

# The diagnostic value of interleukin 6 as a biomarker for gastric cancer

## A meta-analysis and systematic review

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### Abstract

**Background:** Gastric cancer is one of the most common cancers and a main cause of global cancer death. The expression of interleukin 6 is associated with the risk of gastric cancer. But the diagnostic accuracy of interleukin 6 remains unclear. This study was designed to assess the diagnostic performance of interleukin 6 in gastric cancer diagnosis.

**Methods:** The related data was obtained from Oncomine and studied using bioinformatics analysis. The PubMed, Embase, Cochrane Library, Web of science databases were searched for related studies published from inception to July 14, 2020. Measuring tools of diagnostic performance including sensitivity, specificity, and diagnostic odds ratio were pooled using bivariate mixed-effects meta-analysis model. The summary receiver operator characteristic curves were plotted.

**Results:** The result from Oncomine showed that the expression of interleukin 6 in gastric cancer (GC) patients was higher than the normal groups ( $P < .05$ ). Furthermore, a total of 4 eligible articles were enrolled, containing 390 cases and 404 controls. The diagnostic results were as follows: a sensitivity of 0.80 (95% confidence interval [CI] 0.57–0.92), a specificity of 0.86 (95% CI 0.74–0.93), a positive likelihood ratio of 5.76 (95% CI 3.49–9.49), a negative likelihood ratio of 0.23 (95% CI 0.11–0.51) and a diagnostic odds ratio of 24.58 (95% CI 14.14–42.73). The summary area under the receiver operating characteristic curves was 0.90 (95% CI 0.87–0.93).

**Conclusion:** Higher interleukin 6 expression was detected in GC patients, and interleukin 6 could be a helpful indicator of diagnosis of gastric cancer. Further large-scale prospective studies are required for identifying the diagnostic value of interleukin 6 in gastric cancer.

**Abbreviations:** AUC = area under the curve, CA = carbohydrate antigen, CI = confidence interval, DOR = diagnostic odds ratio, FN = false negatives, FP = false positive, GC = gastric cancer, IL-6 = interleukin 6, NLR = negative likelihood ratio, PLR = positive likelihood ratio, TN = true negative, TP = true positives.

**Keywords:** biomarker, gastric cancer, interleukin 6

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JL and XW contributed equally to this study.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## 1. Introduction

Gastric cancer (GC) is one of the most common cancers and a main cause of global cancer deaths.<sup>[1,2]</sup> In 2018, it was estimated that there were 1,033,701 new GC cases and 782,685 deaths caused by GC worldwide.<sup>[2]</sup> The most crucial to reduce GC mortality are accurate diagnosis and tumor treatment at early stage. Until now, there were several detection tools of GC, such as endoscopy, biopsy and serum biomarkers. However, the endoscopy and biopsy are uncomfortable and invasive for patients. Meanwhile, the routine clinical detection of serum biomarkers for example carbohydrate antigen (CA) 19–9 and CA724 are low sensitivity and specificity in the diagnosis of GC.<sup>[3,4]</sup> Therefore, it is a great need for new reliable noninvasive biomarkers for the detection of GC.

Interleukin 6 (IL-6), involved in T-cell, natural killer cells and macrophages differentiation, is one of the important cytokines in the tumor microenvironment.<sup>[5–7]</sup> It has been reported that IL-6 plays important roles in the development of many human cancers, such as primary lung adenocarcinomas and breast cancer.<sup>[8,9]</sup> Numerous studies have shown that IL-6 induces the proliferation of cancer cells, and then contributes to tumor invasion and progression.<sup>[10–13]</sup> GC patients with stage IV showed significant

higher level of serum IL-6 than cases with stage II and III, indicating that IL-6 might be related with the TNM stage, lymph node metastasis and the invasion depth in GC.<sup>[14,15]</sup> Meanwhile, the research carried out by Lin et al<sup>[16]</sup> demonstrated that IL-6 could promote invasion of GC cells through activating the c-Src/RhoA/ROCK signal pathway. Accordingly, IL-6 must be involved in the carcinogenesis of GC.<sup>[17]</sup>

Recent studies showed that high level of serum IL-6 was associated with the cancer cachexia in patients with prostate cancer, and correlated with poor survival of metastatic breast cancer patients.<sup>[18,19]</sup> It was reported that the elevated serum IL-6 level was associated with distant metastasis of esophageal squamous cell carcinoma (ESCC). Meanwhile, the positive IL-6 expression was significantly associated with shorter survival of patients with ESCC, and its inhibitor could decrease the invasion of esophageal cancer cells in vitro and in vivo.<sup>[20]</sup> Compared to the healthy subjects, levels of serum IL-4, C-reactive protein (CRP) and IL-6 were higher in hepatocellular carcinoma patients, and elevated serum IL-6 level was considered to be a risk indicator for hepatocellular carcinoma using with multivariate analysis.<sup>[21,22]</sup> IL-6, therefore, has been regarded as a potential prognostic factor for various cancers.<sup>[26–28]</sup> To date, several studies showed that higher level of serum IL-6 not only was associated with an increased risk of GC,<sup>[23–25]</sup> but also was correlated with invasion depth.<sup>[15]</sup> Thus, high serum IL-6 level in GC patients might be an independent predictor of poor prognosis.<sup>[29]</sup> Previous researches have evidenced that IL-6 can sever as a diagnostic biomarker in many human cancers.<sup>[29,30]</sup> However, whether IL-6 is used as a good biomarker for GC diagnosis is not clear.

Therefore, the expression of IL-6 in GC was analyzed by bioinformatics. The meta-analysis was conducted systematically, and the related literatures were reviewed in this study.

## 2. Methods

### 2.1. Bioinformatics

The expression profiles of IL-6 in GC patients and the controls were downloaded from the Oncomine database (<https://www.oncomine.org>), and then the SPSS16.0 was used to analyze the data.

### 2.2. Search strategy and selection criteria

We systematically and comprehensively searched PubMed, Embase, the Cochrane Library and Web of science for studies Published before July 14, 2020. The terms used for literature retrieval were (“Interleukin 6” or “IL6” or “IL6R”) and (“Stomach Neoplasms” or “Gastric Neoplasms” or “Gastric Neoplasm” or “Cancer of Stomach” or “Stomach Cancers” or “Gastric Cancer” or “Gastric adenocarcinoma”) and (“diagnosis” or “sensitivity and specificity” or “ROC curve”). The titles and abstracts of the articles were checked, and the relevant full texts were scanned by 2 reviewers. The references of each primary identified study and review were also examined. This study was reviewed and approved by The Institutional Review Board of Hebei Medical University.

### 2.3. Study selection

In this meta-analysis, eligible studies met the following criteria:

1. the GC patients were confirmed by pathological examination;
2. interleukin 6 concentration was detected before any treatment;

3. the study investigated the correlation between the expression of interleukin 6 and GC;
4. the study provided available data to extract or calculate the 2\*2 table consisting of true positives (TP), false positive (FP), false negatives (FN), and true negative (TN).

The exclusion criteria were:

1. duplicate publications;
2. literatures irrelevant to the diagnostic values of interleukin 6 for GC;
3. case reports, conference abstracts, reviews, editorials, meta-analysis, comments and letters;
4. studies in vitro, on animal models and human cell lines;
5. insufficient data.

### 2.4. Data extraction

Two researchers independently extracted data. The following items from each study were recorded: name of first author, publication year, country, sample type, detection method, sample size (cases/controls), cut-off value, sensitivity, specificity, TP, FP, FN, TN values and QUADAS-2 score.

### 2.5. Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)<sup>[31]</sup> list in Rev Man 5.3 software (RevMan; the Cochrane Collaboration, Oxford, UK) was used to evaluate the quality of the diagnostic test studies. The scale contained 4 domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing. All domains were assessed in terms of risk of bias, but the applicability concern applied to the first 3 domains. The answer of each question was determined by “yes” “no” or “unclear,” and the risk of bias and concern for applicability were estimated as “high,” “low” or “unclear”.

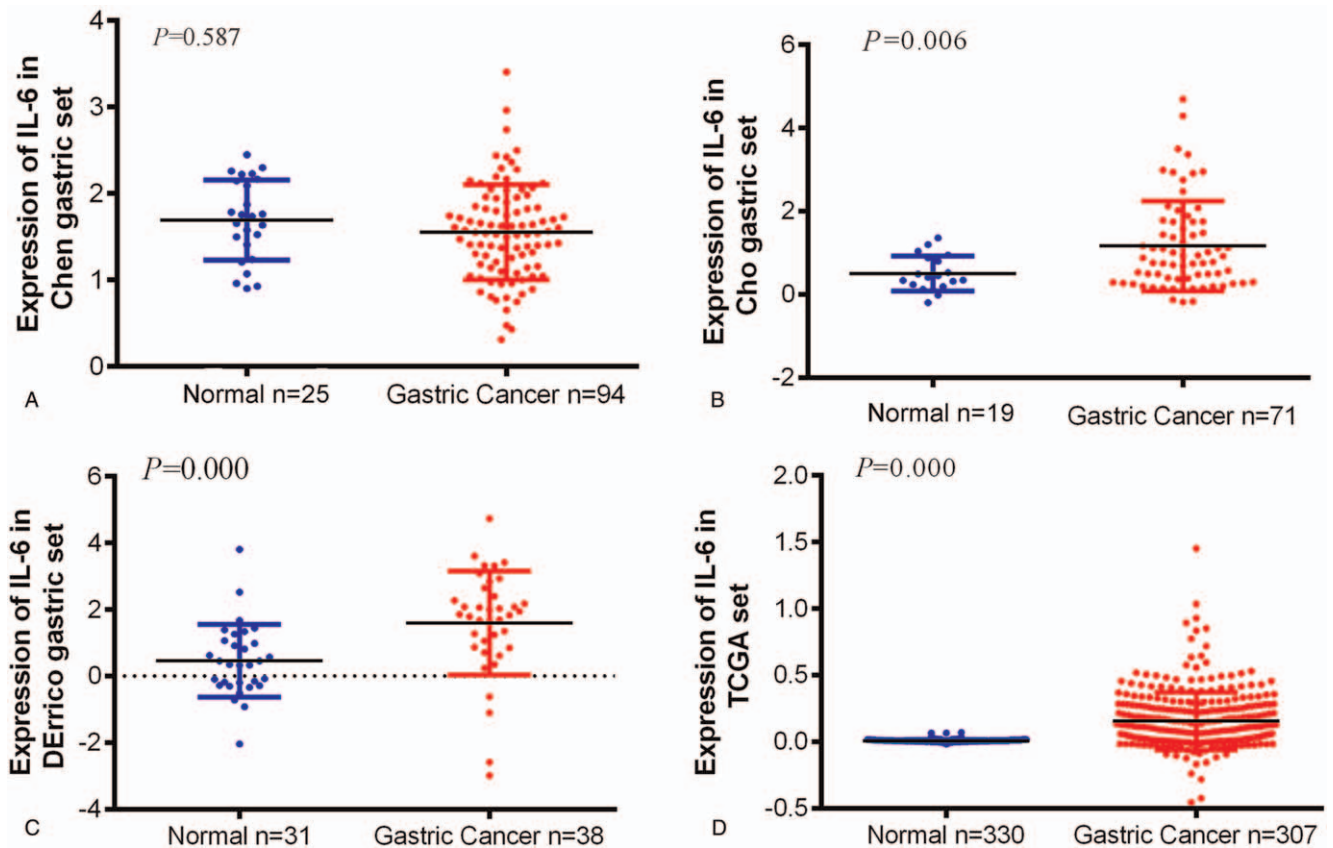
### 2.6. Statistical analysis

The specificity and sensitivity parameters were extracted and the TP, FP, FN, TN were extracted or calculated. Statistical analyses were conducted using the Stata/SE 15.1 software (StataCorp LLC, College Station, TX, USA). The bivariate mixed-effects meta-analysis model was used to evaluate the pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and the area under the summary receiver operating characteristic curves. The area under the summary ROC curve has been considered as a global measure of test performance. The AUSROC values of 0.5–0.7, 0.7–0.9, 0.9–1.0 indicated low, moderate, or high accuracy, respectively.<sup>[32]</sup> Inconsistency index and Cochran Q tests were used to assess the heterogeneity.<sup>[33,34]</sup> The diagnostic threshold effects were analyzed by Spearman’s correlation coefficient and ROC plane analysis. Fagan plot was performed to reveal the relationship between the prior probability specified by user, the likelihood ratio, and the posterior test probability.<sup>[35]</sup>

## 3. Results

### 3.1. Expression levels of interleukin 6 in patients with gastric cancer

The Chen’s, Cho’s, DErrico’s, and TCGA’s Statistics from Oncomine database were used to perform bioinformatics analysis



**Figure 1.** The expression levels of IL-6 in GC compared with those in normal healthy tissues (box plot). Expression of IL-6 at mRNA level in Chen gastric set (A). Expression of IL-6 at mRNA in Cho gastric set (B). Expression of IL-6 at mRNA in DErrico gastric set (C). Expression of IL-6 at DNA level in TCGA set (D).

(Fig. 1A–D). The data of Chen set revealed that there were no significant differences in IL-6 at mRNA level between the GC and normal group ( $P > .05$ ) (Fig. 1A). However, the data of Cho and DErrico datasets analysis showed that the mRNA expression levels of IL-6 were significantly higher in the GC than the normal group ( $P < .05$ ) (Fig. 1B, C). The higher IL-6 DNA level was also detected in GC patients based on the TCGA dataset ( $P < .05$ ) (Fig. 1D).

### 3.2. Study selection and characteristics of eligible studies

A total of 803 articles were searched. Firstly, we removed the duplicated articles ( $n=90$ ). After a scan of titles and abstracts, 169 reviews, 8 meta-analysis, 17 comments, 37 case reports, 14 editorials, 35 conference abstracts and 408 irrelevant articles were removed. After a more detailed evaluation, 21 studies were excluded for not relevant diagnosis and insufficient data. Finally, 4 studies<sup>[23,29,36,37]</sup> were eligible for the meta-analysis, which included 390 cases and 404 controls. The process of literature selection is presented in Figure 2. All of the samples were from serum, and more detailed characteristics of included studies were showed in Table 1.

### 3.3. Quality assessment

The quality of the included studies was evaluated by QUADAS-2. Overall, 2 studies had a score of 4,<sup>[23,29]</sup> and 2 studies had a score of 6<sup>[36,37]</sup> (Fig. 3).

### 3.4. Data analysis

The sensitivity and specificity of IL-6 in diagnosing GC are shown in the corresponding forest plots (Fig. 4A). The indexes from 4 included studies were as follows: sensitivity 0.80 (95% confidence interval [CI], 0.57–0.92), specificity 0.86 (95% CI, 0.74–0.93), PLR 5.76 (95% CI, 3.49–9.49), NLR 0.23 (95% CI, 0.11–0.51) (Fig. 6) and DOR 24.58 (95% CI, 14.14–42.73) (Fig. 4C). The area under the curve (AUC) of IL-6 was 0.90 (95% CI, 0.87–0.93), and the summery receiver operator characteristic curve of the included studies was shown in Figure 4B. Given a pretest probability of 50%, using IL-6 to diagnose GC improved the post-test probability of positive result to 85%, and reduced post-test probability of the negative result to 19% with a NLR of 0.23 (Fig. 4D).

### 3.5. Threshold effect and heterogeneity

In this analysis, the ROC plane showed a non-typical shoulder arm appearance, indicating that there might be no threshold effect (Fig. 5). Furthermore, the calculated Spearman's correlation coefficient was 0.2 ( $P=.8$ ), suggesting that there was no threshold effect. The overall inconsistency index for bivariate model was 98% (95% CI 96–99%), reflecting that heterogeneity existed among the studies. The subgroup, meta-regression and sensitivity analyses could not be conducted to identify the source of the heterogeneity, because that only 4 studies were included in this meta-analysis.

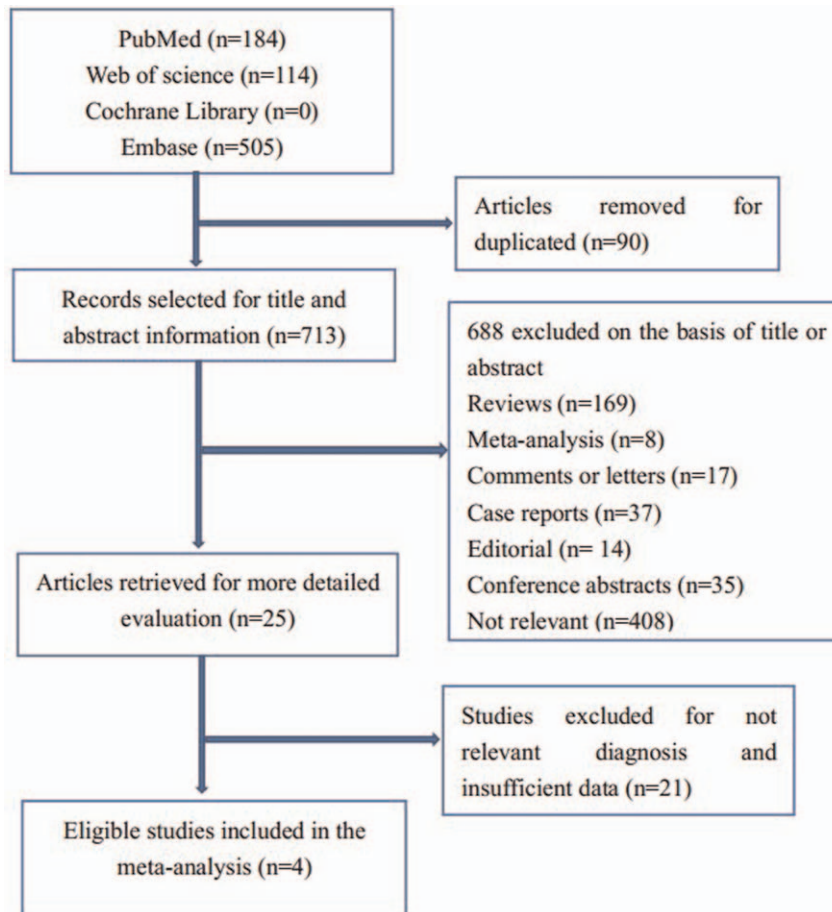


Figure 2. Flow diagram of the study selection process and exclusion reasons.

#### 4. Discussion

GC is responsible for one of the highest cancer-related mortality. The key to reduce the mortality is accurate diagnosis tools. The universal screening methods are invasion and uncomfortable, and the investigated biomarkers such as the carcinoembryonic antigen, CA 19–9 and CA724 are low sensitivity or specificity for the diagnosis of GC.<sup>[38]</sup> Therefore, it is necessary to explore the reliable noninvasive biomarkers to detect GC. Previous studies showed that IL-6 was elevated in multiple human cancers, but it was challenging to regard the IL-6 as an independent deterministic diagnostic biomarker for a single type of cancer.<sup>[39,40]</sup> In GC, IL-6 was reported to play important roles in the tumorigenesis owing to the different IL-6 expression levels observed between

GC patients and healthy controls.<sup>[14,24,41]</sup> However, the diagnostic accuracy of IL-6 for GC remains unclear.

Recently, a meta-analysis to assess the diagnosis value of serum IL-6 in colorectal cancer suggested that IL-6 could be used to screening out the colorectal cancer patients from healthy subjects.<sup>[42]</sup> It has been evidenced that the IL-6 levels were elevated significantly in advanced gastrointestinal cancer patients.<sup>[43]</sup> One previous research on IL-17 and IL-23 showed that patients with gastric neoplasms have significantly lower IL-23 levels with comparison to healthy individuals, while IL-17 levels existed no significant difference between GC and healthy individuals.<sup>[44]</sup> Although the systemic levels of examined interleukins had no associations with tumor TNM staging,

Table 1

Characteristics of the enrolled studies.

Author	Year	Country	Sample type	Method	Cases/controls	Cut-off (pg/mL)	TP	FP	FN	TN	Sensitivity %	Specificity %	QUADAS-2 score
Ashizawa T	2005	Japan	Serum	CLEIA	33/15	1.97	27	5	6	10	81.8	66.7	4
Lukaszewicz-Zajac M	2011	Poland	Serum	ELISA	92/70	2.46	78	15	14	55	85	78.86	6
Sánchez-Zaucó N	2017	Mexico	Serum	xMAP	89/115	3.25	35	4	54	111	39	97	4
Li J	2018	China	Serum	Luminex 200	176/204	20.31	162	43	14	161	92.05	78.92	6

FN = false negative, FP = false positive, QUADAS-2 = quality assessment of diagnostic accuracy studies 2, TP = true positive.



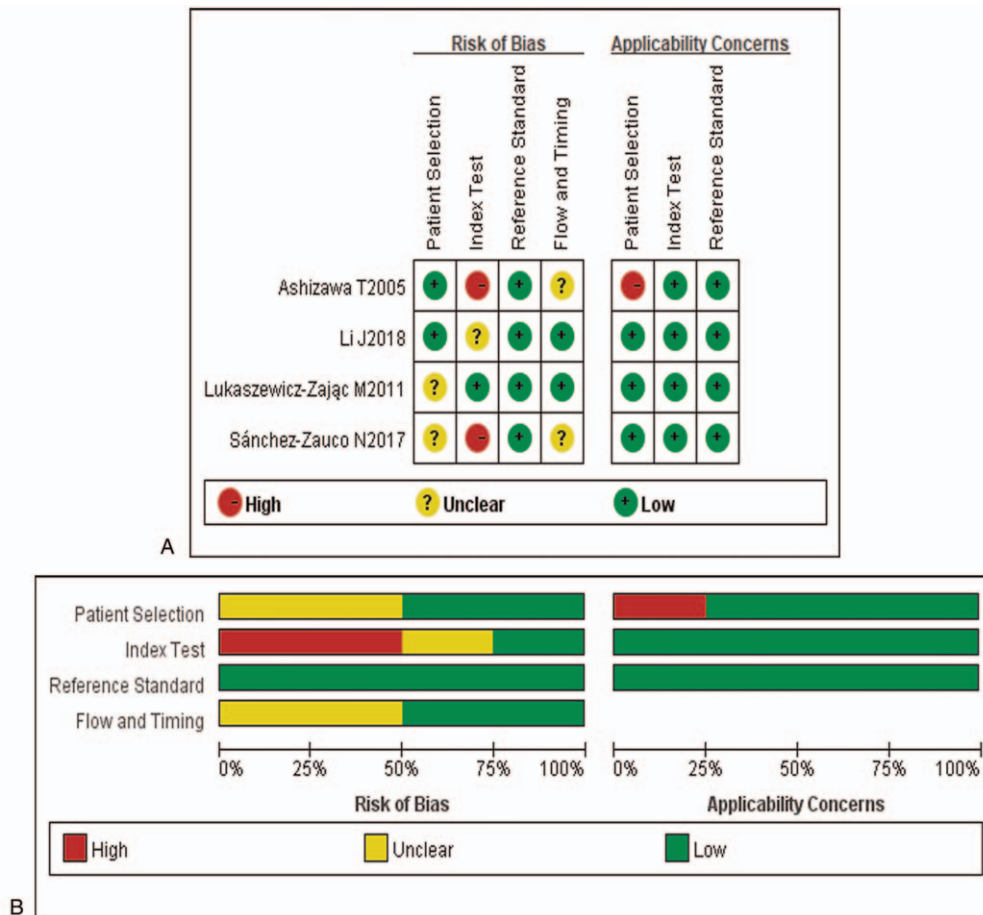
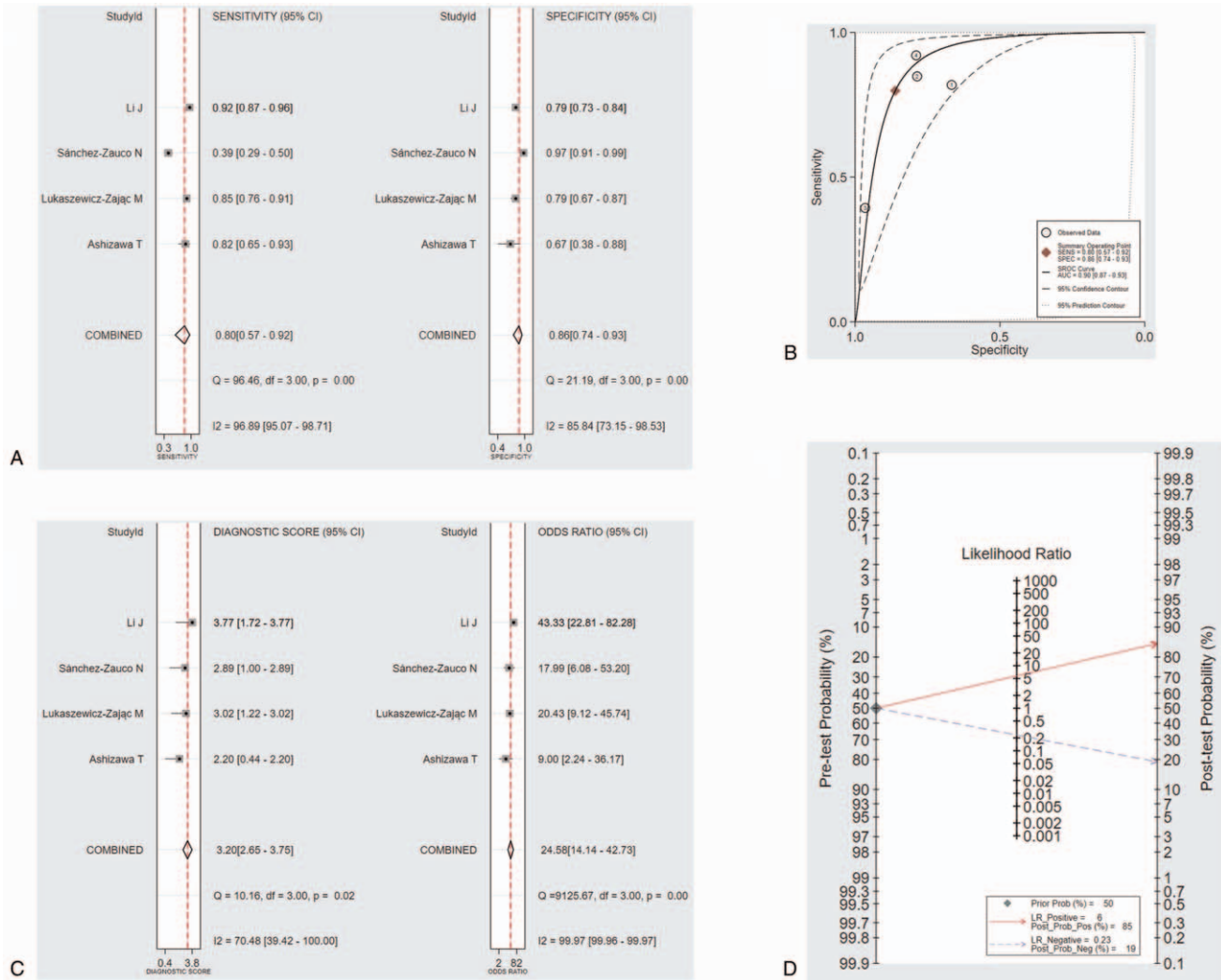


Figure 3. Summary of the methodological quality of the included studies according to the QUADAS-2 criteria.

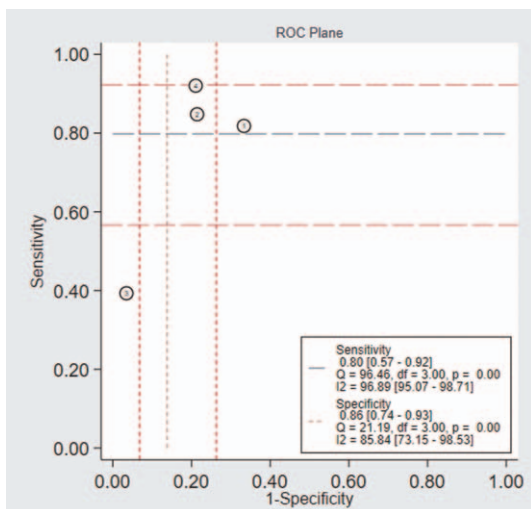
IL-17 levels interestingly differed between patients with early and advanced gastric carcinoma.<sup>[44]</sup> The other comprehensive study for several interleukins including IL-1, IL-6, IL-8, IL-10, and IL-12 demonstrated that patients with GC had significant higher IL-6 level, and lower IL-8 and IL-10 level, compared with the controls. Meanwhile, IL-6/IL-8 and IL-6/IL-10 ratios were also higher in GC patients, indicating that the ratios of interleukins might hold diagnostic potential in confirming or excluding GC (with a sensitivity and specificity of approximately 54%–72%).<sup>[39]</sup> However, there were inconsistent results between different studies.<sup>[39,45]</sup> For example, 1 study found that IL-6 protein expression was elevated in GC tumor tissue, and was related to the TNM stage using western blot and immunohistochemistry.<sup>[45]</sup> However, high-sensitivity ELISA analysis revealed that serum IL-6 levels and the IL-6/IL-8, IL-6/IL-10 ratios were not significantly associated with the TNM stage of GC.<sup>[39]</sup> Due to these inconsistent results, whether the IL levels or IL ratios were enough sensitive or specific as an independent deterministic marker for GC diagnosis remains unclear. In this study, we analyzed the expression levels of IL-6 in GC using bioinformatics analysis based on the Oncomine. The data from Chen dataset showed that there were no statistically significant differences in IL-6 at mRNA level between the GC and normal group. However, Cho and DErrico datasets analysis showed that the mRNA expression levels of IL-6 were higher in GC. And the data from TCGA dataset also revealed that the expression of IL-6

at DNA level was significantly higher in GC patients. Therefore, IL-6 was speculated to be a potential biomarker for GC diagnosis, consistent with the previous research.<sup>[39,44]</sup>

To further clarify the role of IL-6 in GC diagnosis, we searched for related studies published from inception to July 14, 2020 in PubMed, Embase, Cochrane Library, Web of science databases and performed the meta-analysis. Four articles on utilizing serum-based IL-6 diagnosing GC, including 390 patients and 404 controls were carefully reviewed. We found that compared with the healthy control group, serum IL-6 level was significantly upregulated in GC patients, resemble with our analysis based on Oncomine. Summary receiver operator characteristic was used to judge the test performance, and AUC was used to assess the discriminating ability.<sup>[46,47]</sup> An AUC of IL-6 is 0.90 (95% CI, 0.87–0.93), with a sensitivity 0.80 (95% CI, 0.57–0.92) and a specificity 0.86 (95% CI, 0.74–0.93). These results demonstrate that IL-6 has a moderate diagnostic value. The pooled DOR is 24.58 (95%CI 14.14–42.73), indicating that the use of IL-6 for GC diagnosis is credible. The PLR of 5.76 (95% CI, 3.49–9.49) and the NLR of 0.23 (95% CI, 0.11–0.51) imply that patients with GC had 5.8 times higher probability of being IL-6 positive, compared with the healthy adults. The present study showed that the specificity, the sensitivity and the accuracy are as good as the other markers previous reported, such as carcinoembryonic antigen and (CA) 19–9,<sup>[48]</sup> and indicated that IL-6 may be a reliable biomarker in GC detection and diagnosis. However,



**Figure 4.** Forest plots of the pooled sensitivity and specificity of the IL-6 detection for GC (A). Pooled summary receiver operating characteristic curve of IL-6 for the diagnosis of GC in the studies included. Also shows 95% confidence contour and 95% prediction contour (B). Forest plots of the pooled diagnostic odds ratio for IL-6 in the diagnosis of GC (C). Fagan nomogram for evaluating the post-test probabilities (D).



**Figure 5.** ROC space for assessing the threshold effect of IL-6 for GC.

there is high heterogeneity among the selected studies in the present meta-analysis because of the confounding factors, in which threshold effect must be the first considerable factor. We further analyzed the threshold effect using the Spearman's correlation test, and the Spearman's correlation coefficient was 0.2 ( $P = .8$ ). It suggested that threshold effect is not the main source of heterogeneity in our analysis. However, we failed to explore the sources of heterogeneity by meta-regression analysis, sensitivity analysis and subgroup analysis, because only 4 articles were enrolled in our meta-analysis.

It has been reported that IL-6, in the tumor microenvironment, is produced by tumor-infiltrating immune cells, stromal cells, and the tumor cells themselves.<sup>[49]</sup> IL-6 could not only stimulate cancer cells growth and activate the Rho protein, which is associated with invasion and cell-cell adhesion in cancers,<sup>[16,50]</sup> but also promote angiogenesis and suppress apoptosis through elevating the levels of vascular endothelial growth factor (VEGF) in basal cell carcinoma and cervical carcinoma.<sup>[51,52]</sup> In vitro experiments, IL-6/STAT3 signaling could induce GC cell growth through regulating its downstream target lncRNA GACAT3 in GC cell lines (SGC-7901

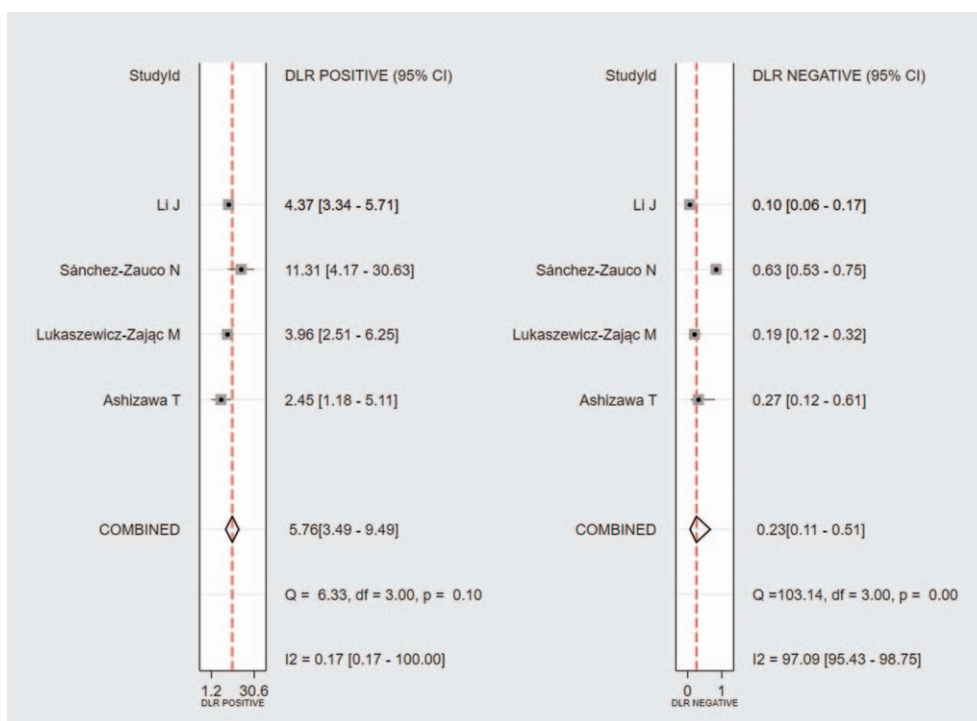


Figure 6. Forest plots of the pooled positive likelihood ratio and negative likelihood ratio for IL-6 in the diagnosis of GC.

and HGC-27 cells).<sup>[53]</sup> Additionally, the inhibitors of JAK/STAT3 (AG490) could reduce cell proliferation and invasion promoted by exogenous IL-6.<sup>[10]</sup> Thus, these data suggested that IL-6 appears to be a promising target for treatment of GC.

There were a few limitations in this study. First, the number of eligible studies and the included participants were small. Second, the sensitivity analysis, meta-regression and subgroup analysis were not performed to interpret heterogeneity. To fetch up these shortages, we added bioinformatics analysis for IL-6 at mRNA and DNA level based on Oncomine datasets. In summary, our study showed that IL-6 expression was significantly higher in GC samples and patients' serum, and then revealed that IL-6 must be a non-invasive, inexpensive and a helpful marker for diagnosis of GC. In the future, the serum levels of IL-6, combined with other biomarkers, are required to be detected in a large population in order to improve the diagnostic accuracy and organ specificity.

### Author contributions

**Conceptualization:** Jie Li, Xianghong Zhang, Liying Xue.

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**Formal analysis:** Xiaozi Wang, Jie Li, Wenjing Liu, Liying Xue.

**Funding acquisition:** Liying Xue.

**Methodology:** Jie Li.

**Software:** Wenjing Liu, Liying Xue.

**Supervision:** Xianghong Zhang, Liying Xue.

**Writing – original draft:** Xiaozi Wang.

**Writing – review & editing:** Jie Li, Xianghong Zhang, Liying Xue.

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