

Prognostic and clinicopathological significance of serum interleukin-6 expression in colorectal cancer: a systematic review and meta-analysis

Zhen Wang¹
Pin Wu^{1,2}
Dang Wu¹
Zhigang Zhang³
Guoming Hu¹
Shuai Zhao¹
Yucheng Lai¹
Jian Huang^{1,4}

¹Cancer Institute, Key Laboratory of Cancer Prevention and Intervention, Key Laboratory of Molecular Biology in Medical Sciences, China National Ministry of Education, ²Department of Thoracic Surgery, ³Department of Gynecology, ⁴Department of Surgical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, People's Republic of China

Correspondence: Jian Huang
Department of Surgical Oncology,
The Second Affiliated Hospital, Zhejiang
University School of Medicine, Zhejiang
University, 88 Jiefang Road, Hangzhou
310009, Zhejiang Province, People's
Republic of China
Email drhuangjian@zju.edu.cn

Purpose: Interleukin-6 (IL-6) plays an important role in human colorectal cancer (CRC) development. However, the exact clinical and prognostic significance of IL-6 in CRC is still unclear. Here, we conducted this meta-analysis to explore this issue in detail.

Methods: A meta-analysis was performed to clarify the association between serum IL-6 expression and clinical outcomes in articles published up to June 2015. Weighted mean difference (WMD) and its corresponding 95% confidence interval (CI) were used to assess the association between serum IL-6 expression and the clinicopathological characteristics of CRC. Hazard ratio (HR) with 95% CI was used to quantify the predictive value of IL-6 on CRC prognosis.

Results: Fourteen studies comprising 1,245 patients were included. Analysis of these data showed that serum IL-6 expression was highly correlated with poor 5-year overall survival (OS) rate (HR =0.43, 95% CI: 0.31–0.59, $P=0.755$). Simultaneously, we also found that serum IL-6 expression was associated with certain clinical parameters of CRC, such as tumor invasion (T category: T0–T2, T3–T4) (WMD =3.15, 95% CI: 1.92–4.39, $P=0.816$), distant metastasis (M category: M0, M1) (WMD =4.69, 95% CI: 3.33–6.06, $P=0.377$), and tumor stage (I–II, III–IV) (WMD =2.65, 95% CI: 1.09–4.21, $P=0.066$).

Conclusion: A high serum IL-6 expression is associated with adverse OS in CRC. The IL-6 expression can be an important supplement in establishing prognostic score for clinical decision.

Keywords: interleukin-6, colorectal cancer, prognosis, meta-analysis

Introduction

Colorectal cancer (CRC) is a worldwide disease which is the third most common cause of cancer in both women and men and is also the third most common cause of cancer death after lung and prostate cancer in men and lung and breast cancer in women.¹ Inflammation plays an important role in CRC development, including tumor initiation, progression, and metastasis. Numerous inflammatory cytokines have been regarded as potential diagnostic and prognostic markers in CRC. Among these, interleukin-6 (IL-6) seems to be of central importance in human CRC development. IL-6, a 184-amino acid protein with a molecular weight of approximately 20.3 kDa, is a pleiotropic cytokine produced by multiple cells, including monocytes, macrophages, and others cells such as fibroblasts, keratinocytes, endothelial cells, lymphocytes, and tumor cells.² It plays a crucial role in regulating the inflammation and immune responses.³ Lahm et al first found that IL-6 had a growth-promoting effect on CRC cell lines in vitro in 1992.⁴ Chung and Chang⁵ revealed that levels of IL-6 were elevated in the serum and tumor tissues of CRC patients. Moreover, IL-6 expression level is gradually elevated during the progression from colorectal adenoma to carcinoma.⁶

Nowadays, we know that IL-6 signaling has two significant pathways. IL-6 can bind to its receptor (IL-6R α) on the cell surface in classic signaling pathway, or binds to soluble IL-6 receptor (sIL-6R) in trans-signaling pathway, and then form a hexameric signaling complex including coreceptor gp130 (glycoprotein 130, IL-6R β) homodimer and two IL-6-IL-6R heterodimers, thus activating the Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) pathway, which regulates tumor proliferation, prevents apoptosis and induces tumor angiogenesis.⁷⁻⁹ Many researchers have approved that IL-6-JAK-STAT3 signaling plays an important role in multiple tumor models including breast, lung, colon, ovarian, and prostate cancer.¹⁰ IL-6R α is only expressed on a limited number of cell types, such as hepatocytes, megakaryocytes and monocytes, macrophages, B-cells, and T-cells, while sIL-6R exists throughout the body. It is suggested that proinflammatory effects of IL-6 are mainly attributed to trans-signaling pathway, while the classic signaling pathway contributes to anti-inflammatory effects.¹¹

In consideration of the important role of IL-6 in tumor development, many researchers were involved in doing related studies, including correlating IL-6 expression with risk, clinicopathological features, and prognosis of CRC. The associated data seemed inconsistent. Several previous meta-analyses which investigated the association between serum IL-6 expressions with CRC risk showed no significant correlation.¹²⁻¹⁵ However, the clinical significance and accurate prognostic value of IL-6 in CRC have not been fully assessed. Therefore, we conducted the first meta-analysis aiming to evaluate the value of serum IL-6 as a prognostic marker for CRC and to research the relationship between serum IL-6 and clinical stage of CRC.

Materials and methods

Publication search

This meta-analysis was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.¹⁶ We searched literature from electronic databases PubMed, MEDLINE, and ISI Web of Science up to June 2015. The search terms included “(interleukin 6 or IL-6) and (colorectal or colon or rectal) and (carcinoma or tumor or cancer or neoplasm)”. The reference lists and supplemental materials associated with the studies and review articles were examined manually to further identify any additional relevant publications.

Selection criteria

The studies aiming to explore the association between serum IL-6 expression and CRC were included. The inclusion

criteria were as follows: 1) articles evaluating the relationship between preoperative serum IL-6 expression and parameters such as clinicopathological features including Tumor Node Metastasis classification and survival outcome of CRC and 2) full text, original research articles published in English.

Articles were excluded from the analyses based on the following criteria: 1) they were letters to the editor, reviews, comments, duplicated studies, and articles published in books; 2) papers were published in non-English language; 3) the articles focused on the tissue IL-6 expression; 4) the patients included in the studies underwent preoperative chemotherapy (neoadjuvant chemotherapy); 5) insufficient data was extracted from the articles or the full text could not be found.

Data extraction

All data were extracted independently by two investigators. Any further uncertainties were addressed by joint inspection of the papers and discussion. The following data were obtained from each article: the first author; publication year; country; number of patients; method of IL-6 detection; serum IL-6 expression of different T category, N category, distant metastasis (liver metastasis), and tumor stage (I–II, III–IV); the cut-off value of IL-6; and most importantly, the 5-year overall survival (OS) and the 3-year disease-free survival (DFS) rate. The quality of studies was evaluated according to the Newcastle–Ottawa scale.¹⁷

The T, N, M category was determined according to the American Joint Committee on Cancer guidelines. Because the cut-off value for IL-6 expression varied among studies, we defined IL-6-high expression values with respect to the original articles. To avoid bias from some studies that had very long-term follow-up data, OS was standardized to include 5 years of follow-up, while DFS was standardized to include 3 years of follow-up in the included studies. If included articles only provided survival data in a Kaplan–Meier curve, the software GetDataGraph Digitizer 2.24 (<http://getdata-graph-digitizer.com/>) was used to extract the data.

Data analysis

The guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group were applied in the statistical analyses. Because most of the including studies compared serum IL-6 expression quantity in different T, N, M category with its stage, weighted mean difference (WMD) with 95% confidence interval (CI) was used to assess the association between IL-6 expression level and clinicopathological characteristics of CRC. Hazard ratios (HR) and their

95% CIs were used to quantify the predictive ability of IL-6 expression level on CRC prognosis. WMD with 95% CI and HR with 95% CI were calculated using STATA 12.0 (Stata Corp LP, College Station, TX, USA). The heterogeneity among the studies was measured using the Q -test and I^2 test. Both fixed- and random-effects models could be used in the absence of heterogeneity, but random-effects models were more appropriate when heterogeneity was present. The publication bias was assessed by Begg rank correlation method (software Stata 12.0). All P -values were for a two-sided test and $P < 0.05$ was considered statistically significant.

Results

Search results

The detailed steps of article identification and inclusion and exclusion criteria are described in Figure 1. In the initial search, 2,052 published articles were identified according to the search strategies. After screening the titles and abstracts, 1,383 articles were excluded because they were beyond the scope of the study (eg, pathological features, OS, or DFS). Among the rest of included articles, 655 studies were excluded because their focus was on IL-6 mRNA, gene polymorphism, signaling pathway, review, experimental animal models, serum IL-6 level after chemotherapy, and non-English articles. Finally, using explicit inclusion and exclusion criteria mentioned above, a total of 14 eligible studies were included in the final meta-analysis.

Characteristics of eligible studies

The details of the 14 eligible studies are listed in Table 1. Of these 14 publications, 11 studies assessed the relationships between serum IL-6 expression and CRC clinicopathologic features, while 7 studies evaluated the association of IL-6 expression and CRC prognosis (OS and DFS). Approximately 1,245 participants were enrolled with a median sample size of 89 (range from 24 to 208) per study. Among them, 7 were from East Asia, including Japan (3), China (2), Korea (2), and 1 was from Middle East Iran; 5 were from Europe, including Poland (2), Italy (1), Finland (1), and Greece (1); 1 was from Egypt, Africa. We did not obtain any studies from North and South America. Enzyme-linked immunosorbent assay (ELISA) method was adopted in all the included studies except one study where Bio-Plex premanufactured 27-Plex Cytokine Panel (Bio-Rad, Hercules, CA, USA) was used, which shares the same mechanism with ELISA. Meanwhile, the quality of the 14 included studies was considered accessible according to the Newcastle–Ottawa scale.¹⁸

Correlation of serum IL-6 expression with clinicopathological parameters

Serum IL-6 expression was associated with certain clinical parameters of CRC such as tumor category (T category: T0–2, T3–4) (WMD = 3.15, 95% CI: 1.92–4.39, $P = 0.816$, and $P = 0.0\%$ fixed effect), distant metastasis (M category: M0, M1) (WMD = 4.69, 95% CI: 3.33–6.06, $P = 0.377$,

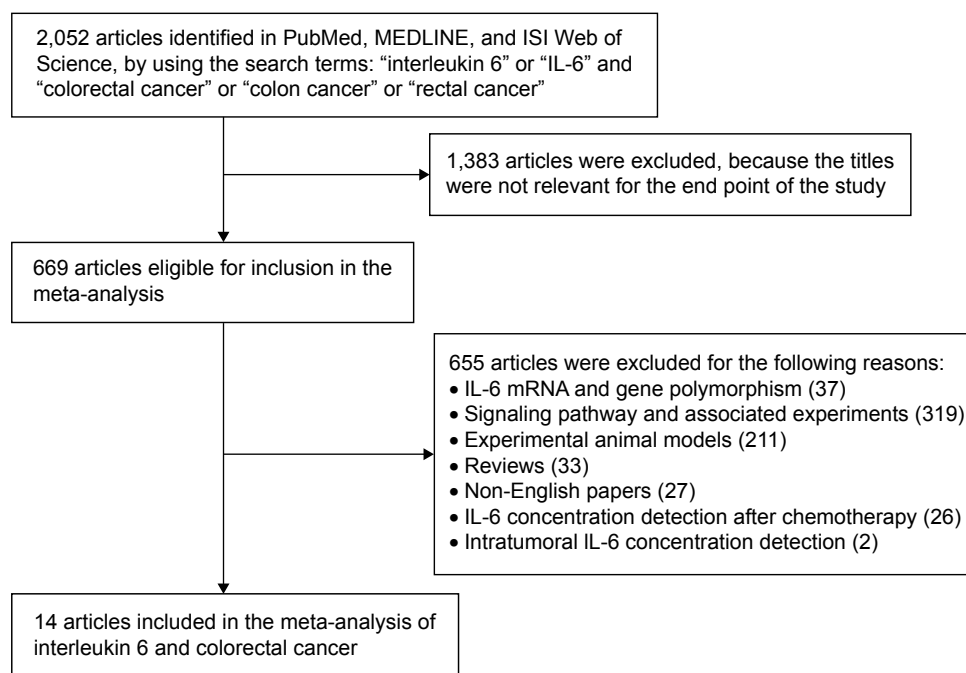


Figure 1 Flowchart of the selection of the studies for inclusion in the meta-analysis.
Abbreviation: IL-6, interleukin-6.

Table 1 Main characteristics of the eligible results

Study (references)	Year	Country	N pts	Median age, years ^a	Method	Cut-off (pg/mL)	Tumor stage ^b	T category ^c	N category ^c	M category ^c	Tumor stage ^c	5-year OS ^c	3-year DFS ^c	NOS score
Lee et al ³⁸	2013	Korea	77	64.4 (43–79)	ELISA	9	III						✓	7
Shimazaki et al ³⁹	2013	Japan	46	70.3 (43–86)	ELISA	2.41	I–IV	✓	✓	✓	✓	✓		7
Kantola et al ⁴⁰	2012	Finland	148	67.9±11.2	BPpCP	NA	I–IV				✓			8
Eldesoky et al ⁴¹	2011	Egypt	35	49±13.2	ELISA	NA	I–IV	✓		✓				8
Yeh et al ³	2010	Taiwan (ROC)	99	63.8 (30–82)	ELISA	10	I–IV	✓	✓	✓	✓	✓		7
Kwon et al ⁴²	2010	Korea	132	62 (26–83)	ELISA	11.68	I–III	✓	✓	✓	✓	✓		7
Groblewska et al ⁴³	2008	Poland	76	NA (27–83)	ELISA	13.1	II–IV	✓		✓	✓			8
Dymicka-Piekarska et al ⁴⁴	2007	Poland	42	NA (42–78)	ELISA	NA	I–III			✓	✓			8
Esfandi et al ⁴⁵	2006	Iran	50	57.26 (33–77)	ELISA	NA	I–IV				✓	✓		8
Nikiteas et al ⁴⁶	2005	Greece	74	66.83 (33–86)	ELISA	8	I–IV							7
Chung and Chang ⁵	2003	Taiwan (ROC)	164	NA (18–90)	ELISA	12	I–IV	✓		✓	✓			7
Belluco et al ⁴⁷	2000	Italy	208	64 (27–92)	ELISA	10	I–IV				✓	✓		7
Kinoshita et al ⁴⁸	1999	Japan	70	64.3 (33–86)	ELISA	8.3	I–IV	✓	✓	✓	✓			8
Ueda et al ⁴⁹	1994	Japan	24	NA (NA)	ELISA	NA	I–IV	✓	✓	✓				8

Notes: ^aData shown as either median (range) or mean ± SD. ^bThis column shows which tumor stages were included in the study. ^cThe results reported in each study included this detail if ticked, and did not include the detail if not ticked. Bio-Plex premanufactured 27-Plex Cytokine Panel manufactured by Bio-Rad, Hercules, CA, USA.

Abbreviations: BPpCP, Bio-Plex Premanufactured Cytokine 27-Plex Panel; DFS, disease-free survival; ELISA, enzyme-linked immunosorbent assay; NA, not available; NOS, Newcastle-Ottawa Scale; N pts, number of patients; OS, overall survival; ROC, Republic of China.

and $I^2=6.6\%$ fixed effect), and tumor stage (I–II, III–IV) (WMD =2.65, 95% CI: 1.09–4.21, $P=0.066$, and $I^2=49.2\%$ random effect) (Figure 2).

However, there was no statistically significant association between IL-6 expression and lymph node metastasis (N category: N0, N1–2) (WMD =2.45, 95% CI: –1.56 to 6.46, $P=0.154$, and $I^2=36.0\%$ random effect) (Figure 2).

Impact of serum IL-6 expression on 5-year OS and 3-year DFS rates

Five studies (408 patients) investigated the association between serum IL-6 expression and OS. The presence of IL-6 expression was highly correlated with poor 5-year OS rate (Figure 3A, HR =0.43, 95% CI: 0.31–0.59, $P=0.755$, and $I^2=0.0\%$ fixed effect). This indicated that IL-6 was an independent prognostic factor in CRC. In addition, three studies investigated the association between IL-6 expression and DFS, but no statistically significant association was found with obvious heterogeneity (Figure 3B, HR =0.36, 95% CI: 0.08–1.72, $P=0.004$, and $I^2=82.1\%$ random effect).

Publication bias

No evidence of potential publication bias for the studies included in our meta-analysis was observed when assessed with Begg's tests (Figures 4 and 5).

Discussion

In our search strategy, we excluded the studies that focus on serum levels of IL-6 after surgical operation or chemotherapy which may cause deviation. Surgery could increase the body's stress level, which triggers proinflammatory response, while chemotherapy could decrease the level of IL-6.¹⁹

The results from the present meta-analysis showed a poor prognostic outcome in patients expressing high levels of serum IL-6. The results also indicated that IL-6 expression was significantly associated with tumor local invasion, distant metastasis, and tumor stage. Owing to lack of enough data to perform statistical analysis and the presence of significant heterogeneity ($I^2=82.1\%$ random effect) from a 3-year DFS rate, we could not reach a specific conclusion approximately 3-year DFS.

In this meta-analysis, IL-6 was significantly associated with the 5-year OS of CRC patients, indicating that IL-6 could promote tumor proliferation. Because of its low molecular weight, IL-6 can freely diffuse through intercellular junction and appear in the tumor microenvironment rapidly, which is the basis for IL-6 to function. IL-6 can promote cancer cell entry into the cell cycle through activating STAT3 which increases the expression of cyclin D1, D2, B1, and c-Myc,

and decrease the expression of the cyclin-dependent kinase (Cdk) inhibitor p21.²⁰⁻²³ IL-6 can also increase telomerase activity, thus preventing cellular senescence.²⁴ Besides, IL-6 can promote noncancer cells conversion into cancer

stem cells, which possess properties of self-renewal and repopulation potential.²⁵ Furthermore, IL-6 can regulate tumor cell proliferation by interacting with growth factor signaling, including epidermal growth factor family

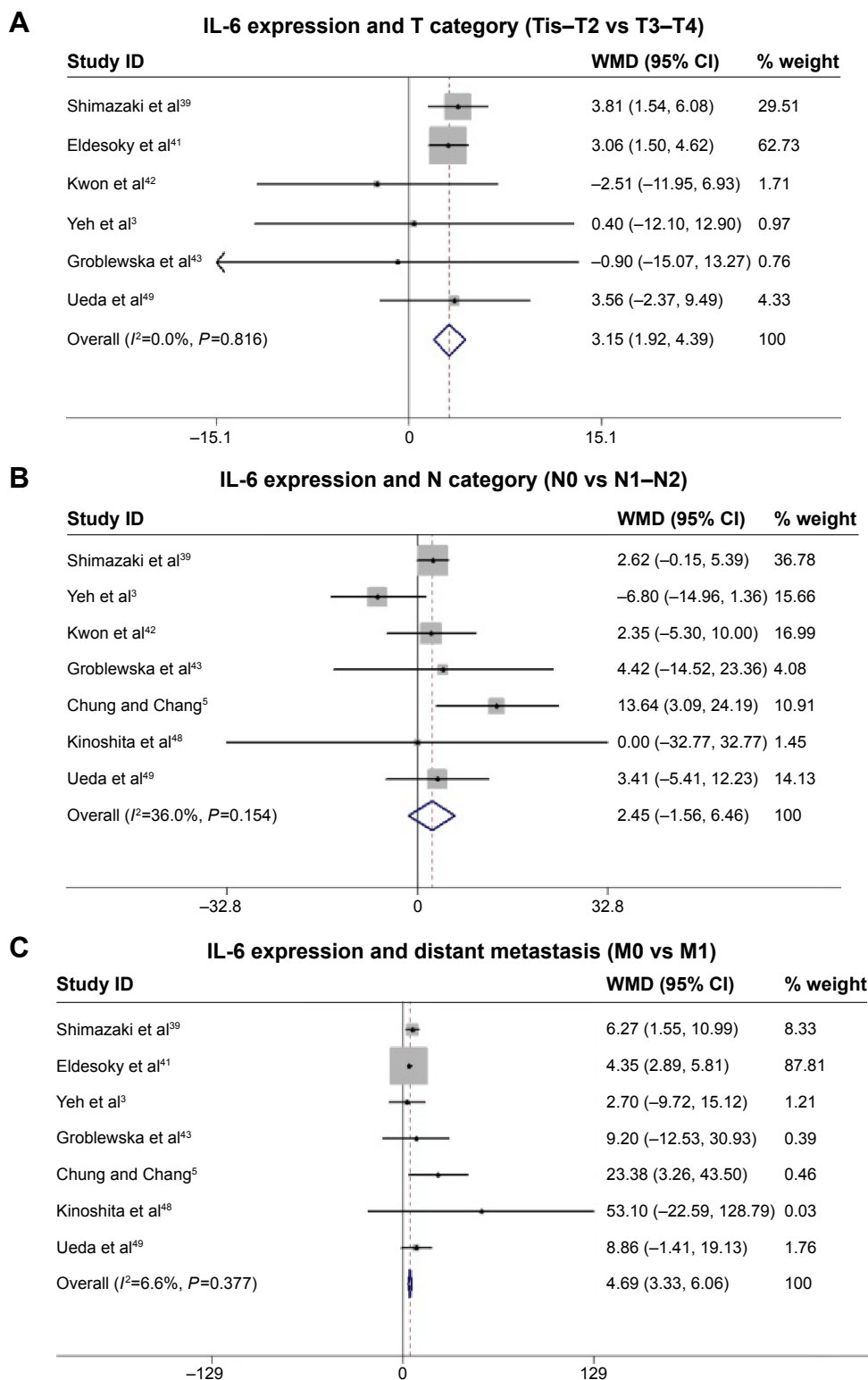


Figure 2 (Continued)

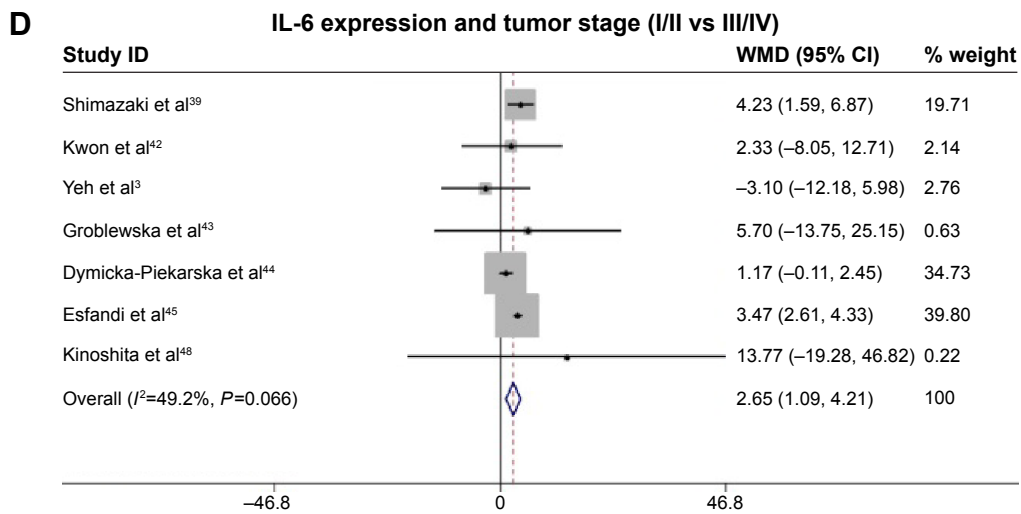


Figure 2 The forest plot of weighted mean difference in the meta-analysis.

Notes: Association between IL-6 and clinicopathological features such as tumor category (A), N category (B), distant metastasis (C), and tumor stage (D). Weights are from random-effects analysis.

Abbreviations: IL-6, interleukin-6; CI, confidence interval; TIS, carcinoma in situ; WMD, weighted mean difference.

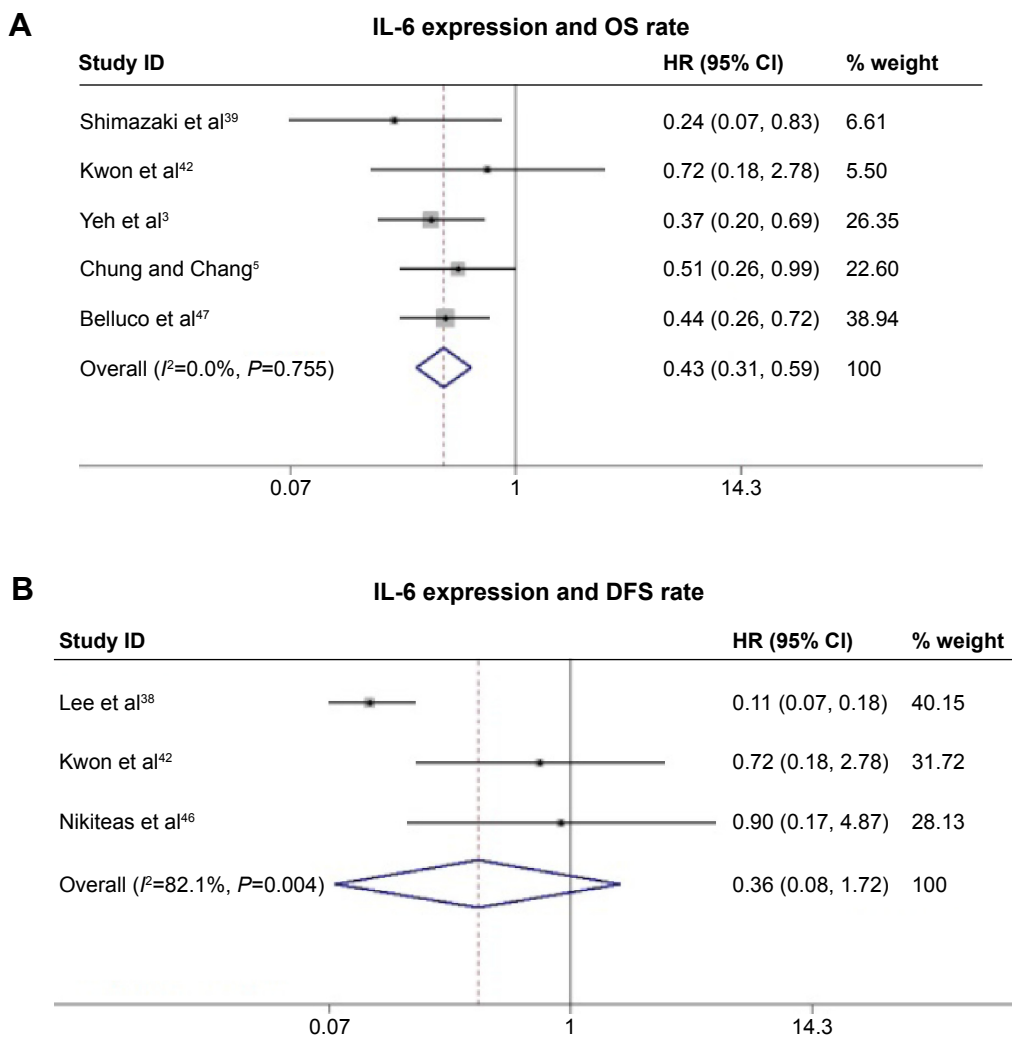


Figure 3 The forest plot of HR in the meta-analysis.

Notes: 5-year OS rate (A) and 3-year DFS rate (B). Weights are from random-effects analysis.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; IL-6, interleukin-6; OS, overall survival; CI, confidence interval.

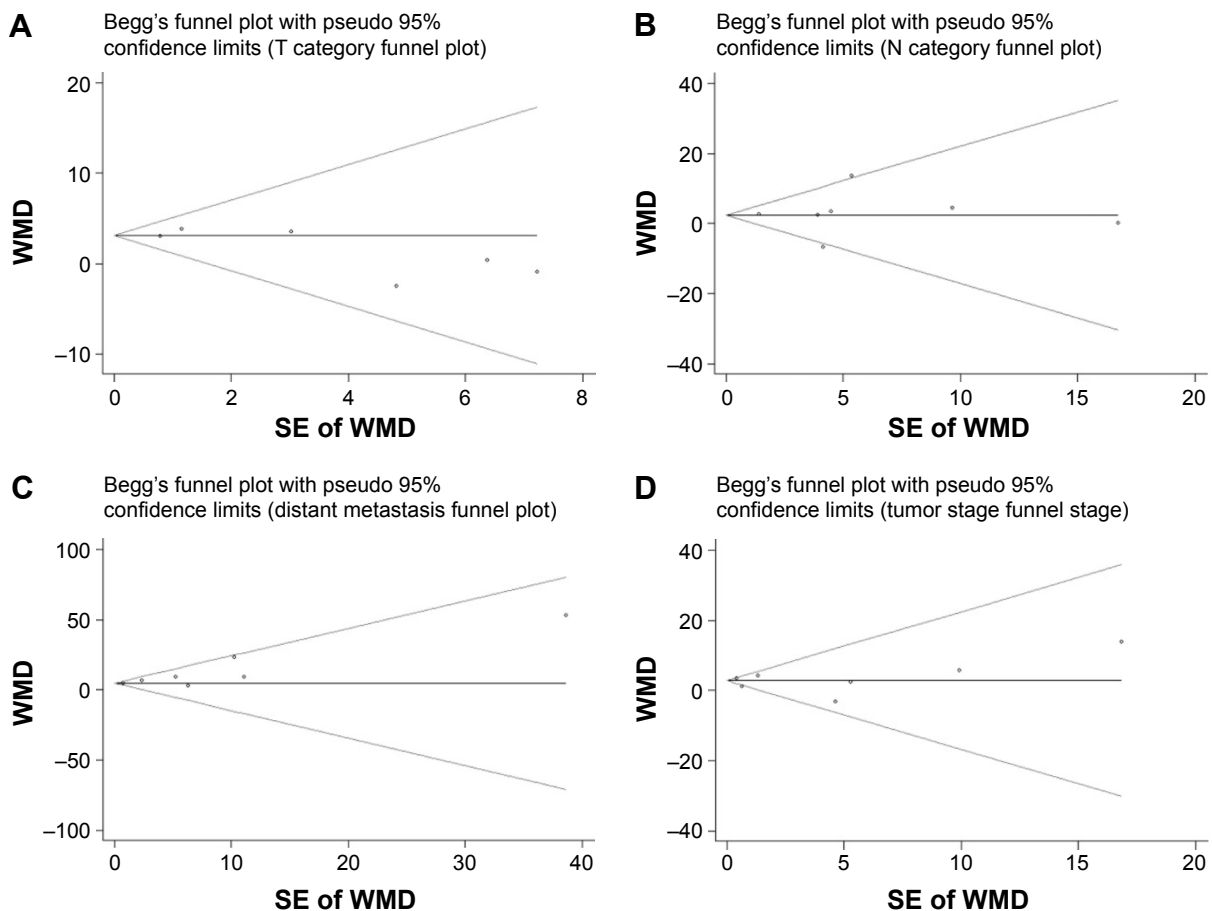


Figure 4 Begg's test results of IL-6 and clinicopathological features.
Notes: T category (A), N category (B), distant metastasis (C), and tumor stage (D).
Abbreviations: IL-6, interleukin-6; SE, standard error; WMD, weighted mean difference.

members and hepatocyte growth factor.²³ IL-6 also provides a key regulatory signal in the T-cell differentiation pathway, downregulating T-lymphocytic function and impairing adaptive immune response, thus allowing tumor cells to escape immune surveillance.^{8,26} All of these discoveries illustrated

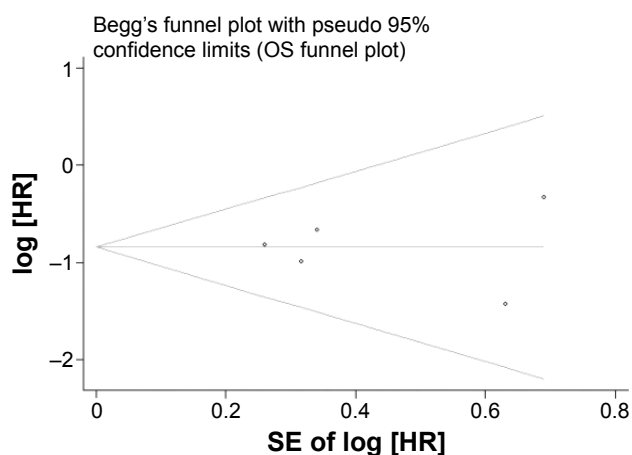


Figure 5 Begg's test results of the 5-year OS rate.
Abbreviations: OS, overall survival; SE, standard error.

the protumor function of IL-6 via promoting tumor cell growth inordinately and inhibiting apoptosis.

IL-6 has also been found to be significantly associated with tumor local invasion and distant metastasis based on the data from this meta-analysis. IL-6 can induce matrix metalloproteinase (MMP)-2, MMP-7, and MMP-9, which play a role in extracellular matrix degradation and tumor invasion, via activation of the IL-6-JAK-STAT3 pathway. In addition, IL-6 can lead to epithelial-mesenchymal transition, which facilitates cancer cells invasion of other tissues and blood vessels, thus causing distant metastases.²⁷⁻³¹ Besides, IL-6 also promotes local invasion and forms distant secondary tumor implants through its proangiogenic function mainly via IL-6-JAK-STAT3 pathway, thus leading to hypoxia inducible factor-1-mediated VEGF-A transcription, as well as endothelial cell proliferation and migration.³²⁻³⁵

Nowadays, the pivotal role of IL-6/STAT3 signaling in CRC development has attracted more and more attention. Inhibiting IL-6 in tumor cells is likely to prevent tumor invasion and metastasis. Several therapeutics inhibiting this

pathway have been developed and have shown a promising future for the treatment of human disease during recent years. These include anti-IL-6 agents like siltuximab or anti-IL-6R antibodies like tocilizumab, soluble gp130Fc, and selective small molecule JAK inhibitors like CEP-33779.^{36,37} Now, tocilizumab has been approved by the US Food and Drug Administration for clinical use. We hope that the preclinical data will reach their promise and become a potential therapy for the cancer patients refractory to conventional chemotherapy drugs.

Some limitations should be considered in this meta-analysis. First, the cut-off value was different between the included studies, which could cause heterogeneity among the studies. Therefore, more studies with the same cut-off values should be recruited and combined for further analysis. Second, because of the lack of data relating the IL-6 expression and DFS, which is also an important aspect reflecting the prognosis, we could not conclude an accurate result now. Third, the lack of concrete data made us unable to further explore the association of CRC with more detailed factors like age via subgroup analysis.

Conclusion

To our knowledge, this meta-analysis is the first study to systematically and quantitatively evaluate the association between serum IL-6 and clinicopathological features and prognostic factors in CRC. Our results showed that serum IL-6 expression has a significant negative correlation with the 5-year OS rates in CRC patients. Besides, serum IL-6 expression was also related to tumor local invasion and distant metastasis. Thus, elevated serum IL-6 expression indicated a poor prognostic significance for CRC patients, and IL-6 expression could be an important supplement in establishing prognostic score for clinical decision. We hope there will be more studies to further evaluate the application of IL-6 as a biomarker for CRC prognosis and to assess whether IL-6 could change in the process of CRC chemotherapy or neoadjuvant therapy.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure

The authors report no conflicts of interest in this work.

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