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The advanced lung cancer inflammation index is a prognostic factor for gastrointestinal cancer patients undergoing surgery: a systematic review and meta-analysis

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Abstract

Background The advanced lung cancer inflammation index (ALI) is a comprehensive assessment indicator that can reflect inflammation and nutrition conditions. However, there are some controversies about whether ALI is an independent prognostic factor for gastrointestinal cancer patients undergoing surgical resection. Thus, we aimed to clarify its prognostic value and explore the potential mechanisms.

Methods Four databases including PubMed, Embase, the Cochrane Library, and CNKI were used for searching eligible studies from inception to June 28, 2022. All gastrointestinal cancers, including colorectal cancer (CRC), gastric cancer (GC), esophageal cancer (EC), liver cancer, cholangiocarcinoma, and pancreatic cancer were enrolled for analysis. We focused on prognosis most in the current meta-analysis. Survival indicators, including overall survival (OS), disease-free survival (DFS), and cancer-special survival (CSS) were compared between the high ALI group and the low ALI group. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was submitted as a supplementary document.

Results We finally included fourteen studies involving 5091 patients in this meta-analysis. After pooling the hazard ratios (HRs) and 95% confidence intervals (CIs), ALI was found to be an independent prognostic factor for both OS (HR = 2.09, I^2 = 92%, 95% CI = 1.53 to 2.85, $P < 0.01$), DFS (HR = 1.48, I^2 = 83%, 95% CI = 1.18 to 1.87, $P < 0.01$), and CSS (HR = 1.28, I^2 = 1%, 95% CI = 1.02 to 1.60, P = 0.03) in gastrointestinal cancer. After subgroup analysis, we found that ALI was still closely related to OS for CRC (HR = 2.26, I^2 = 93%, 95% CI = 1.53 to 3.32, $P < 0.01$) and GC (HR = 1.51, I^2 = 40%, 95% CI = 1.13 to 2.04, $P = 0.006$) patients. As for DFS, ALI also has a predictive value on the prognosis of CRC (HR = 1.54, I^2 = 85%, 95% CI = 1.14 to 2.07, $P = 0.005$) and GC (HR = 1.37, I^2 = 0%, 95% CI = 1.09 to 1.73, $P = 0.007$) patients.

Conclusion ALI affected gastrointestinal cancer patients in terms of OS, DFS, and CSS. Meanwhile, ALI was a prognostic factor both for CRC and GC patients after subgroup analysis. Patients with low ALI had poorer prognoses. We recommended that surgeons should perform aggressive interventions in patients with low ALI before the operation.

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Keywords Advanced lung cancer inflammation index, Gastrointestinal cancer, Colorectal cancer, Gastric cancer, Surgery, Prognosis

Introduction

Gastrointestinal cancer is common cancer that includes colorectal cancer (CRC) and gastric cancer (GC), esophageal cancer (EC), liver cancer, cholangiocarcinoma, and pancreatic cancer. According to the Global Cancer Epidemiological Statistics published in 2018, CRC was the fourth most common cancer and the second leading cause of cancer-related death, and GC was the third leading cause of cancer-related death [1]. Despite the continuous improvement of the economy and techniques, radical resection remains the main strategy for the treatment of gastrointestinal cancer [2–5]. However, the mortality of patients after surgery is still high, with a 5-year survival rate of nearly 50% [6–8]. Some studies have demonstrated that patients with low body mass index (BMI), low albumin (Alb) levels, and high inflammatory conditions have a higher risk of postoperative complications and poor survival [9–12]. More sensitive prognostic indicators are needed to instruct doctors to take measures in advance and to improve the survival and quality of life of gastrointestinal cancer patients.

The advanced lung cancer inflammation index (ALI) is a new marker. It is calculated by the patient's BMI, serum Alb level, and neutrophil-to-lymphocyte ratio (NLR) (ALI = BMI × ALB/NLR) [13]. Some studies have revealed that BMI has a prognostic value for malignant diseases [14, 15]. Lee J et al. performed a 16-study meta-analysis and revealed that overweight CRC patients had worse survival [15]. Alb is synthesized in the liver and is the main component of total serum protein in the body, which mainly reflects nutrition status [16]. Gonzalez-Trejo S reported that serum albumin was a prognostic factor for CRC [17]. NLR is the ratio of neutrophils to lymphocytes. When the body is in an inflammatory state, neutrophils are elevated, and lymphocytes are decreased [18, 19]. Moreover, high levels of neutrophils can promote tumor progression and inhibit the antitumor effects of lymphocytes [20]. Thus, the NLR was established as an inflammation indicator and could be considered a balance between pro-tumor status and antitumor status. Therefore, ALI could reflect the inflammation and nutrition state. Currently, some studies have reported that ALI can predict the survival of many cancers, including CRC [21–27], GC [28, 29], EC [30, 31], liver cancer [32], cholangiocarcinoma [33], pancreatic cancer [34, 35], and B-cell lymphoma [36].

Many studies have discussed the relationship between ALI and gastrointestinal cancer. Pian G, Yin CZ, and Barth DA et al. demonstrated that there was no significant difference in ALI between patients receiving CRC surgery or GC surgery [22, 28, 34]. Others thought that a low ALI level would lead to a poor prognosis for gastrointestinal cancer patients [21, 23–27, 29–33]. Therefore, we aimed to explore the exact prognostic ability of ALI for patients with gastrointestinal cancer undergoing surgery.

Methods

We conducted this current meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [37]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was submitted as a supplementary document. The registration ID of this meta-analysis on PROSPERO is CRD42022362548, and the link is https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022362548.

Literature search

We searched studies in four databases including PubMed, Embase, the Cochrane Library, and CNKI on Dec 10, 2022. ALI was searched as "Advanced lung cancer inflammation index" OR "ALI" OR "BMI x ALB / NLR" OR "BMI x serum albumin / NLR" OR "body mass index x serum albumin / neutrophil-to lymphocyte". As for gastrointestinal cancer, the search strategy was "gastrointestinal cancer" OR "gastrointestinal neoplasms" OR "colon cancer" OR "rectal cancer" OR "colorectal cancer" OR "rectum cancer" OR "colorectal neoplasm" OR "colon neoplasm" OR "rectal neoplasm" OR "rectum neoplasm" OR "colorectal carcinoma" OR "colon carcinoma" OR "rectum carcinoma" OR "rectal carcinoma" OR "CRC" OR "gastric cancer" OR "gastric carcinoma" OR "gastric neoplasms" OR "stomach cancer" OR "stomach carcinoma" OR "stomach neoplasms" OR "liver cancer" OR "hepatocellular carcinoma cancer" OR "esophageal cancer" OR "esophageal neoplasm" OR "esophagus cancer" OR "esophagus neoplasm" OR "esophageal squamous cell carcinoma" OR "cholangiocarcinoma" OR "extrahepatic cholangiocarcinoma" OR "gallbladder cancer" OR "gallbladder neoplasms" OR "bile duct cancer" OR "bile duct

neoplasms" OR "pancreatic cancer" OR "pancreatic carcinoma". The search scope was limited to titles and abstracts. Language and study design had no limitations.

Inclusion and exclusion criteria

The inclusion criteria for our meta-analysis included: 1, Patients with gastrointestinal cancer (CRC, GC, EC, liver cancer, cholangiocarcinoma, or pancreatic cancer) who received radical or palliative intent surgery; 2, Patients were divided into the high ALI group and the low ALI group; and 3, Prognosis including OS, DFS, or CSS was reported (both effect value and survival curves were allowed). The exclusion criteria included: 1, Studies' types were reviews, case reports, letters, conferences, comments, or preprint articles; and 2, Data was repeated or overlapped. When two studies had overlapped data, the study with a larger sample size would be included. The PICO framework was more intuitive and was shown in a supplementary document.

Study selection

According to the search strategy, two authors searched studies based on the search strategy in four databases independently. Titles and abstracts would be scanned first. Then, the full text was screened based on the inclusion and exclusion criteria. If there was a disagreement on study inclusion, a group discussion would be held to solve the resolution.

Data collection

Two authors collected studies' characteristics and patients' information independently, then the data were checked to reach a consistent. Characteristics of the studies included the first author, year, country, study period, sample size, the cut-off value of ALI, prognosis, included patients, follow-up, and Newcastle–Ottawa Scale (NOS) score. The prognosis included OS, DFS, and CSS. The baseline information included age, sex, carcinoembryonic antigen (CEA), carbohydrate antigen 19–9 (CA 19–9), preoperative anemia, chemotherapy, lymph node metastasis, vessel invasion, neural invasion, distant metastasis, histology, and postoperative complication.

Quality assessment

Our meta-analysis assessed the study quality in accordance with the Newcastle–Ottawa Scale (NOS) according to comparison selection, comparability between groups, and the determination of results [38]. High-quality studies have scores higher than 8 points, and medium-quality studies have scores of 7 or 8 points.

Statistical analysis

In this meta-analysis, we focused on the prognosis of gastrointestinal cancer patients. The hazard ratios (HRs) and 95% confidence intervals (CIs) of OS, DFS, or CSS were pooled for analysis. HRs from the multivariate analysis were preferred, without which univariate analysis would be replaced. I^2 value and chi-squared test were used to evaluate statistical heterogeneity. According to the Cochrane handbook, the $I^2 < 30\%$ was considered low heterogeneity, the I^2 range from 30 to 60% was considered moderate heterogeneity, and the $I^2 > 60\%$ was considered high heterogeneity. The fixed effects model was used when the I^2 value $\leq 50\%$, and $p < 0.05$ was thought of as statistically significant. The random effects model was used when the I^2 value $> 50\%$, and $p < 0.1$ was thought of as statistically significant. Subgroup analysis was used to assess the risk of heterogeneity. As for sensitive analysis, each study was excluded at a time, and repeat meta-analyses were conducted. The funnel plot was used for assessing the publication bias. RevMan 5.3 (The Cochrane Collaboration, London, United Kingdom) was used for all data analysis.

Results

Study selection

We searched 229 studies in four databases according to the search strategy (68 studies in PubMed, 135 studies in Embase, 24 studies in the Cochrane Library, and 2 studies in CNKI). After duplicates removing, the titles and abstracts were scanned for initial selection. Then, 22 studies were left for full-text assessment. Finally, 14 studies after qualitative synthesis with sufficient data were included (Fig. 1).

Baseline characteristics of studies

Fourteen studies involving 5091 patients were included in the current meta-analysis. Studies were conducted in China, Japan, Korea, and Austria ranged from 2014 to 2022. The cut-off values of ALI ranged from 18.0 to 43.5 in eleven studies, and the value in another study was 70.4. Twelve studies reported OS, eight studies reported DFS/ progression-free survival (PFS)/ relapse-free survival (RFS), and two studies reported CSS. More information, including study period, sample size, cancer type of included patients, follow-up, and NOS scores are also shown in Table 1.

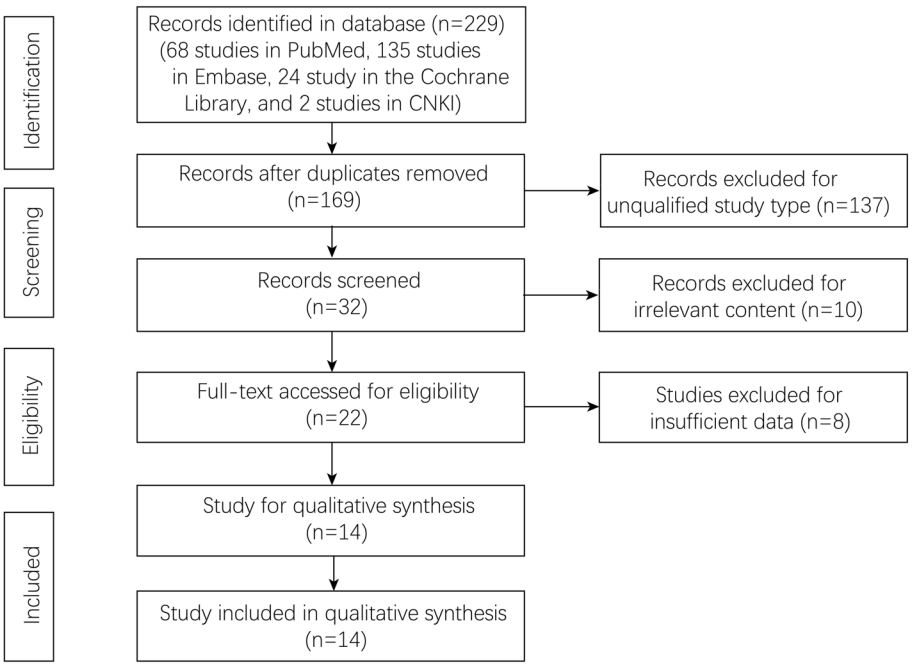

Fig. 1 Flowchart of study selection

Baseline characteristics of patients

Compared to the low ALI group, the high ALI group had a lower proportion of older patients (OR = 0.74, $I^2 = 0\%$, 95% CI = 0.64 to 0.85, $P < 0.0001$) and males (OR = 0.49, $I^2 = 92\%$, 95% CI = 0.25 to 0.98, $P = 0.04$), less preoperative anemia (OR = 0.53, $I^2 = 0\%$, 95% CI = 0.36 to 0.78, $P = 0.001$), chemotherapy (OR = 0.75, $I^2 = 0\%$, 95% CI = 0.61 to 0.92, $P = 0.006$), less distant metastasis (OR = 0.42, $I^2 = 52\%$, 95% CI = 0.26 to 0.66, $P = 0.0002$). No significant differences were found in CEA levels, CA 19–9, lymph node metastasis, vessel invasion, neural invasion, histology, and postoperative complication ($P \geq 0.05$ in the fixed effects model or $P \geq 0.1$ in the random effects model) (Table 2).

Clinical impact of the preoperative ALI on the survival outcome

After pooling the HRs and 95% CIs of OS from fourteen studies, ALI was a prognostic predictor for OS (HR = 2.09, $I^2 = 92\%$, 95% CI = 1.01 to 1.76, $P < 0.01$), DFS (HR = 1.48, $I^2 = 83\%$, 95% CI = 1.18 to 1.87, $P < 0.01$) and CSS (HR = 1.28, $I^2 = 1\%$, 95% CI = 1.02 to 1.60, P = 0.03) in gastrointestinal cancer patients after surgery (Fig. 2). Subgroup analysis was conducted for CRC patients and GC patients independently. As for OS, we found that there was still a close association between ALI and CRC (HR = 2.26, $I^2 = 93\%$, 95% CI = 1.53 to 3.32, $P < 0.01$) and GC (HR = 1.51, $I^2 = 40\%$, 95% CI = 1.13 to 2.04, $P = 0.006$) (Fig. 3). As for DFS, the prognostic value of ALI was also shown in CRC (HR = 1.54, $I^2 = 85\%$, 95% CI = 1.14 to 2.07, $P = 0.005$) and GC (HR = 1.37, $I^2 = 0\%$, 95% CI = 1.09 to 1.73, $P = 0.007$) (Fig. 4).

Sensitivity analysis

We excluded each study at a time for repeated analysis, and the exclusion of any one study did not significantly alter the results. The funnel plot was performed for assessing the publication bias of OS, DFS, and CSS (Fig. 5). Unfortunately, only a small publication bias was found in the CSS due to the symmetry of its funnel plot, which meant that the result of the CSS was reliable. The source of publication bias in OS and DFS might be that no published studies with a negative outcome or no correlation were found currently.

Discussion

Our meta-analysis enrolled 5091 patients from fourteen studies. We found that a low ALI was an independent prognostic factor for OS, DFS, and CSS in gastrointestinal cancer patients. Further subgroup analysis reported that ALI had prognostic effects for both CRC and GC patients.

Gastrointestinal cancer is a malignant wasting disease that can be accompanied by obstruction or bleeding,

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year	Country	Study date	Sample size			Cut-off value	Prognosis	Patients included	Follow-up (month)	NOS score
				High ALI	Low ALI	Total					
Horino T [21]	2021	Japan	2005–2019	532	281	813	NA	OS、RFS	CRC	NA	9
Pian G [22]	2020	Korea	2009–2018	32	100	132	70.4	OS、DFS	CRC patients with liver metastases	NA	6
Kusunoki K [23]	2020	Japan	2005–2011	224	74	298	NA	OS、DFS	CRC	36.8 (39.7 ± 29.0)[a]	8
Xie HL [24]	2020	China	2012–2014	423	239	662	manle31.6; female24.4	OS、PFS	CRC	63 (1–80)[b]	9
Shinutani M [25]	2019	Japan	2008–2016	92	67	159	28.9	OS	unresectable metastatic CRC patients underwent combination chemotherapy	21.6 (1.2–94.0)[b]	6
Chen C [26]	2022	China	2012–2016	130	179	309	25.71	OS	CRC	60 (1–98)[b]	8
Yin CZ [28]	2021	Japan	1992–2011	NA	NA	620	30.0	OS、DFS	GC	52.8 ± 39.9[c]	9
Zhang X [29]	2022	China	2010–2017	362	253	615	39.77	OS、DFS	GC	40 (25–64)[b]	9
Deng Y [27]	2022	China	2012–2016	205	236	441	36.3	OS、DFS	right-sided colon cancer	65 (3–110)[b]	8
Tan X [30]	2021	China	2013–2018	57	101	158	31.24	OS	EC	29–88[d]	7
Feng JF [31]	2014	China	2006–2008	173	120	293	18.0	CSS	EC	35–71[d]	8
Li Q [32]	2022	China	2017–2020	35	30	65	34.7	OS	advanced HCC	at least 24 months	7
Wu H [33]	2022	China	2016–2019	35	62	97	31.8	OS、DFS	cholangiocarcinoma	20 (3–70)[b]	7
Barth DA [34]	2020	Austria	2003–2015	NA	NA	429	43.5	CSS	PC	NA	9

Abbreviations: CRC colorectal cancer, *GC* gastric cancer, *EC* Esophageal cancer, *HCC* hepatocellular carcinoma, *PC* pancreatic cancer; NOS, Newcastle–Ottawa Scale, *OS* overall survival, *DFS* disease-free survival, *PFS* progression-free survival, *RFS* relapse-free survival, *CSS* cancer-specific survival

[a] median (mean ± standard deviation)

[b] median (ranges)

[c] mean ± standard deviation

[d] range

Table 2 Summary of characteristics between High ALI group and Low ALI group

Characteristics	Studies	Participants (High ALI/ Low ALI)	Odds Ratio (95% CI)	Model	Heterogeneity
Age					
Young	8	Reference	Reference	Reference	Reference
Old	8	2056/ 1426	0.74 [0.64, 0.85]; $P<0.0001$	FE	$I^2=0\%$; $P=0.83$
Sex					
Female	8	Reference	Reference	Reference	Reference
Male	8	1799/ 1238	0.49 [0.25, 0.98]; $P=0.04$	RE	$I^2=92\%$; $P<0.00001$
CEA					
≤ 5	6	Reference	Reference	Reference	Reference
> 5	6	1359/ 1014	0.74 [0.49, 1.11]; $P=0.15$	RE	$I^2=78\%$; $P=0.0003$
CA 19–9					
≤ 37	3	Reference	Reference	Reference	Reference
> 37	3	774/ 496	0.87 [0.65, 1.16]; $P=0.35$	FE	$I^2=20\%$; $P=0.29$
Preoperative anemia	2	242/ 215	0.53 [0.36, 0.78]; $P=0.001$	FE	$I^2=0\%$; $P=0.96$
Chemotherapy	5	878/ 832	0.75 [0.61, 0.92]; $P=0.006$	FE	$I^2=0\%$; $P=0.47$
Lymph node metastasis	3	936/ 535	1.00 [0.78, 1.28]; $P=0.98$	FE	$I^2=37\%$; $P=0.20$
Vessel invasion	4	950/ 612	0.78 [0.60, 1.02]; $P=0.07$	FE	$I^2=0\%$; $P=0.75$
Neural invasion	3	372/ 384	0.75 [0.51, 1.12]; $P=0.16$	FE	$I^2=3\%$; $P=0.36$
Distant metastasis	3	777/ 492	0.42 [0.26, 0.66]; $P=0.0002$	RE	$I^2=52\%$; $P=0.13$
Histology					
Well/ Moderate	7	Reference	Reference	Reference	Reference
Poor	7	1554/ 1080	0.16 [0.02, 1.46]; $P=0.10$	RE	$I^2=99\%$; $P<0.00001$
Postoperative complication	3	626/ 416	0.74 [0.36, 1.53]; $P=0.41$	RE	$I^2=54\%$; $P=0.12$

Abbreviations: ALI advanced lung cancer inflammation index, *CI* confidence intervals, *CEA* carcinoembryonic antigen, *CA 19–9* carbohydrate antigen 19–9

which causes malnutrition [39]. Malnutrition was related to high incidences of poor survival and postoperative complications [40]. Therefore, some nutritional parameters including BMI [14, 15] and Alb levels [16, 17], have prognostic value for gastrointestinal cancer patients. ALI is a combined score that is calculated by BMI, Alb levels, and NLR. The prognostic value of ALI was first reported in non-small cell lung cancer [13]. It can reflect the nutrition status of the host [13].

Some studies have researched the relationship between ALI and gastrointestinal cancer. Most studies demonstrated that ALI could predict prognosis including OS and DFS for colorectal cancer patients [21, 23–25, 27]. Zhang X showed that preoperative ALI was an independent prognostic factor for GC patients undergoing curative gastrectomy [29]. ALI was also revealed to be a prognostic predictor for EC, liver cancer, and cholangiocarcinoma [30–33]. However, Pian G, Yin CZ, and Barth DA reported that there was no significant difference between ALI and DFS after gastrointestinal surgery [22, 28, 34]. Therefore, the extra relationship and potential mechanism need to be analyzed.

ALI not only predicts the prognosis of gastrointestinal cancer patients by reflecting the body's nutritional status but also the response to inflammatory conditions. It was reported that inflammation was an important process for the occurrence and development of gastrointestinal cancer [41]. When inflammatory factors and inflammatory cells were activated, new lymphatic vessels and blood vessels formed, which created a microenvironment conducive to the growth and differentiation of tumor cells. Tumors can also disrupt immune cell function, and then, tumor cells can more easily invade and metastasize. Many inflammatory indicators, including the albumin-to-globulin ratio (AGR), NLR, and systemic immune-inflammation index, are independent prognostic factors for gastrointestinal cancer [42–47]. ALI, an inflammatory indicator, might also have use for gastrointestinal cancer patients.

Current studies are controversial regarding the prognostic predictive value of ALI in patients with gastrointestinal cancers. Our meta-analysis was the first study to summarize the outcomes and mainly solved the

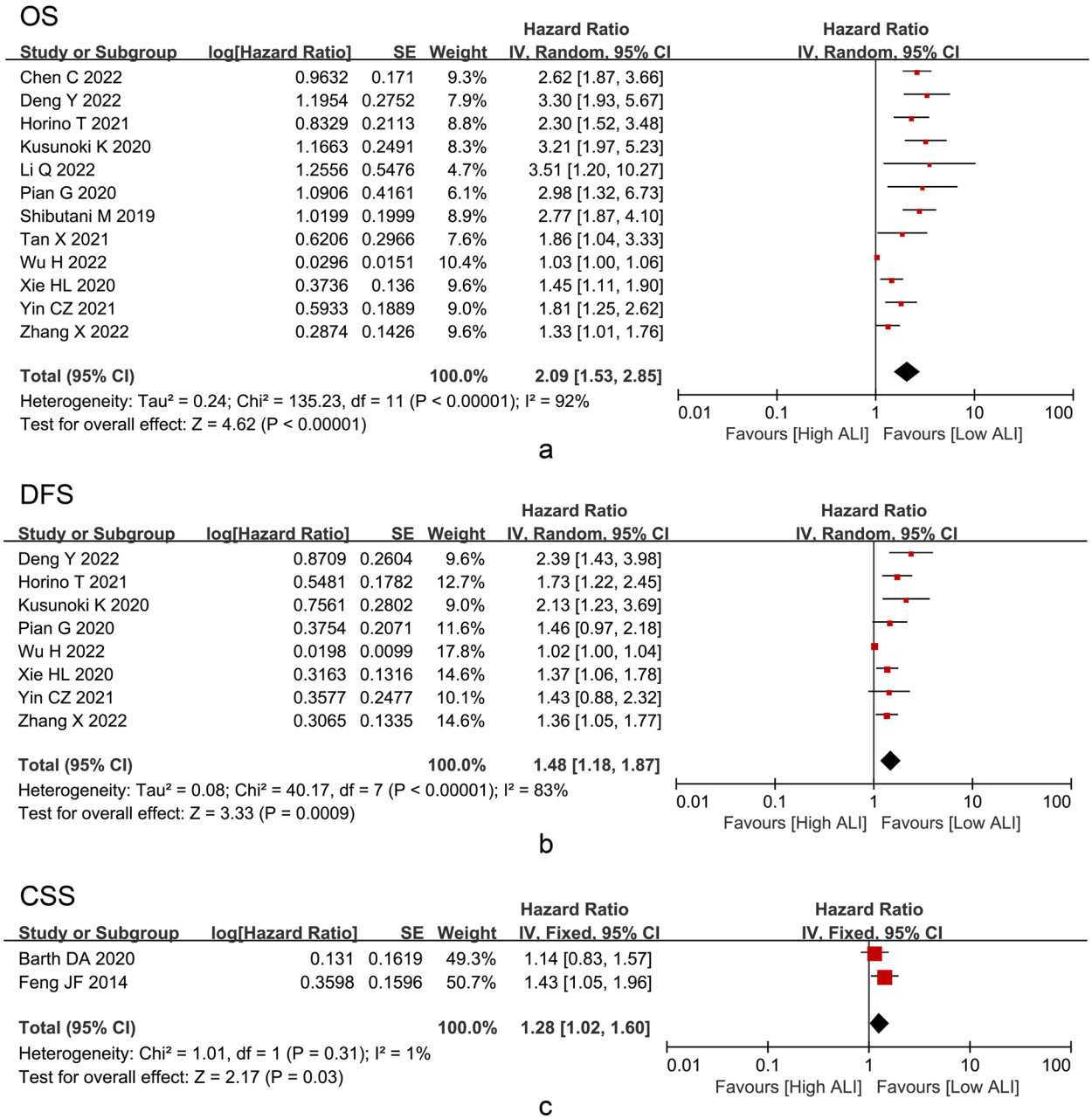

Fig. 2 **a** OS, **b** DFS, and **c** CSS of the low ALI group and the high ALI group. Abbreviations: OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; ALI, advanced lung cancer inflammation index

inconsistency of ALI in DFS. Moreover, the included studies were relatively new, with the earliest one published in 2019. Then, we included all gastrointestinal cancer studies for analysis. In addition, almost all the included studies were published in Asia, which means that the results of our study are reliable for Asian individuals. However, the results could not be extrapolated worldwide because of the differences in metabolic profiles between different nations.

However, there were some other limitations in this meta-analysis. First, we only included fourteen retrospective studies without any randomized controlled trials or cohort studies. Second, the cutoff value of studies was not consistent, which might lead to error. Third, the

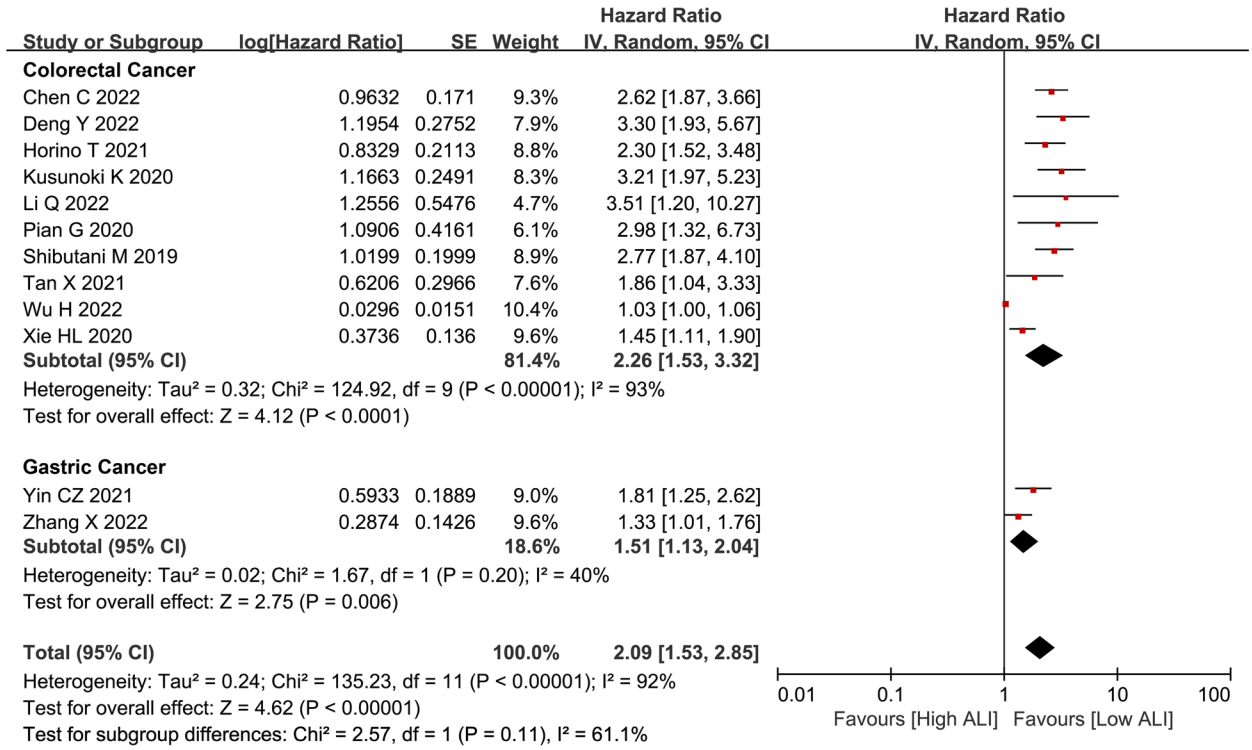

Fig. 3 Subgroup analysis for OS. Abbreviations: OS, overall survival; ALI, advanced lung cancer inflammation index

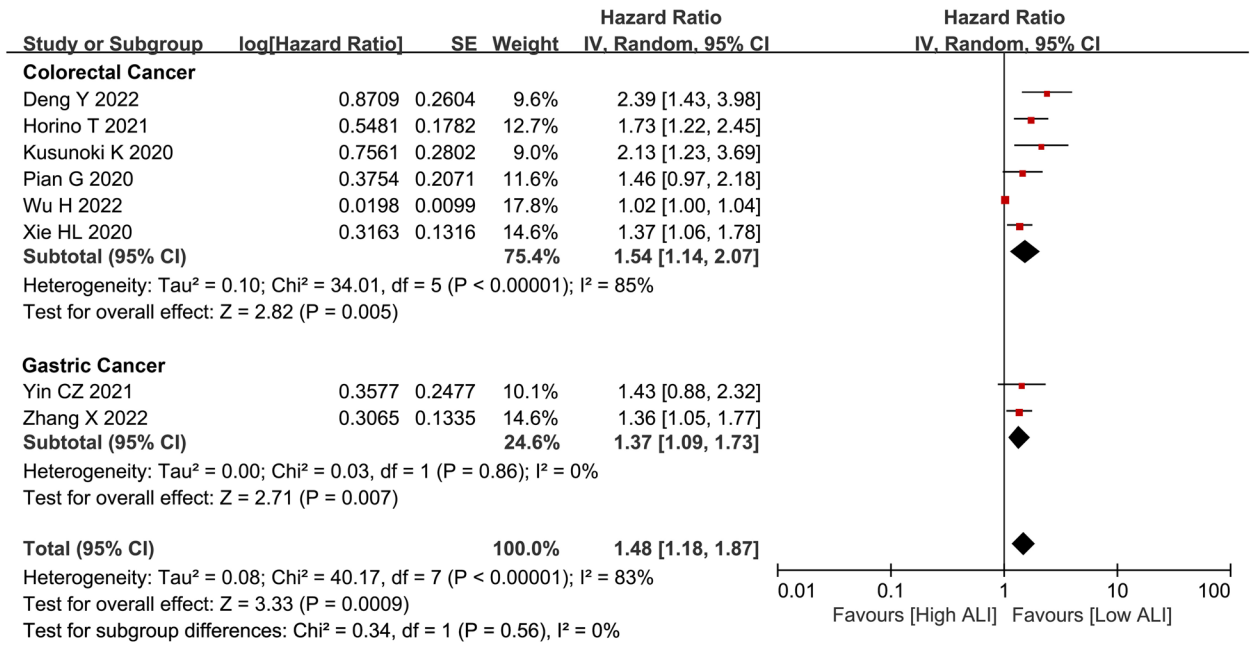

Fig. 4 Subgroup analysis for DFS. Abbreviations: DFS, disease-free survival; ALI, advanced lung cancer inflammation index

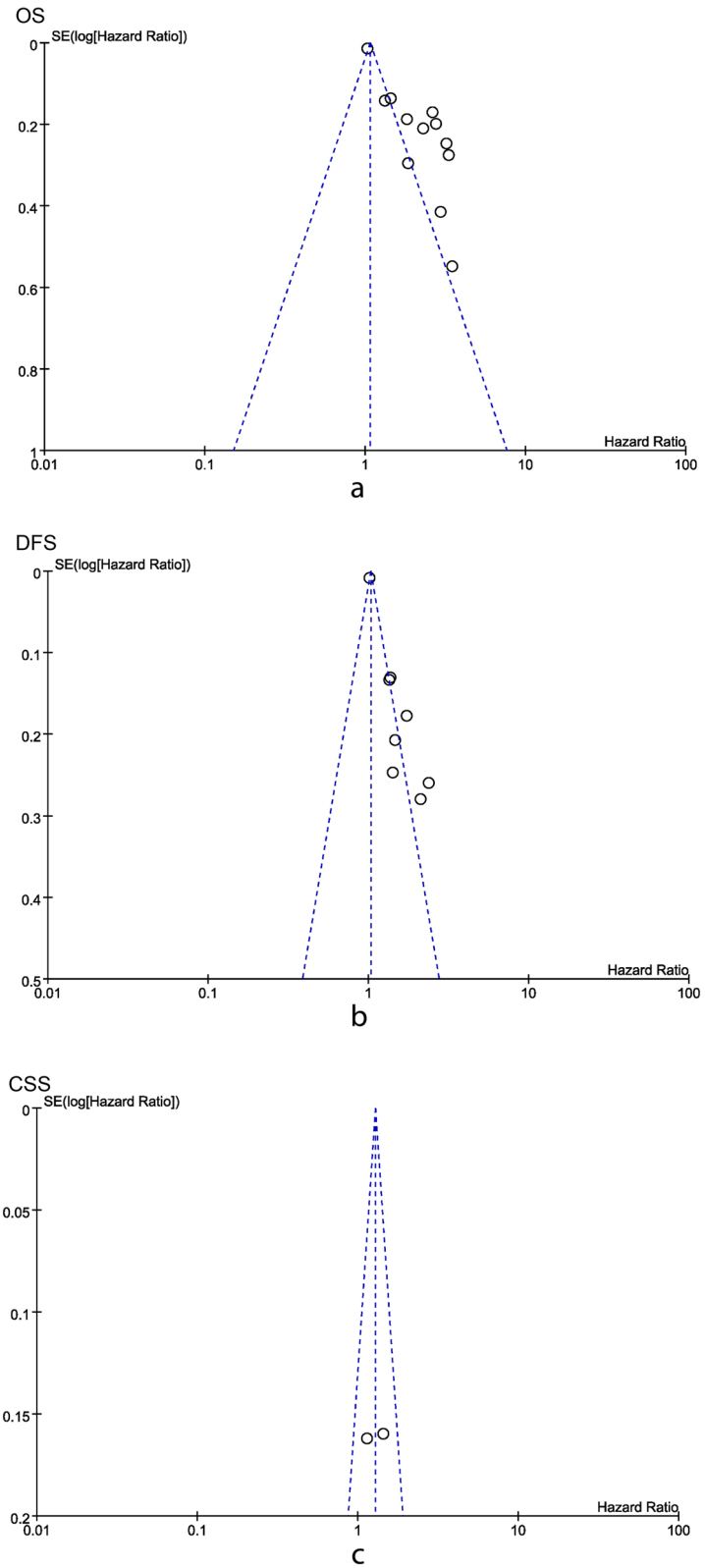

Fig. 5 Funnel plots for **a** OS, **b** DFS, and **c** CSS

potential association between ALI and curative or palliative surgery needs to be explored further.

In conclusion, gastrointestinal cancer patients with a low ALI had a higher risk of poor prognosis after surgery. ALI was an independent prognostic factor for both OS and DFS. Doctors need to pay more attention to patients with low ALI to improve their prognosis.

Abbreviations

CRC	Colorectal cancer
GC	Gastric cancer
ALI	Advanced lung cancer inflammation index
OS	Overall survival
DFS	Disease-free survival
PFS	Progression-free survival
RFS	Relapse-free survival
HRs	Hazard ratios
CIs	Confidence intervals
BMI	Body mass index
Alb	Albumin
TNM	Tumor node metastasis
NLR	Neutrophil-to-lymphocyte ratio
CEA	Carcinoembryonic antigen
NOS	Newcastle–Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-023-02972-4.

Additional file 1. PRISMA 2020 Checklist.

Additional file 2. PICO Framework.

Additional file 3. Search Strategy.

Additional file 4. PRISMA flow chart.

Additional file 5: Table S1. Results of quality assessment using the Newcastle-Ottawa Scale for cohort studies.

Additional file 6: Table S2.

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Authors' contributions
Data extraction, Xu-Rui Liu and Lian-Lian Wang; quality assessments, Dong Peng and Zheng-Qiang Wei; data analysis, Xiao-Yu Liu, Bing Kang, and Chao Yuan; writing the main manuscript text, Xu-Rui Liu, Lian-Lian Wang, and Bin Zhang; writing-review and editing, Xiao-Yu Liu, Bing Kang, and Chao Yuan. Dong Peng prepared Figures. 1–3. All authors read and approved the final manuscript.

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Availability of data and materials
All the data used in this study can be obtained from the original articles.

Declarations

Ethics approval and consent to participate
Not appliance.

Consent for publication
Not appliance.

Competing interests
The authors declare no competing interests

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