

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

Zhen Wang<sup>1</sup>Pin Wu<sup>1,2</sup>Dang Wu<sup>1</sup>Zhigang Zhang<sup>3</sup>Guoming Hu<sup>1</sup>Shuai Zhao<sup>1</sup>Yucheng Lai<sup>1</sup>Jian Huang<sup>1,4</sup>

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

**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.<sup>1</sup> 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.<sup>2</sup> It plays a crucial role in regulating the inflammation and immune responses.<sup>3</sup> Lahm et al first found that IL-6 had a growth-promoting effect on CRC cell lines in vitro in 1992.<sup>4</sup> Chung and Chang<sup>5</sup> 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.<sup>6</sup>

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

Nowadays, we know that IL-6 signaling has two significant pathways. IL-6 can bind to its receptor (IL-6R $\alpha$ ) 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 $\beta$ ) 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.<sup>7–9</sup> 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.<sup>10</sup> IL-6R $\alpha$  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.<sup>11</sup>

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.<sup>12–15</sup> 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.<sup>16</sup> 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.<sup>17</sup>

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

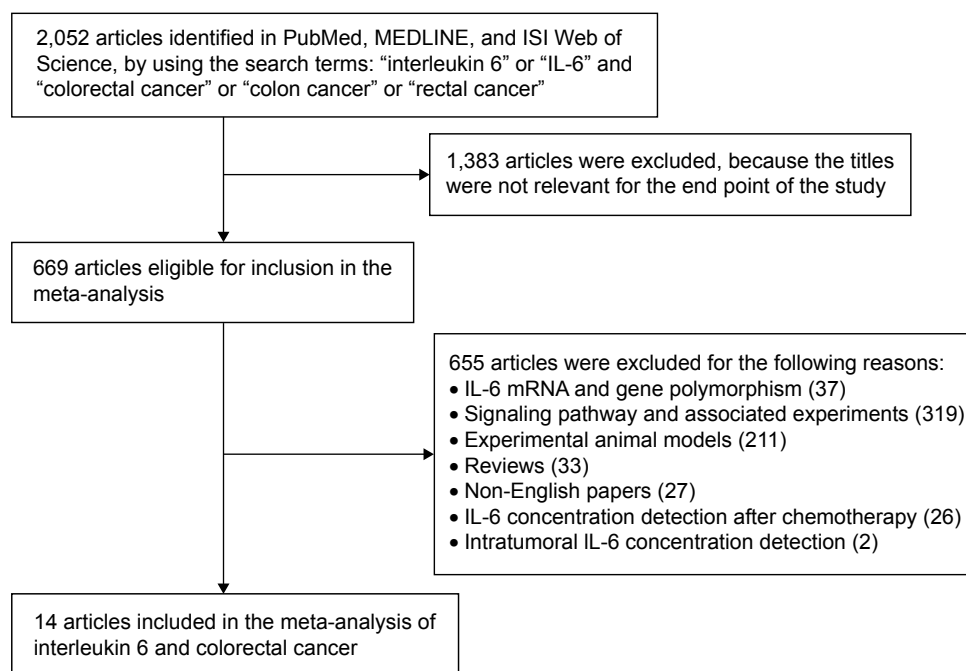
The detailed steps of article identification and inclusion and exclusion criteria are described in Figure 1. In the initial search, 2,052 published articles were identified according to the search strategies. After screening the titles and abstracts, 1,383 articles were excluded because they were beyond 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.<sup>18</sup>

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

Notes: <sup>a</sup>Data shown as either median (range) or mean ± SD. <sup>b</sup>This column shows which tumor stages were included in the study. <sup>c</sup>The 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.<sup>19</sup>

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.<sup>20–23</sup> IL-6 can also increase telomerase activity, thus preventing cellular senescence.<sup>24</sup> Besides, IL-6 can promote noncancer cells conversion into cancer

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

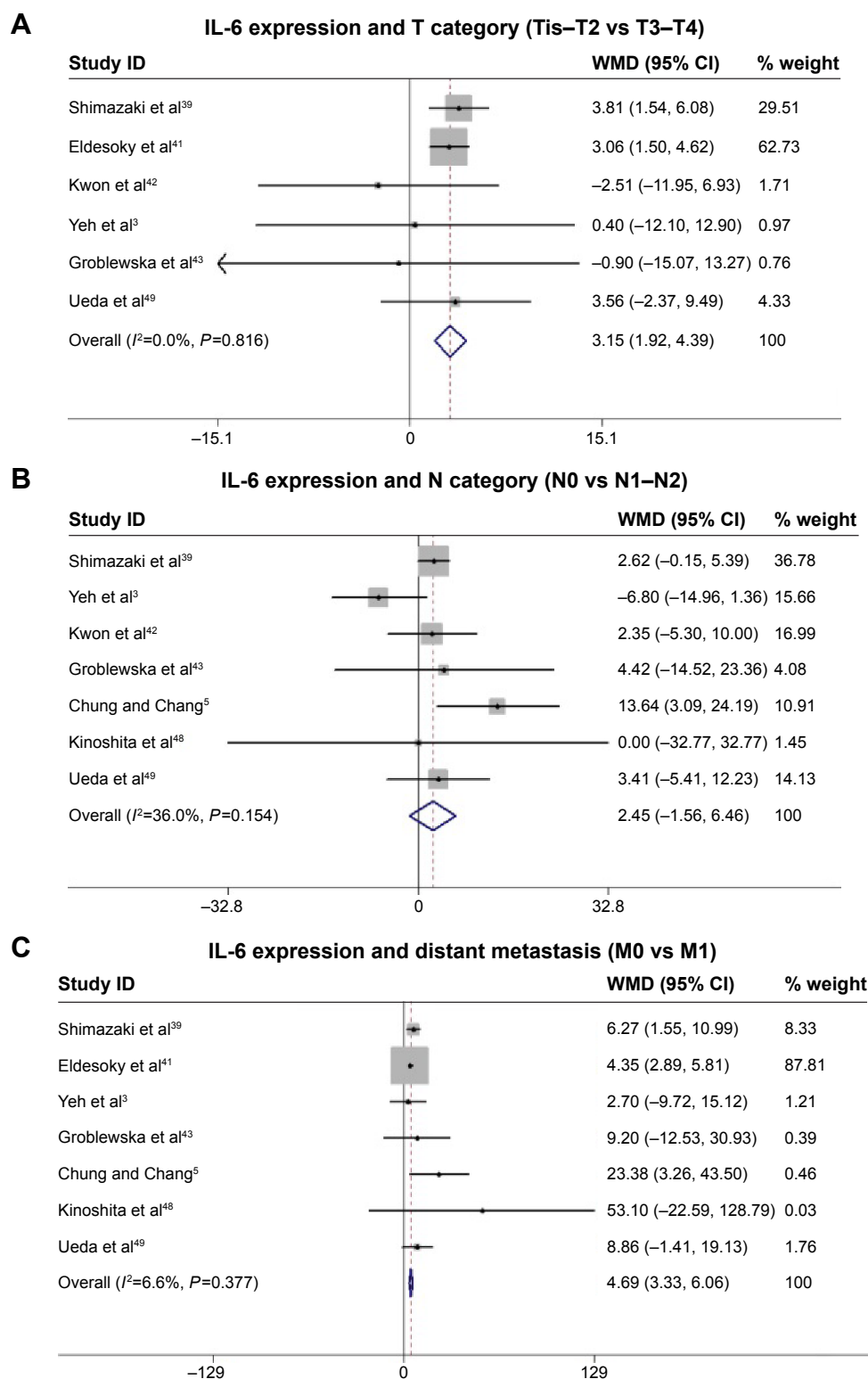
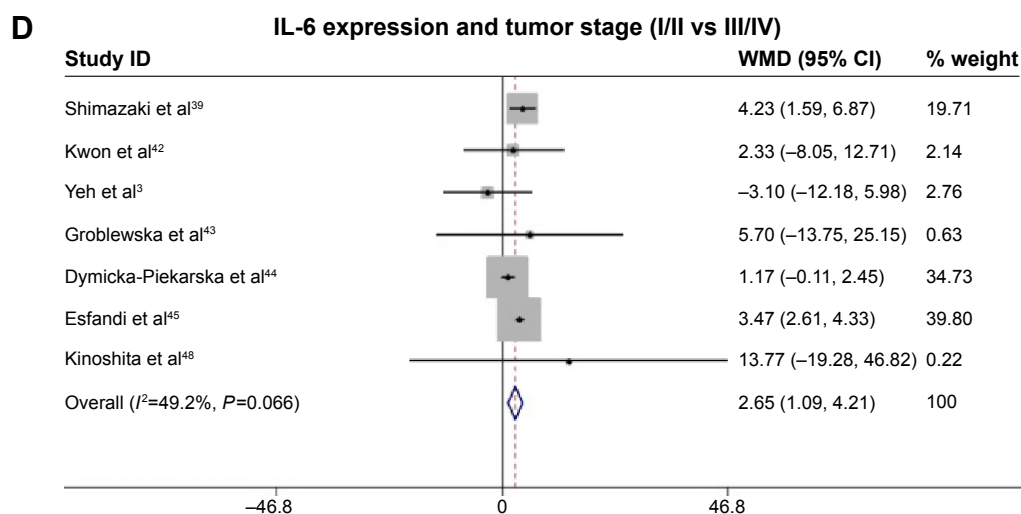


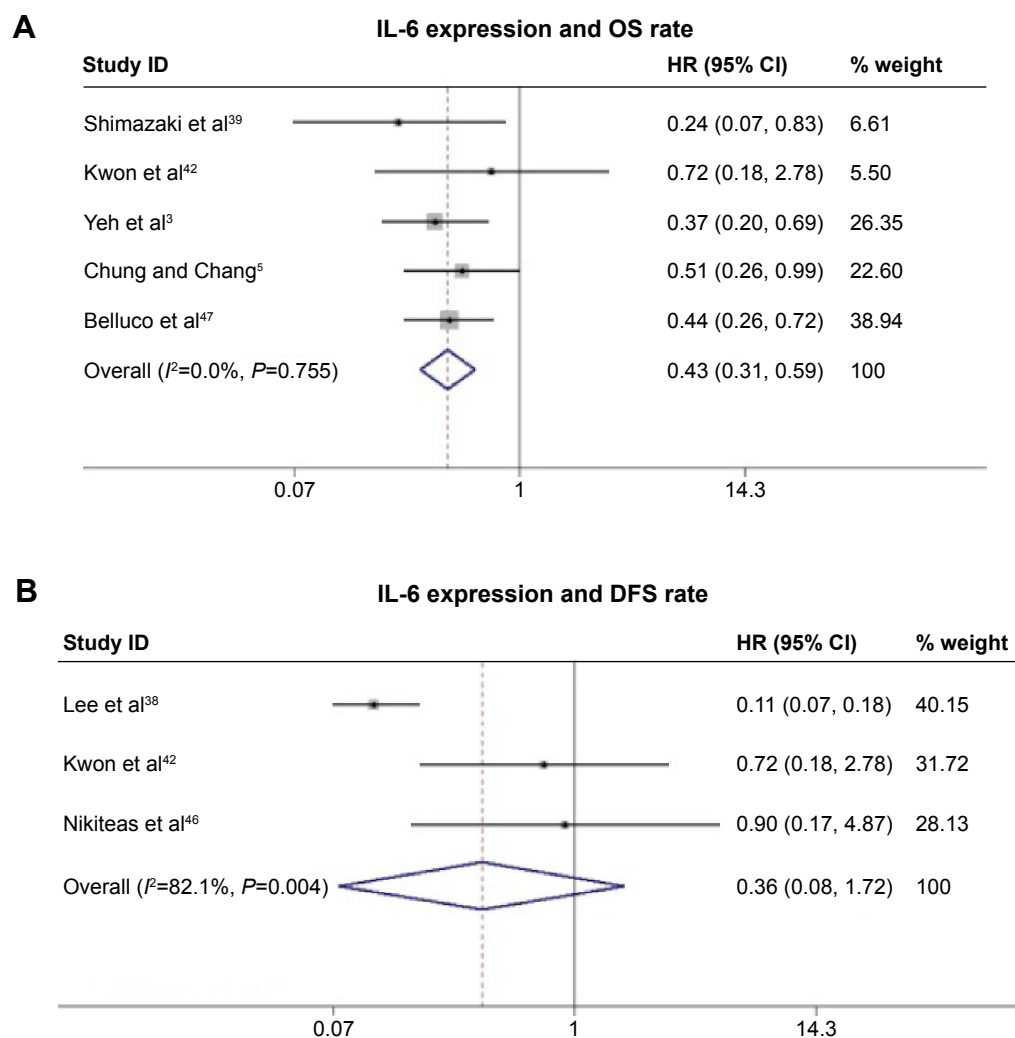
Figure 2 (Continued)



**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.

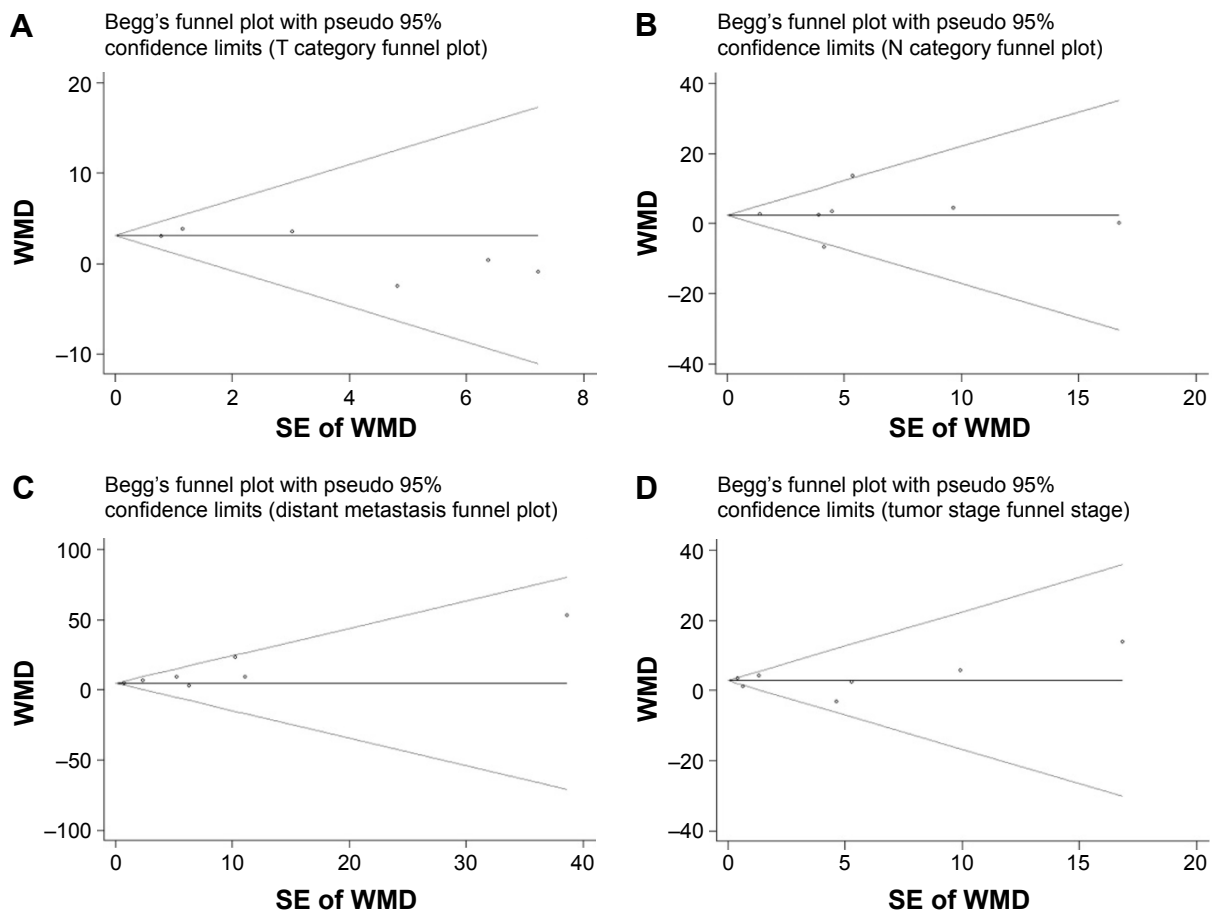
**Abbreviations:** IL-6, interleukin-6; CI, confidence interval; TIS, carcinoma in situ; WMD, weighted mean difference.



**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).

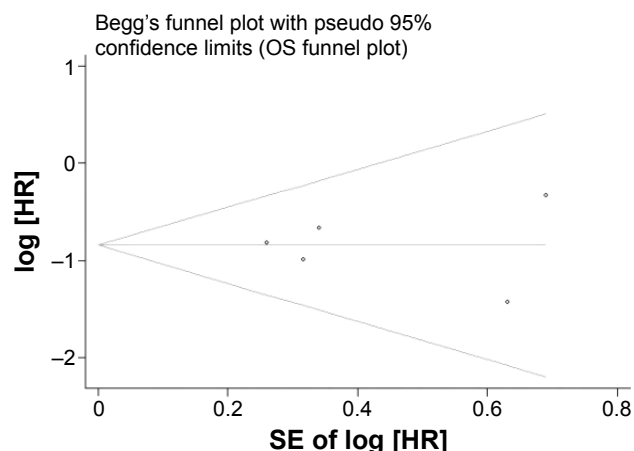
**Abbreviations:** IL-6, interleukin-6; SE, standard error; WMD, weighted mean difference.

members and hepatocyte growth factor.<sup>23</sup> 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.<sup>8,26</sup> All of these discoveries illustrated

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.<sup>27-31</sup> 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.<sup>32-35</sup>

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



**Figure 5** Begg's test results of the 5-year OS rate.

**Abbreviations:** OS, overall survival; SE, standard error.

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.<sup>36,37</sup> 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.

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5–29.
2. Kishimoto T. The biology of interleukin-6. *Blood*. 1989;74(1):1–10.
3. Yeh KY, Li YY, Hsieh LL, et al. Analysis of the effect of serum interleukin-6 (IL-6) and soluble IL-6 receptor levels on survival of patients with colorectal cancer. *Jpn J Clin Oncol*. 2010;40(6):580–587.
4. Lahm H, Petral-Malec D, Yilmaz-Ceyhan A, et al. Growth stimulation of a human colorectal carcinoma cell line by interleukin-1 and -6 and antagonistic effects of transforming growth factor beta 1. *Eur J Cancer*. 1992;28a(11):1894–1899.
5. Chung YC, Chang YF. Serum interleukin-6 levels reflect the disease status of colorectal cancer. *J Surg Oncol*. 2003;83(4):222–226.
6. Brozek W, Bises G, Girsch T, Cross HS, Kaiser HE, Peterlik M. Role of interleukin-6 in modulation of human colon carcinoma cell growth. *Anticancer Res*. 2004;24(5D):3598–3599.
7. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. *Eur J Cancer*. 2005;41(16):2502–2512.
8. Naugler WE, Karin M. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. *Trends Mol Med*. 2008;14(3):109–119.
9. Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. *Nat Rev Cancer*. 2014;14(11):736–746.
10. Yao X, Huang J, Zhong H, et al. Targeting interleukin-6 in inflammatory autoimmune diseases and cancers. *Pharmacol Ther*. 2014;141(2):125–139.
11. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta*. 2011;1813(5):878–888.
12. Heikkilä K, Harris R, Lowe G, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. *Cancer Causes Control*. 2009;20(1):15–26.
13. Joshi RK, Kim WJ, Lee SA. Association between obesity-related adipokines and colorectal cancer: a case-control study and meta-analysis. *World J Gastroenterol*. 2014;20(24):7941–7949.
14. Joshi RK, Lee SA. Obesity related adipokines and colorectal cancer: a review and meta-analysis. *Asian Pac J Cancer Prev*. 2014;15(1):397–405.
15. Zhou B, Shu B, Yang J, Liu J, Xi T, Xing Y. C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. *Cancer Causes Control*. 2014;25(10):1397–1405.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603–605.
18. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Accessed July 29, 2015.
19. Gaiolla RD, Domingues MA, Niero-Melo L, de Oliveira DE. Serum levels of interleukins 6, 10, and 13 before and after treatment of classic Hodgkin lymphoma. *Arch Pathol Lab Med*. 2011;135(4):483–489.
20. Becker C, Fantini MC, Schramm C, et al. TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. *Immunity*. 2004;21(4):491–501.
21. Grivennikov S, Karin E, Terziev J, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell*. 2009;15(2):103–113.
22. Bollrath J, Phesse TJ, von Burstin VA, et al. gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell*. 2009;15(2):91–102.
23. Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. *Semin Immunol*. 2014;26(1):54–74.

24. Yamagiwa Y, Meng F, Patel T. Interleukin-6 decreases senescence and increases telomerase activity in malignant human cholangiocytes. *Life Sci*. 2006;78(21):2494–2502.
25. Kim SY, Kang JW, Song X, et al. Role of the IL-6-JAK1-STAT3-Oct-4 pathway in the conversion of non-stem cancer cells into cancer stem-like cells. *Cell Signal*. 2013;25(4):961–969.
26. Guthrie GJ, Roxburgh CS, Horgan PG, McMillan DC. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? *Cancer Treat Rev*. 2013;39(1):89–96.
27. Nieto MA. Epithelial plasticity: a common theme in embryonic and cancer cells. *Science*. 2013;342(6159):1234850.
28. De Craene B, Berx G. Regulatory networks defining EMT during cancer initiation and progression. *Nat Rev Cancer*. 2013;13(2):97–110.
29. Tsai JH, Yang J. Epithelial-mesenchymal plasticity in carcinoma metastasis. *Genes Dev*. 2013;27(20):2192–2206.
30. Tam WL, Weinberg RA. The epigenetics of epithelial-mesenchymal plasticity in cancer. *Nat Med*. 2013;19(11):1438–1449.
31. Creighton CJ, Gibbons DL, Kurie JM. The role of epithelial-mesenchymal transition programming in invasion and metastasis: a clinical perspective. *Cancer Manag Res*. 2013;5:187–195.
32. Middleton K, Jones J, Lwin Z, Coward JJ. Interleukin-6: an angiogenic target in solid tumours. *Crit Rev Oncol Hematol*. 2014;89(1):129–139.
33. Xu Q, Briggs J, Park S, et al. Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways. *Oncogene*. 2005;24(36):5552–5560.
34. Jung JE, Lee HG, Cho IH, et al. STAT3 is a potential modulator of HIF-1-mediated VEGF expression in human renal carcinoma cells. *FASEB J*. 2005;19(10):1296–1298.
35. Hsu CP, Chung YC. Influence of interleukin-6 on the invasiveness of human colorectal carcinoma. *Anticancer Res*. 2006;26(6b):4607–4614.
36. Jones SA, Scheller J, Rose-John S. Therapeutic strategies for the clinical blockade of IL-6/gp130 signaling. *J Clin Invest*. 2011;121(9):3375–3383.
37. Waldner MJ, Foersch S, Neurath MF. Interleukin-6 – a key regulator of colorectal cancer development. *Int J Biol Sci*. 2012;8(9):1248–1253.
38. Lee WS, Baek JH, You DH, Nam MJ. Prognostic value of circulating cytokines for stage III colon cancer. *J Surg Res*. 2013;182(1):49–54.
39. Shimazaki J, Goto Y, Nishida K, et al. In patients with colorectal cancer, preoperative serum interleukin-6 level and granulocyte/lymphocyte ratio are clinically relevant biomarkers of long-term cancer progression. *Oncology*. 2013;84(6):356–361.
40. Kantola T, Klintrup K, Vayrynen JP, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. *Br J Cancer*. 2012;107(10):1729–1736.
41. Eldesoky A, Shouma A, Mosaad Y, Elhawary A. Clinical relevance of serum vascular endothelial growth factor and interleukin-6 in patients with colorectal cancer. *Saudi J Gastroenterol*. 2011;17(3):170–173.
42. Kwon KA, Kim SH, Oh SY, et al. Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. *BMC Cancer*. 2010;10:203.
43. Groblewska M, Mroczko B, Wereszczynska-Siemiatkowska U, et al. Serum interleukin 6 (IL-6) and C-reactive protein (CRP) levels in colorectal adenoma and cancer patients. *Clin Chem Lab Med*. 2008;46(10):1423–1428.
44. Dymicka-Piekarska V, Matowicka-Karna J, Gryko M, Kemona-Chetnik I, Kemona H. Relationship between soluble P-selectin and inflammatory factors (interleukin-6 and C-reactive protein) in colorectal cancer. *Thromb Res*. 2007;120(4):585–590.
45. Esfandi F, Ghobadloo SM, Basati G. Interleukin-6 level in patients with colorectal cancer. *Cancer Lett*. 2006;244(1):76–78.
46. Nikiteas NI, Tzanakis N, Gazouli M, et al. Serum IL-6, TNF alpha and CRP levels in Greek colorectal cancer patients: prognostic implications. *World J Gastroenterol*. 2005;11(11):1639–1643.
47. Belluco C, Nitti D, Frantz M, et al. Interleukin-6 blood level is associated with circulating carcinoembryonic antigen and prognosis in patients with colorectal cancer. *Ann Surg Oncol*. 2000;7(2):133–138.
48. Kinoshita T, Ito H, Miki C. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. *Cancer*. 1999;85(12):2526–2531.
49. Ueda T, Shimada E, Urakawa T. Serum levels of cytokines in patients with colorectal cancer: possible involvement of interleukin-6 and interleukin-8 in hematogenous metastasis. *J Gastroenterol*. 1994;29(4):423–429.

## OncoTargets and Therapy

### Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on

Submit your manuscript here: <http://www.dovepress.com/oncotargets-and-therapy-journal>

patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress