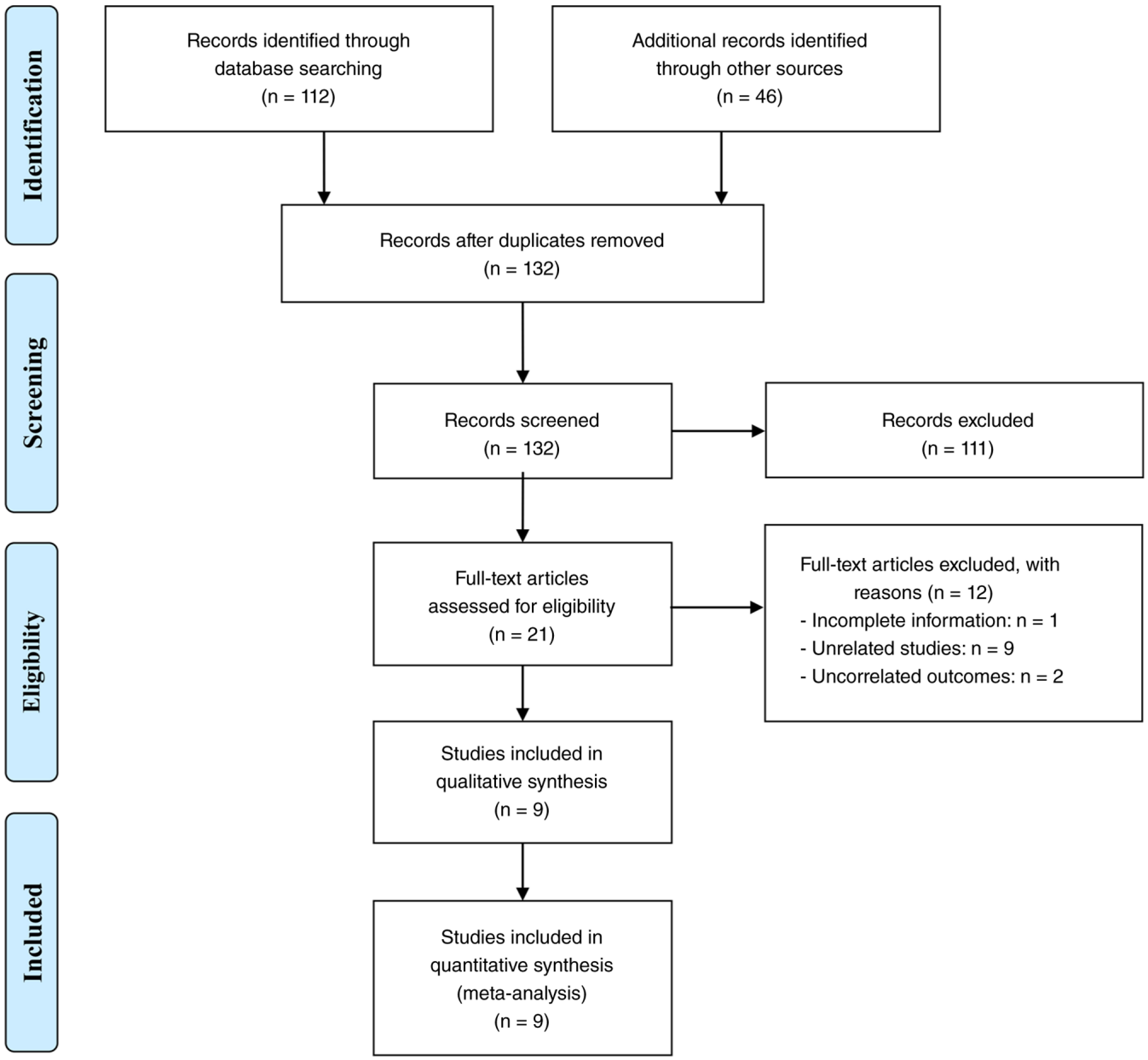


Figure 1. Flow diagram of identifying eligible studies.

value <5, the pooled HR was 2.43 (95% CI, 0.97-6.11; P=0.059), but substantial heterogeneity was observed (I^2=75.5%; P=0.043), and the result should therefore be interpreted cautiously.

Sensitivity analysis was conducted using a leave-one-out method to evaluate the robustness of the pooled HR for OS (Fig. 5A). Specifically, each included study was sequentially excluded, and the pooled HR was recalculated after each omission. The overall pooled estimate was 1.90 (95% CI, 1.63-2.21). After sequential exclusion of individual studies, the recalculated pooled HRs remained stable, ranging from 1.85 to 1.96. The lowest pooled estimate was observed after excluding Xie *et al* (20) (HR=1.85, 95% CI, 1.60-2.14), whereas the highest pooled estimate was observed after excluding Feng *et al* (17) (HR=1.96; 95% CI, 1.68-2.29). Notably, all recalculated 95% CIs remained above the null value of 1.0, and the direction and statistical significance of the association were unchanged (Fig. 5A). These findings indicate that no single study had a disproportionate influence on the overall result, supporting the robustness and stability of the pooled estimate. The funnel plot appeared symmetrical (Fig. 5B), and Begg's (P=0.266) and Egger's (P=0.482) tests did not suggest significant publication bias.

Association between preoperative LAR and RFS. A total of four studies involving 5,243 patients evaluated the prognostic significance of LAR for RFS in patients with GIC. The pooled results indicated that a higher LAR was significantly associated with worse RFS (HR=1.83; 95% CI, 1.52-2.20; P<0.001; Fig. 6A).

Sensitivity analysis was conducted using a leave-one-out approach to evaluate the robustness of the pooled HR for RFS. The overall pooled HR was 1.83 (95% CI, 1.52-2.20). After sequentially excluding each included study, the

Table I. Main characteristics of the studies included.

Author, year	Sample size	Age, years	Sex, male/female	Cancer type	Treatment	Study period	Country	Cut-point	Cut-off determination method	NOS	(Refs.)
Shu *et al*, 2023	3,868	62.9[a]	2,279/1,589	Colorectal cancer	Surgery	01/2011-01/2020	China	12.3	X-tile software	8	(19)
Shiratori *et al*, 2023	236	66 (41-83)[b]	193/43	Esophageal carcinoma	Surgery	09/2008-03/2020	Japan	6.2	ROC curve analysis	8	(18)
Wu *et al*, 2023	382	203/179[d]	231/151	Colorectal cancer	N/A	10/2015-11/2019	China	N/A	Continuous variable; median split	6	(21)
Çağlar *et al*, 2023	91	63.4±12.1	63/28	Gastric cancer	Surgery	2016-2020	Turkey	5.5	ROC curve analysis	7	(16)
Xie *et al*, 2022	126	66 (19-89)[c]	66/60	Colorectal	Surgery cancer	06/2012-12/2015	China	4.9	ROC curve analysis	7	(20)
Aday *et al*, 2020 (gastric cancer cohort)	81	60.2±13.8	55/26	Gastric cancer	Surgery	06/2013-06/2019	Turkey	5.5	Time-dependent ROC analysis	6	(15)
Aday *et al*, 2020 (colorectal cancer cohort)	295	55.8±14.1	178/117	Colorectal cancer	Surgery	01/2013-06/2019	Turkey	5.3	Time-dependent ROC analysis	7	(14)
Feng *et al*, 2019	346	147/199[d]	270/76	Esophageal carcinoma	Surgery	01/2007-12/2010	China	5.5	X-tile software	8	(17)
Hu *et al*, 2022	954	58.5±11.9	557/397	Colorectal cancer	Surgery	07/2013-09/2017	China	4.5	RCS analysis with Cox models	7	(22)

[a]Mean, [b]median (range), [c]median (interquartile range), [d]>60/<60. ROC, receiver operating characteristic; RCS, restricted cubic spline; NOS, Newcastle-Ottawa Scale.

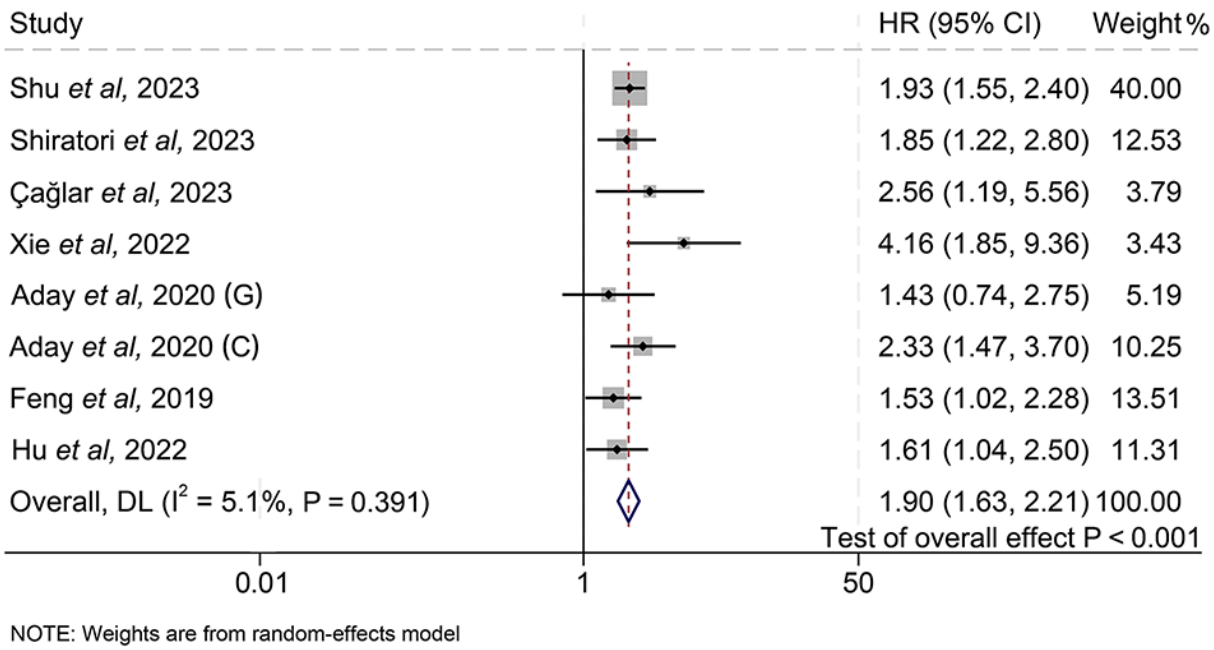


Figure 2. Forest plots depicting the association between the baseline lactate dehydrogenase/albumin ratio and overall survival. HR, hazard ratio; CI, confidence interval; DL, DerSimonian-Laird random-effects model; (G), gastric cancer cohort; (C), colorectal cancer cohort.

recalculated pooled HRs remained statistically significant and ranged from 1.76 to 2.03, with corresponding 95% CIs ranging from 1.41 to 2.93. The lowest estimate was obtained after excluding Xie *et al* (20) (HR=1.76; 95% CI, 1.48-2.09), and the highest estimate was obtained after excluding Shu *et al* (19) (HR=2.03; 95% CI, 1.41-2.93). Since all recalculated 95% CIs were >1.0 and the direction of the association remained unchanged, the pooled result was not driven by any single study and was considered robust (Fig. 6B).

Begg's (P=0.308) and Egger's (P=0.290) tests did not indicate significant publication bias; however, these findings should be interpreted cautiously because only a limited number of studies were included.

Association between preoperative LAR and major postoperative complications. A total of two studies involving 4,163 patients were included to assess the association between LAR and major postoperative complications. The pooled results indicated that patients with a higher LAR had a significantly higher risk of major postoperative complications than those with a lower LAR (OR=2.36; 95% CI, 1.49-3.74; P<0.001; Fig. 7).

Discussion

The present meta-analysis indicated that elevated preoperative LAR was significantly associated with worse OS, worse RFS and a higher risk of major postoperative complications in patients with GIC. These findings suggest that LAR, a low-cost and readily available biomarker derived from routine preoperative blood tests, shows clinical value for prognostic assessment and perioperative risk stratification. Subgroup analyses further revealed that the association between LAR and prognosis remained consistent across different cancer types, Cox model types, countries and LAR cut-off values.

Metabolic reprogramming is a hallmark of tumor progression (23), and LDH is a key enzyme involved in glucose metabolism and promotes the conversion of pyruvate to lactate. Even under normoxic conditions, tumor cells often heavily rely on glycolysis, leading to increased lactate production. Lactate accumulation contributes to acidification of the tumor microenvironment (24), which may promote tumor invasion, metastasis (25), immune evasion (26) and angiogenesis (27). Therefore, elevated LDH may reflect aggressive tumor biology and a higher tumor burden. LDH is widely distributed in multiple tissues, and cellular injury can lead to its release into the bloodstream. In addition, elevated serum LDH levels may occur as a result of tumor-associated tissue destruction, rapid tumor growth, hypoxia or metastasis. Previous studies have reported that elevated LDH is associated with poor prognosis in various malignancies, such as renal cell carcinoma and nasopharyngeal carcinoma (28,29). Importantly, this association has also been reported in GICs. For example, elevated pretreatment serum LDH has been associated with unfavorable survival outcomes in patients with colorectal cancer and gastric cancer. These findings suggest that LDH is not only a general marker of tumor burden and aggressive tumor biology, but may also have prognostic relevance in GICs (30,31).

Serum albumin reflects nutritional status and systemic inflammation, both of which are closely related to cancer outcomes. Malnutrition and systemic inflammation can suppress hepatic albumin synthesis, leading to decreased serum albumin levels. Albumin-based prognostic markers have been shown to predict outcomes in multiple cancers. For example, Matsunaga *et al* (32) reported that systemic inflammatory

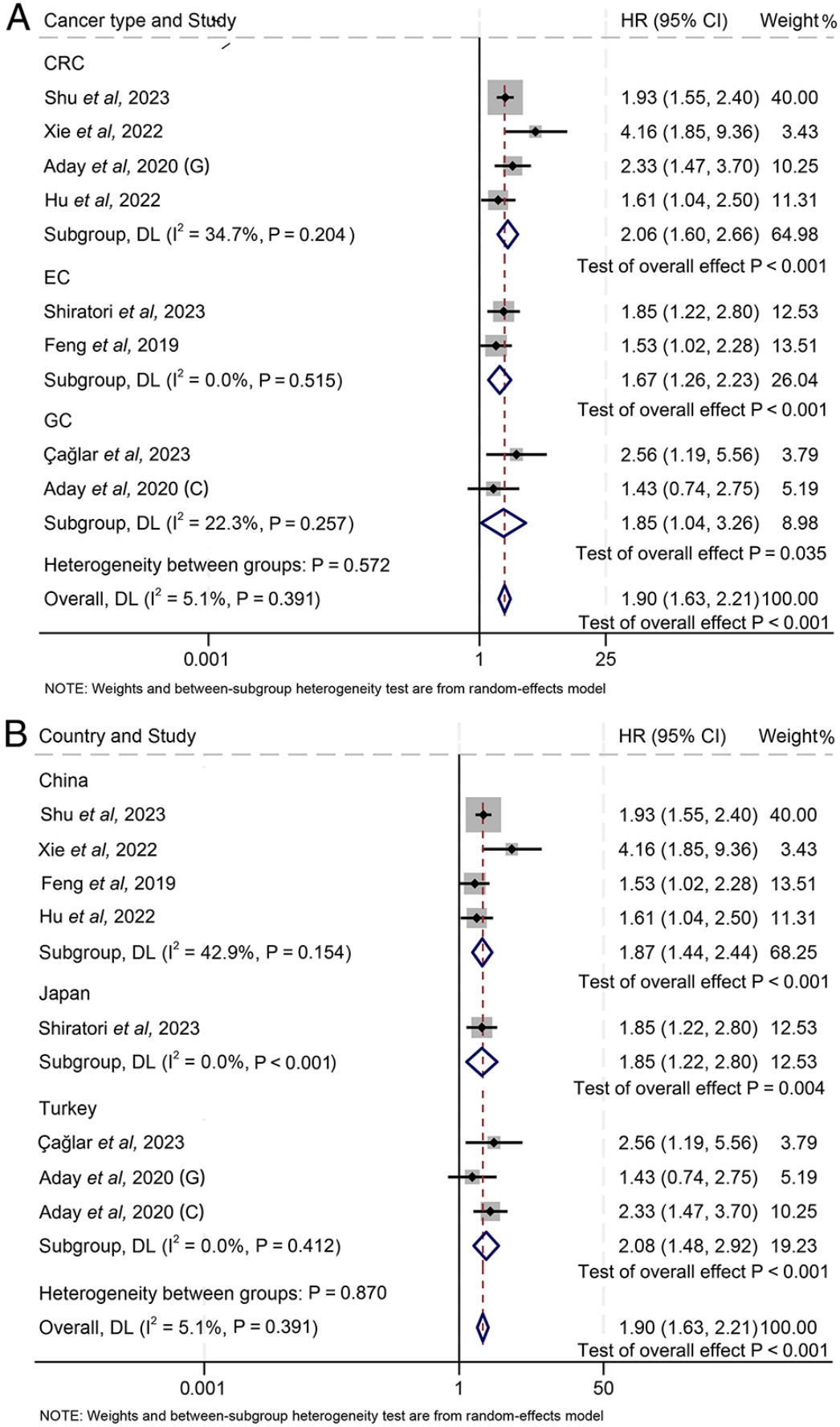
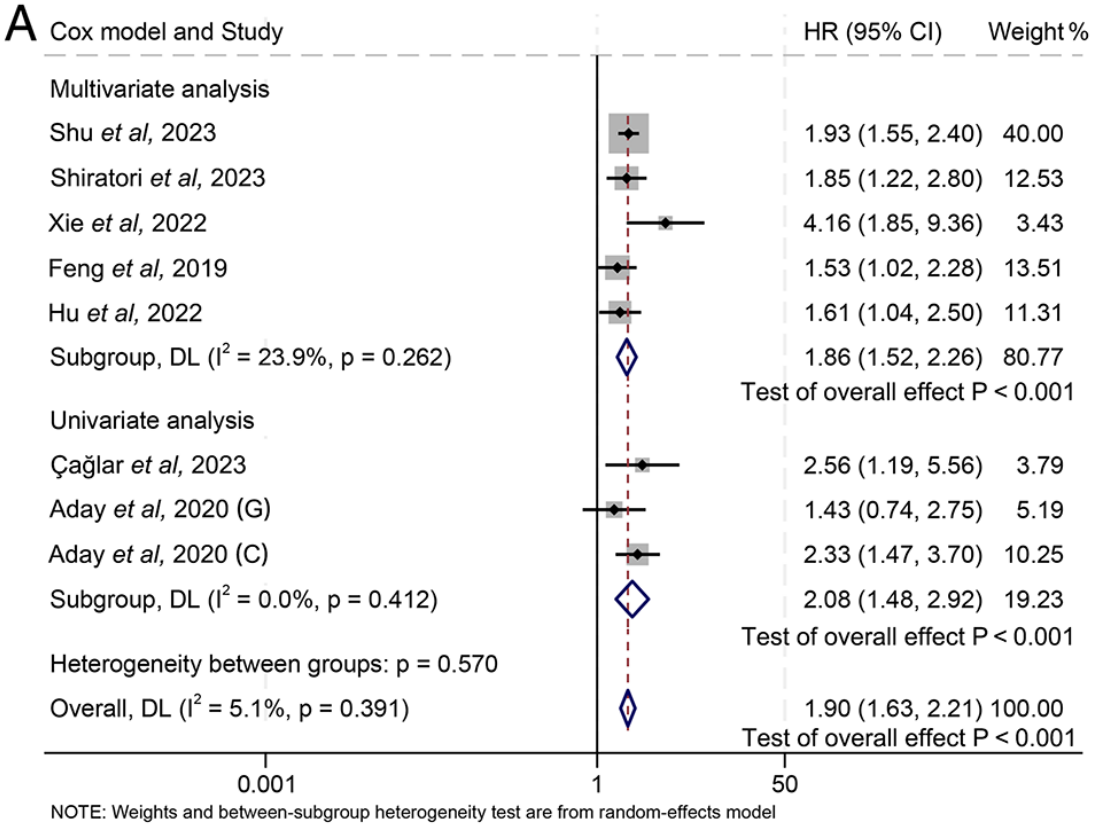


Figure 3. (A) Subgroup analysis stratified by cancer type illustrates the relationship between the lactate dehydrogenase/albumin ratio and overall survival. (B) Subgroup analysis stratified by country illustrates the relationship between the lactate dehydrogenase/albumin ratio and overall survival. HR, hazard ratio; CI, confidence interval; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; DL, DerSimonian-Laird random-effects model; (G), gastric cancer cohort; (C), colorectal cancer cohort.



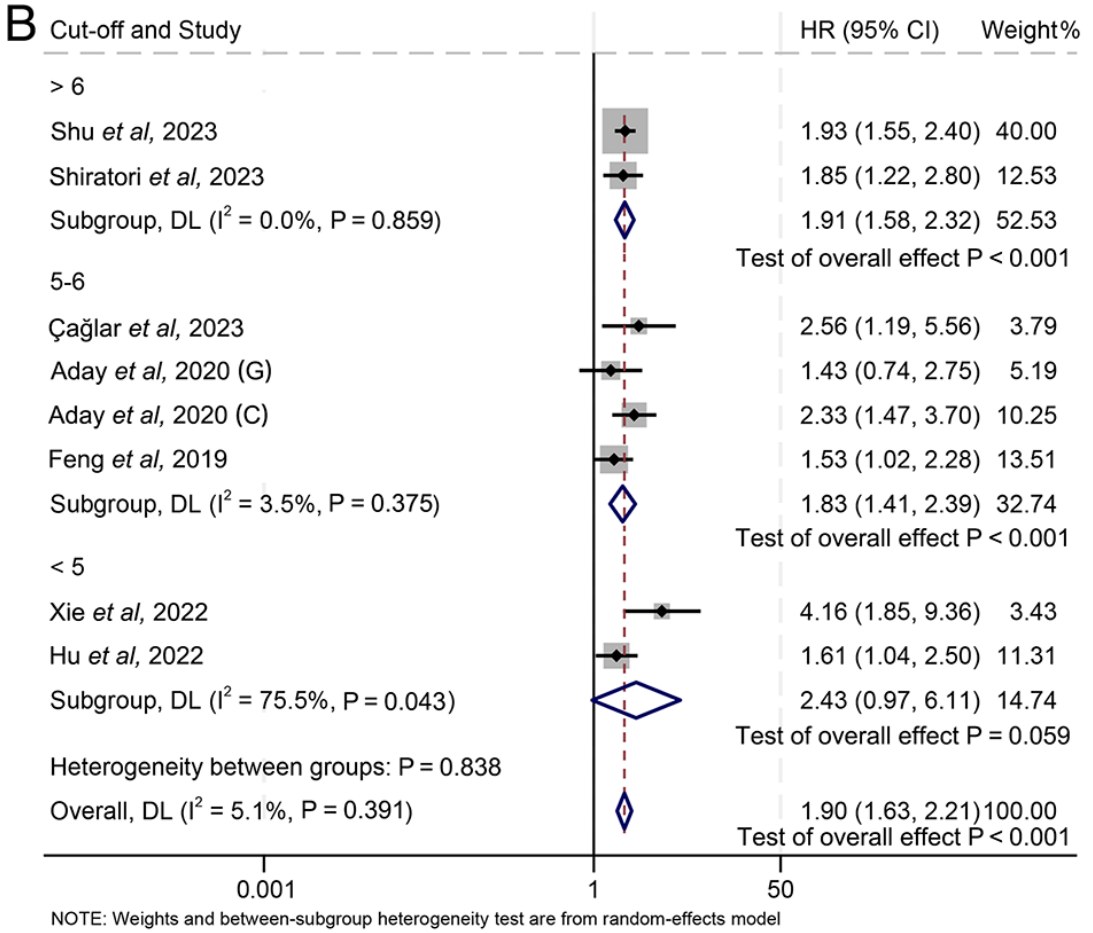


Figure 4. (A) Subgroup analysis stratified by the Cox model and (B) cut-off value (>6, 5-6 and <5) demonstrating the association between the serum lactate dehydrogenase/albumin ratio and overall survival. HR, hazard ratio; CI, confidence interval; DL, DerSimonian-Laird random-effects model; (G), gastric cancer cohort; (C), colorectal cancer cohort.

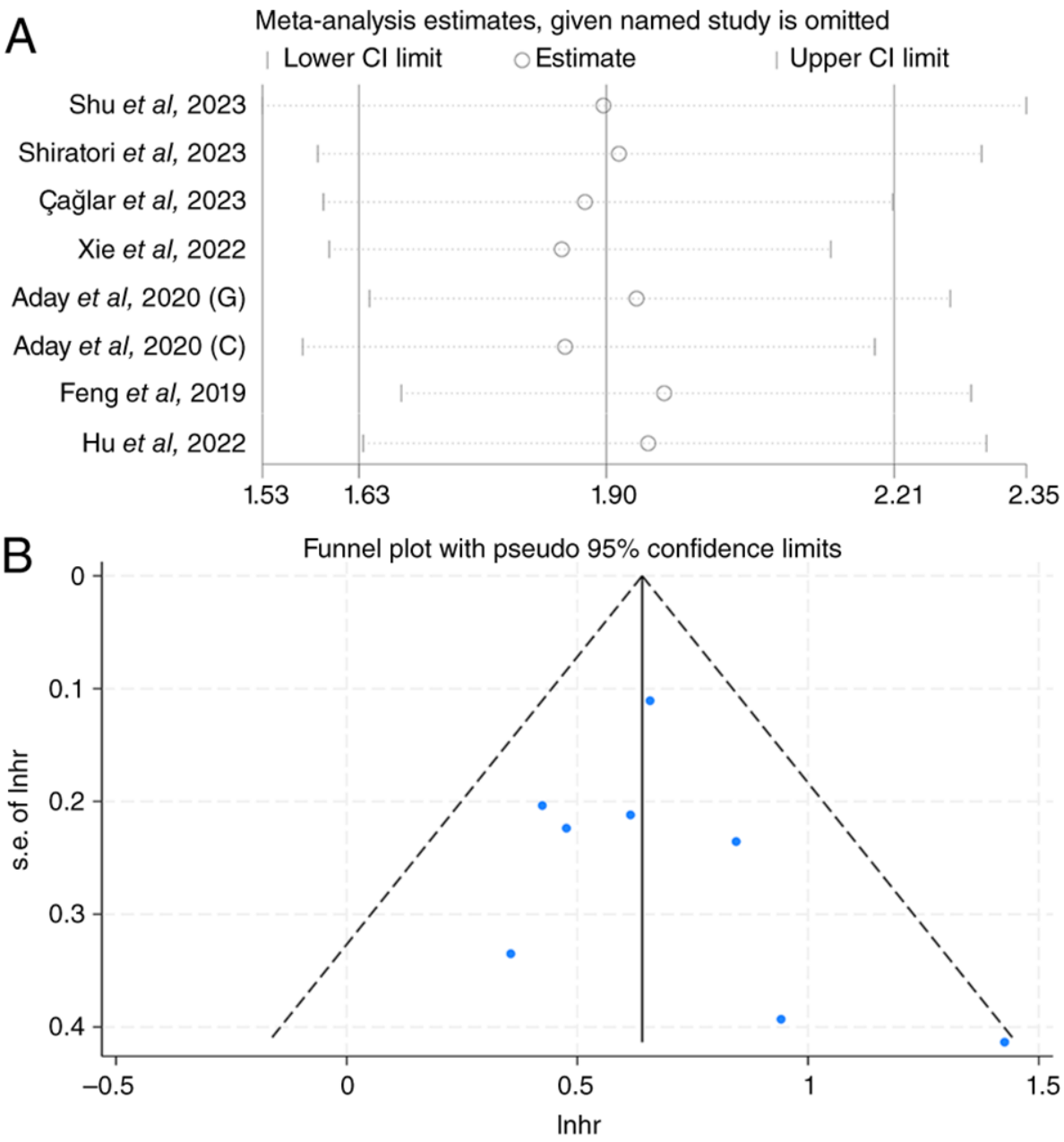


Figure 5. (A) Sensitivity analysis of the association between baseline lactate dehydrogenase/albumin ratio and overall survival. (B) Funnel plots of the relationship between lactate dehydrogenase/albumin ratio and overall survival. The lnhr was used as the effect size in the meta-analysis and funnel plot. HR, hazard ratio; CI, confidence interval; lnhr, natural logarithm of the hazard ratio; (G), gastric cancer cohort; (C), colorectal cancer cohort.

response, together with sarcopenia, was associated with poor prognosis in patients with esophageal cancer, which is a type of GIC. Yue *et al* (33) also demonstrated that the pretreatment albumin-to-globulin ratio was a significant prognostic marker in patients with diffuse large B-cell lymphoma. These findings indicate that albumin-related markers may reflect both nutritional and inflammatory status. Importantly, because esophageal cancer is included within GICs, the relationship between albumin-related prognostic factors and outcomes has been previously reported in at least one type of GIC.

Because LDH and albumin may each be affected by various non-cancer-related conditions, their combined assessment as LAR may provide a more comprehensive indicator of tumor metabolism, systemic inflammation and nutritional status. The present findings support the potential use of LAR as part of routine preoperative evaluation to improve risk stratification and guide individualized management.

Several limitations of the present meta-analysis should be acknowledged. First, all included studies were retrospective cohort studies, which may have introduced selection bias and residual confounding. Although a majority of the studies adjusted for clinicopathological factors, the possibility of unmeasured confounders cannot be completely excluded. Therefore, the findings of the present study should be interpreted as associations rather than evidence of causality. Second, the geographic distribution of the included studies was relatively limited. A majority of the studies were conducted in China and Turkey, and only one study was from

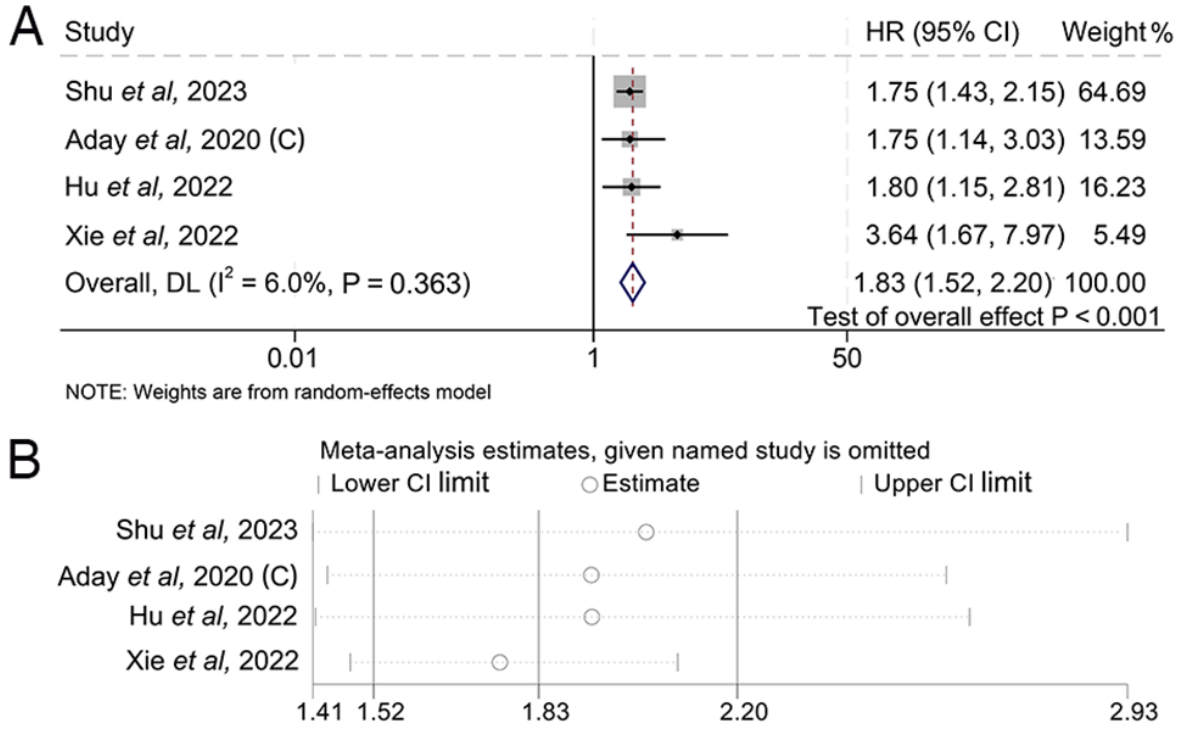


Figure 6. (A) Forest plots depicting the association between the serum lactate dehydrogenase/albumin ratio and recurrence-free survival. (B) Sensitivity analysis of the association between lactate dehydrogenase/albumin ratio and recurrence-free survival. HR, hazard ratio; CI, confidence interval; (C), colorectal cancer cohort.

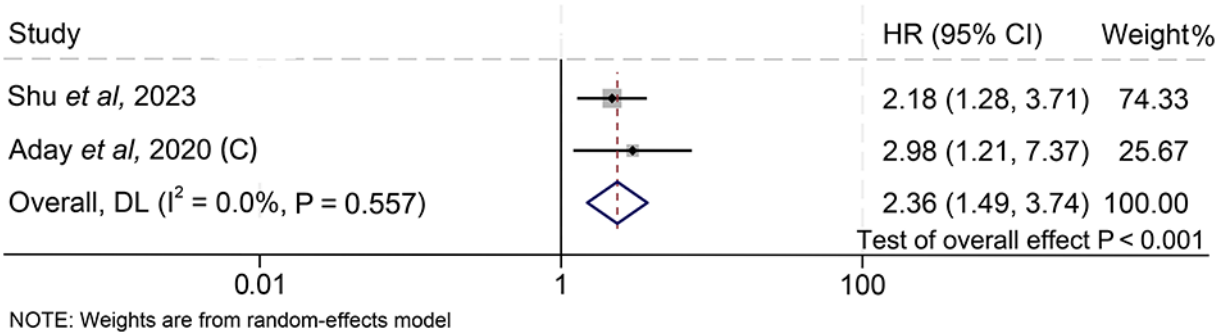


Figure 7. Forest plots depicting the association between the baseline lactate dehydrogenase/albumin ratio and major complications. CI, confidence interval; DL, DerSimonian-Laird random-effects model; (C), colorectal cancer cohort.

Japan. Therefore, the generalizability of the present findings to other ethnic groups, healthcare systems and geographic regions remains uncertain. Further validation in large, multi-center cohorts from different countries is needed. Third, the LAR cut-off values varied across the included studies. The original studies used different methods to determine the optimal LAR threshold, including time-dependent receiver operating characteristic (ROC) analysis, conventional ROC analysis, X-tile software, restricted cubic spline analysis and median-based grouping. This methodological heterogeneity may limit the direct clinical application of LAR. To address this issue, subgroup analysis was performed based on LAR cut-off values, and the association between elevated LAR and poor prognosis remained stable. However, a standardized and clinically applicable LAR cut-off value remains to be established. In addition, although several included studies reported clinicopathological variables, such as tumor stage and tumor markers (such as carcinoembryonic antigen), these data were not consistently available and were reported using heterogeneous definitions and statistical methods. Therefore, the association between LAR and tumor stage or tumor markers could not quantitatively assessed. Future studies should further investigate whether elevated LAR is associated with advanced tumor stage, increased tumor marker levels and other aggressive clinicopathological features.

In conclusion, the present meta-analysis indicated that elevated preoperative LAR is significantly associated with worse survival outcomes and an increased risk of major postoperative complications in patients with GICs. As an inexpensive and easily accessible biomarker, LAR may help clinicians improve preoperative risk assessment, perioperative decision-making and postoperative management. Further

prospective multicenter studies are warranted to validate these findings and establish standardized LAR cut-off values for clinical use.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YY, LY, KL and TH conceptualized and designed the study. YY, LY, KL and TH were responsible for data collection, assembly, analysis and interpretation. Additionally, YY, LY, KL and TH contributed to manuscript drafting and were actively involved in its revision. YY and TH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

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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