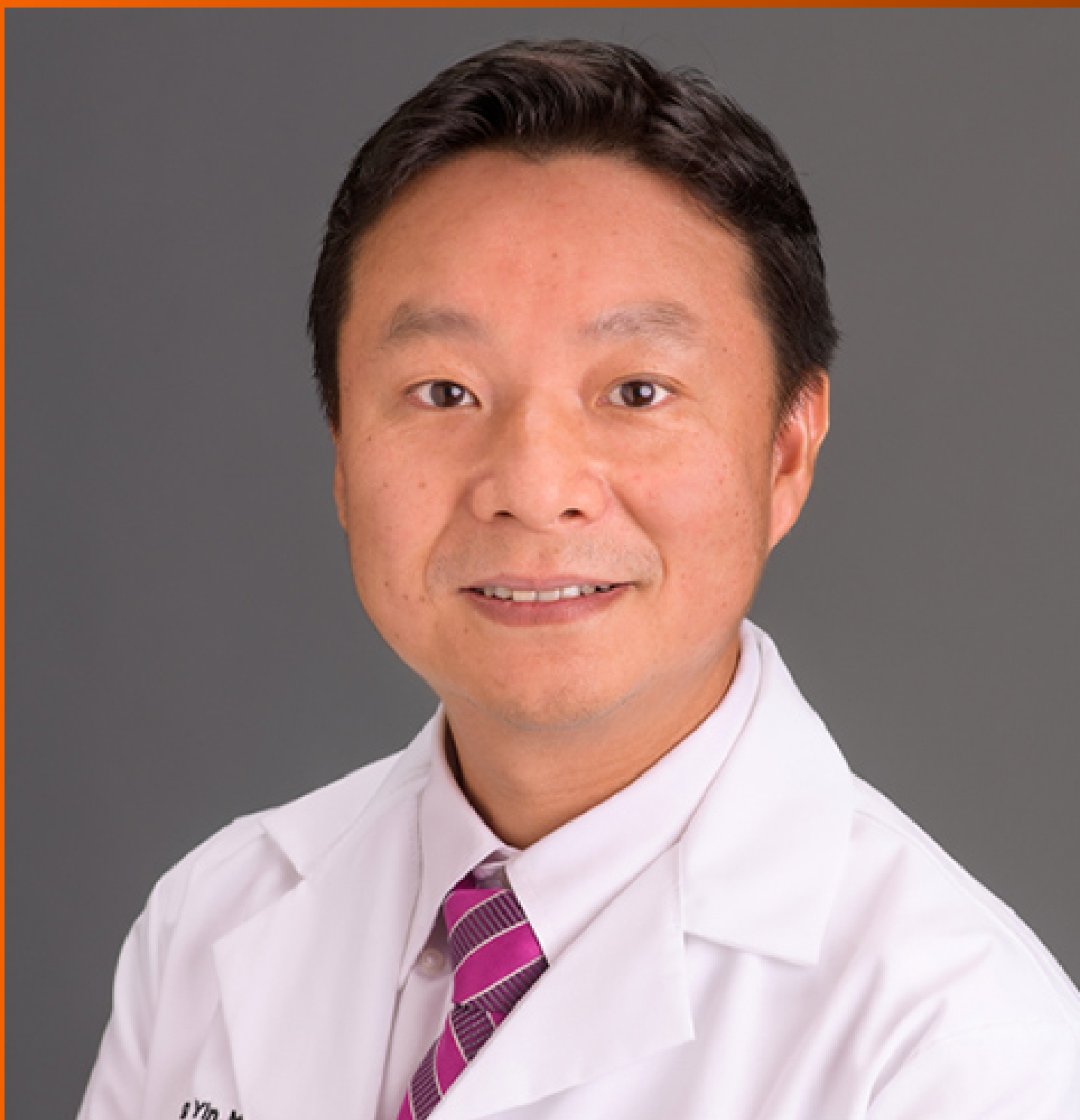


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## Prognostic value of YKL-40 in colorectal carcinoma patients: A meta-analysis

Jian Wang, Shi Qi, Yu-Bing Zhu, Lei Ding

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### Abstract

#### BACKGROUND

In recent years, the predictive role of YKL-40 for long-term survival in colorectal cancer patients has been gradually investigated. However, whether it is a reliable and valuable prognostic indicator for patients with colorectal carcinoma has not been verified.

#### AIM

To identify the prognostic value of serum/plasma concentration of YKL-40 or expression status of YKL-40 in tumor cells in colorectal carcinoma patients.

#### METHODS

Several electronic databases including the PubMed, EMBASE, Web of Science, CNKI, VIP and WanFang were searched for relevant studies. The hazard ratios (HR) and 95% confidence intervals (CI) were combined and the primary and secondary outcomes were overall survival (OS) and progression-free survival (PFS), respectively. All statistical analysis were conducted by STATA 15.0 software.

#### RESULTS

A total of nine studies involving 2545 patients were included. The pooled results indicated that YKL-40 was significantly associated with poor OS (HR = 1.80, 95%CI: 1.32-2.45,  $P < 0.001$ ) and PFS (HR = 1.62, 95%CI: 1.22-2.16,  $P = 0.001$ ). Subgroup analysis stratified by the treatment, tumor type and source of YKL-40 showed similar results.

#### CONCLUSION

Elevated serum/plasma concentration of YKL-40 or positive expression in tumor cells was related with worse prognosis of colorectal carcinoma patients. YKL-40

might serve as a novel and reliable indicator for the evaluation of prognosis in colorectal cancer.

**Key Words:** YKL-40; Colorectal carcinoma; Prognosis; Meta-analysis

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**Core Tip:** Our study demonstrated that YKL-40 was significantly associated with poor OS ( $P < 0.001$ ) and PFS ( $P = 0.001$ ). Subgroup analysis stratified by the treatment, tumor type and source of YKL-40 showed similar results. Elevated serum/plasma concentration of YKL-40 or positive expression in tumor cells was related with worse prognosis of colorectal carcinoma patients. YKL-40 might serve as a novel and reliable indicator for the evaluation of prognosis in colorectal cancer.

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## INTRODUCTION

Colorectal carcinoma is one of the most common cancers worldwide, although a slow decline of the overall risk of colorectal cancer is observed in recent years, especially in elderly population[1-3]. Despite of the great advances in the surgical, neoadjuvant and adjuvant treatments, colorectal cancer patients still suffer from poor prognosis[4]. Moreover, most of colorectal cancer patients received surgical treatment, even those with distant metastasis, but 30%-50% of stage II-III patients and 50% with stage IV patients who receive the surgery will develop a recurrence[5-7].

Up to now, the main predictor of prognosis is still the disease stage at the time of diagnosis. Unfortunately, patients in the same stage of tumor progression might undergo a different course of disease. Thus, it is still an urgent issue to identify more biomarkers to predict posttreatment survival accurately and contribute to the formulation of appropriate treatment strategies, which is crucial to reduce the mortality of colorectal carcinoma patients.

In recent years, a number of studies have indicated that Chitinase-3-like protein 1, also known YKL-40, might be a potential candidate biomarker and therapeutic target in cancers[8-10]. It has been reported that YKL-40 is a highly conserved glycoprotein binding to heparin that is produced by immune cells such as the macrophages, neutrophils, as well as the tumor cells and tumor-associated macrophages[8]. According to previous literatures, the encoding gene of YKL-40 is located on the chromosome 1q32.1 and its increasing expression is usually observed in normal cells with high proliferation, differentiation ability and cellular activity[9,10]. Besides, the overexpression of YKL-40 gene has been reported in several cancers such as the glioblastoma, melanoma, small cell lung cancer and colorectal carcinoma[11,12]. High tissue expression of YKL-40 protein detected by the immunohistochemistry in the glioblastoma is related with poor differentiation, advanced disease stage, poorer radiation response and also worse prognosis[13]. Furthermore, it is also reported that the serum concentration of YKL-40 is elevated in several tumors such as the breast cancer, melanoma, ovarian cancer and renal cell cancer and associated with poor response to therapies, advanced disease stage and poor survival[14-17]. Several investigators explored the clinical role of YKL-40 in colorectal carcinoma patients, especially its prognostic value[18-28]. However, inconsistent results have been reported in their studies.

Thus, the aim of the current meta-analysis was to identify the prognostic value of YKL-40 in colorectal carcinoma, which might help with evaluation of prognosis and formulation of treatment strategy for colorectal cancer patients.

## MATERIALS AND METHODS

This systematic review and meta-analysis were conducted according to the Preferred reporting items for systematic reviews and meta-analyses guidelines[29].

### Literature search

The PubMed, EMBASE, Web of Science, CNKI, VIP and WanFang databases were searched up to September 27, 2021. The following key words were used: YKL-40, colon, rectum, rectal, colorectal,



tumor, cancer, carcinoma, neoplasm, prognosis, survival and prognostic. Meanwhile, the references of included studies were also assessed for availability.

### **Inclusion and exclusion criteria**

The following inclusion criteria were applied: (1) Patients were pathologically diagnosed with primary colorectal carcinoma; (2) Patients were divided into two groups (elevated *vs* normal serum/plasma concentration or positive *vs* negative expression in tumor cells) and the long-term survival of patients were compared between the two groups; (3) HR with corresponding 95%CI for OS or PFS were provided or could be calculated from the Kaplan-Meier survival curves; and (4) High-quality studies with the (Newcastle-Ottawa scale, NOS) score of 6 or higher[30].

The following exclusion criteria were applied: (1) Duplicated or overlapped data; and (2) Conference abstracts, case reports, letters or reviews.

### **Data extraction**

The following information were collected from included studies: Author, publication year, sample size, gender, age, country, tumor stage, number of colon carcinoma patients, type of treatment (surgery *vs* non-surgery) and tumor, threshold of YKL-40 and endpoints with corresponding HR with 95%CI.

### **Quality assessment**

The quality of included studies was evaluated according to the NOS score[30] and only high-quality studies with a NOS score of 6 or higher were included.

The literature retrieval, selection, data extraction and quality assessment were all conducted by two authors independently (Jian Wang and Yu-Bing Zhu) and any differences were resolved by team discussion.

### **Statistical analysis**

All statistical analyses were performed by STATA 15.0 software. The HR with corresponding 95%CI were combined to assess the association between YKL-40 and prognosis of colorectal carcinoma patients. If the HRs with 95%CI were not provided in articles directly, then they would be calculated from the Kaplan-Meier survival curves[31]. The heterogeneity among included studies was evaluated by  $I^2$  statistics and Q test. When obvious heterogeneity was observed presenting as the  $I^2 > 50\%$  or (and)  $P < 0.1$ , the random effect model was used; otherwise, the fix effect model was used[32]. The sensitivity analysis and subgroup analysis based on the treatment (surgery *vs* no-surgery), tumor type (colorectal carcinoma *vs* rectal carcinoma *vs* colon carcinoma) and source of YKL-40 (serum/plasma *vs* tissue) were performed to detect the source of heterogeneity and evaluated the stability of pooled results. Besides, the Begg's funnel plot and Egger's test were conducted to detect publication bias[33]. Significant publication bias was defined as  $P < 0.05$ .

## **RESULTS**

### **Literature retrieval process**

Initially, 159 records from the six electronic databases were identified and then 42 duplicated records were removed. Eight-six irrelevant publications and 14 unavailable records were excluded after reading the titles and abstracts. Then eight studies were excluded because of the insufficient data ( $n = 6$ ) or overlapping data ( $n = 2$ ) and nine studies were included into this meta-analysis finally[20-28] (Figure 1).

### **Basic characteristics of included studies**

All included studies were retrospective and a total of 2545 patients were enrolled. Among these 2545 patients, 1480 patients were male. Most of them were from Eastern countries, applied the tumor-node-metastasis (TNM) stage system for tumor staging evaluation, focused on the colorectal carcinoma and detected the serum/plasma concentration of YKL-40. Besides, except for the study conducted by Tarpgaard *et al*[27], all the other studies only enrolled operated patients. The detailed information was presented in the Table 1.

### **Association between YKL-40 and OS of colorectal carcinoma patients**

Eight studies involving 2459 patients investigated the predictive role of YKL-40 for OS of colorectal cancer patients[20-23,25-28]. The pooled results demonstrated that YKL-40 was significantly associated with OS of colorectal carcinoma patients (HR = 1.80, 95%CI: 1.32-2.45,  $P < 0.001$ ;  $I^2 = 90.3\%$ ,  $P < 0.001$ ) (Figure 2). Furthermore, subgroup analysis stratified by the treatment (surgery *vs* non-surgery), tumor type (colorectal carcinoma *vs* rectal carcinoma *vs* colon carcinoma) and source of YKL-40 (serum/plasma *vs* tissue) were performed. The subgroup analysis showed similar results, except for the insignificant relationship of YKL-40 with OS in rectal carcinoma patients (HR = 0.69, 95%CI: 0.04-11.5,  $P = 0.796$ ) (Table 2).



Table 1 Basic characteristics of included studies

Ref.	Sample size	Gender (male)	Age (median, range), years	Country	Stage	Number of colon carcinoma	Treatment	Tumor type	Threshold	Endpoints	NOS
Cintin <i>et al</i> [20], 1999	603	355	69 (33-91)	Denmark	Duke A-D	355	Surgery	CRC	247 ug/L (upper 95 <sup>th</sup> percentile)	OS	7
Cintin <i>et al</i> [21], 2002	324	192	68 (37-90)	Denmark	Duke A-D	197	Surgery	CRC	247 ug/L (upper 95 <sup>th</sup> percentile)	OS, PFS	7
Liu <i>et al</i> [24], 2014	86	48	60 (38-76)	China	TNMI I-IV	34	Surgery	CRC	216 ng/mL (median)	PFS	6
Tarpgaard <i>et al</i> [27], 2014	510	301	NR	Denmark	TNM IV	302	Non-surgery	CRC	155 ug/L (upper 95 <sup>th</sup> percentile)	OS, PFS	7
Fuksiewicz <i>et al</i> [22], 2018	83	59	65 (25-82)	Poland	TNM I-III	NR	Surgery	RC	44.6 pg/mL (upper 95 <sup>th</sup> percentile)	OS, PFS	6
Hermunen <i>et al</i> [23], 2020	147	75	60 (31-76)	Finland	TNM II-IV	87	Surgery	CRC	70.7 ng/mL (maximum Youden's index)	OS, PFS	7
Peltonen <i>et al</i> [26], 2020	441	260	64.9 (33-84)	Denmark	TNM IV	258	Surgery (liver resection)	CRC	34.8 ng/mL (upper 95 <sup>th</sup> percentile)	OS, PFS	
Oh <i>et al</i> [25], 2021	265	134	NR	Korea	TNM I-IV	NR	Surgery	CRC	Positive in tumor cells	OS, PFS	7
Yang <i>et al</i> [28], 2021	86	56	60.12 ± 7.32 (mean ± SD)	China	TNMI I-IV	86	Surgery	CC	Positive in tumor cells	OS	7

TNM: Tumor-node-metastasis; CRC: Colorectal cancer; RC: Rectal cancer; CC: Colon cancer; OS: Overall survival; PFS: Progression-free survival; NOS: Newcastle-Ottawa scale; NR: Not reported.

### Association between YKL-40 and PFS of colorectal carcinoma patients

Seven relevant studies involving 1856 participants explored the predictive role of YKL-40 for PFS [21-27]. The pooled results also manifested significant association between YKL-40 and PFS of colorectal carcinoma patients (HR = 1.62, 95% CI: 1.21-2.16,  $P = 0.001$ ;  $I^2\% = 88.3\%$ ,  $P < 0.001$ ) (Figure 3). Then, subgroup analysis based on the treatment (surgery *vs* non-surgery), tumor type (colorectal carcinoma *vs* rectal carcinoma) and source of YKL-40 (serum/plasma *vs* tissue) were further conducted. No significant association of YKL-40 with PFS in patients who did not receive surgery (HR = 1.00, 95% CI: 0.91-1.09,  $P = 1.00$ ) or with rectal cancer (HR = 1.32, 95% CI: 0.39-4.46,  $P = 0.655$ ) (Table 2).

In overall, YKL-40 was supposed to be an important prognostic indicator in colorectal carcinoma patients based on above results.

### Sensitivity analysis and publication bias

The sensitivity analysis and publication bias analysis for OS were further conducted to assess the stability and reliability of the pooled results. The sensitivity analysis showed that the results of this meta-analysis was stable and none of included studies had a significant impact on the results (Figure 4). Begg's funnel plot was basically symmetrical (Figure 5) and the  $P$  value of Egger's test was 0.109, which indicated that no potentially unpublished articles existed.

## DISCUSSION

The current meta-analysis demonstrated that YKL-40 was a relatively reliable and valuable prognostic indicator for colorectal carcinoma patients after including nine relevant studies. However, whether the YKL-40 shows high prognostic value in all groups of colorectal carcinoma patients is still needed to be further verified.

Actually, the specific mechanisms by which YKL-40 affects the disease progression, therapeutic effect and long-term survival are still not very clear now. The study conducted by Faibish *et al* [34] manifested that YKL-40 could affect the invasion of tumor cells through the regulation of matrix metalloproteinase-

**Table 2 Results of meta-analysis**

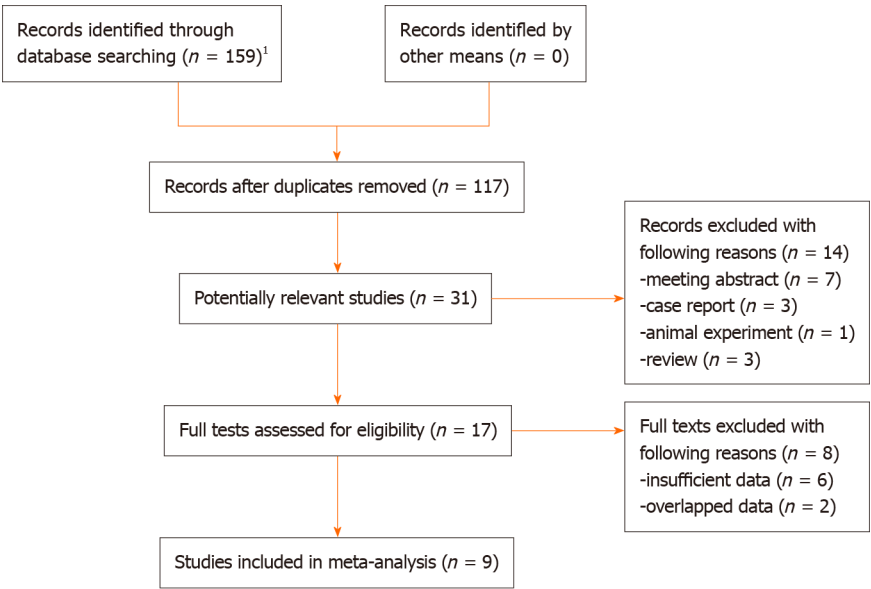
	No. of studies	HR	95%CI	P value	I <sup>2</sup> (%)	P value
Overall survival	8	1.80	1.32-2.45	< 0.001	90.3	< 0.001
Treatment						
Surgery	7	1.99	1.27-3.12	0.003	90.8	< 0.001
Non-surgery	1	1.17	1.05-1.30	0.004	-	-
Tumor type						
Colorectal carcinoma	6	1.83	1.30-2.56	< 0.001	92.9	< 0.001
Rectal carcinoma	1	0.69	0.04-11.45	0.796	-	-
Colon carcinoma	1	1.81	1.13-2.90	0.013	-	-
Source of YKL-40						
Serum	6	1.83	1.26-2.66	0.001	92.7	< 0.001
Tissue	2	1.74	1.28-2.36	< 0.001	0.0	0.816
Progression-free survival	7	1.62	1.22-2.16	0.001	88.3	< 0.001
Treatment						
Surgery	6	1.93	1.21-3.08	.005	87.8	< 0.001
Non-surgery	1	1.00	0.91-1.09	1.000	-	-
Tumor type						
Colorectal carcinoma	6	1.64	1.22-2.20	0.001	90.2	< 0.001
Rectal carcinoma	1	1.32	0.39-4.46	0.655	-	-
Source of YKL-40						
Serum	6	1.54	1.15-2.07	0.004	88.0	< 0.001
Tissue	1	2.00	1.36-2.94	< 0.001	-	-

HR: Hazard ratio; CI: Confidence interval.

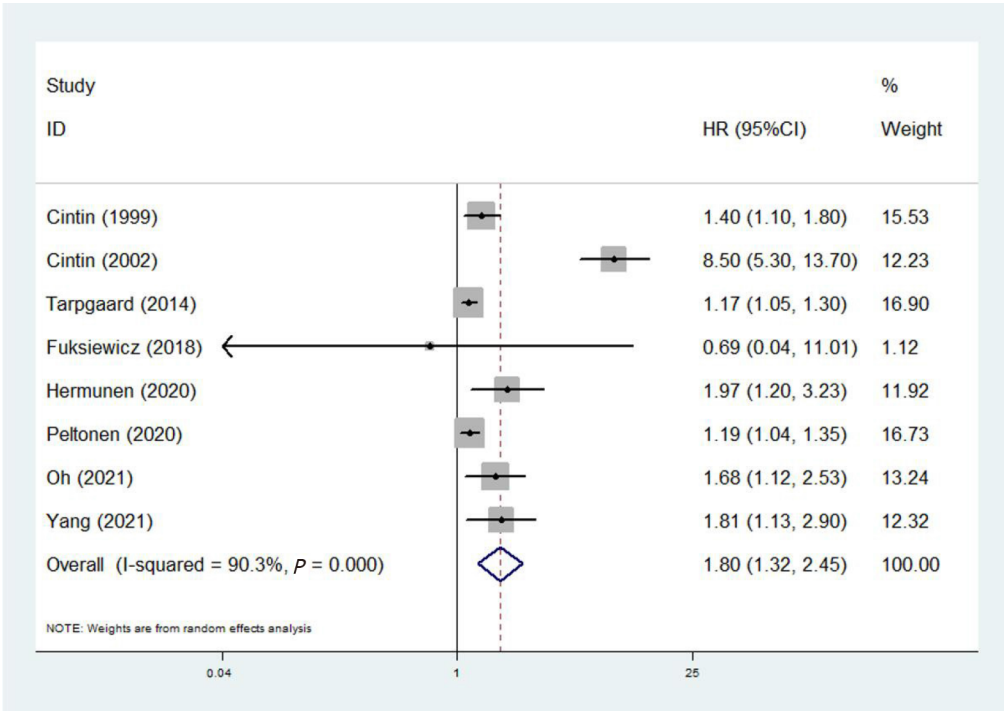
2 (MMP-2) expression, adhesion to extracellular matrix (ECM), cytoskeleton rearrangement and contractility. Besides, Jeet *et al*[35] demonstrated that the knockdown of YKL-40 gene in the bone metastatic C4-2B cells could decrease the ability of migration and invasion. Furthermore, YKL-40 could also promote the chemotaxis of macrophages and angiogenesis accompanied by increased IL-8 and monocyte chemoattractant protein-1 secretion through the mitogen-activated protein kinase signaling pathway[36].

Bian *et al*[37] performed a meta-analysis by including 41 publications involving a total of 7762 patients with solid cancers and demonstrated that elevated serum/plasma YKL-40 was significantly associated with worse OS (HR = 1.44, 95%CI: 1.33-1.56). Actually, in addition to the predictive role for prognosis, YKL-40 might also play an important role in the diagnosis of colorectal cancer. Foksiewicz *et al* [22] indicated that YKL-40 Levels were more valuable in diagnosing rectal cancer [area under the Receiver Operating Characteristic (ROC) curve: 0.769] than CEA (area under the ROC curve: 0.728) in early stage patients. Besides, YKL-40 showed a much higher value in predicting the recurrence of Chinese colorectal cancer (area under the ROC curve: 0.907, comparing with the 0.714 of CEA and 0.759 of CA199)[38]. Therefore, more investigation about the diagnostic role of YKL-40 is still valuable.

Although we demonstrated that YKL-40 was predictive for OS and PFS in colorectal carcinoma patients in overall, whether it could be applied as a reliable prognostic indicator in all colorectal cancer patients is still needed to further explored by more high-quality studies. According to the subgroup analysis, YKL-40 was not related with OS ( $P = 0.796$ ) or PFS ( $P = 0.655$ ) in rectal cancer patients. However, in the study conducted by Foksiewicz *et al*[22], the Kaplan-Meier survival curves showed obvious differences of OS ( $P = 0.040$ ) and PFS ( $P = 0.044$ ) between patients with elevated ( $> 44.6$  ng/mL) and normal serum concentration ( $\leq 44.6$  ng/mL) of YKL-40. After calculating the HR with 95%CI according to the survival curves using the method introduced by Tierney *et al*[31], different results were observed, which might be explained by the bias caused by the statistical method and small sample size. Besides, Tarpgaard *et al*[27] manifested negative association between plasma YKL-40 and PFS according to the multivariate Cox analysis, but the positive results were observed in the univariate Cox analysis (HR = 1.11, 95%CI: 1.03-1.20,  $P = 0.006$ ). Thus, based on the original data presented in the articles, we



**Figure 1** The flow diagram of this meta-analysis. <sup>1</sup>PubMed (n = 28), EMBASE (n = 48), Web of Science (n = 48), CNKI (n = 35), VIP (n = 0), and WanFang (n = 0).



**Figure 2** The association between YKL-40 and overall survival.

still believe that YKL-40 might show high prognostic value in these subgroups of colorectal cancer patients. However, more prospective studies with high-quality are needed to verify this conjecture.

There are several limitations in the current meta-analysis. First, all included studies are retrospective and the overall sample size is relatively small, which might cause some bias. Second, due to the lack of specific data, we failed to conduct more subgroup analysis based on other important parameters such as the disease stage, age and thresholds of serum/plasma concentration of YKL-40. Third, the comparison of expression status in tissues and serum/plasma levels in predicting long-term survival of colorectal carcinoma patients was not performed.

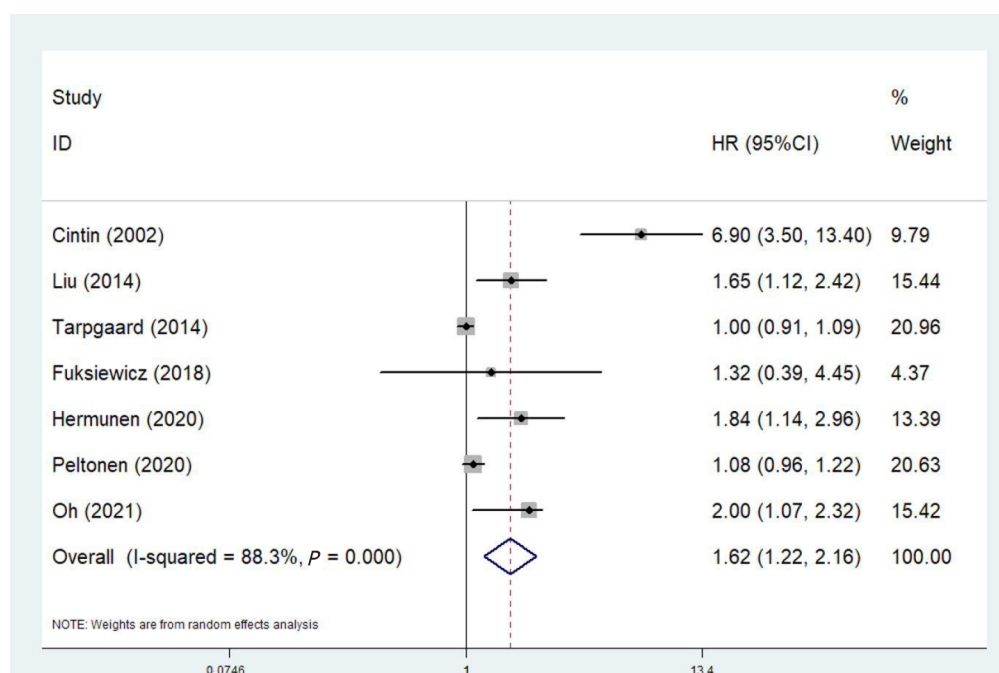


Figure 3 The association between YKL-40 and progression-free survival.

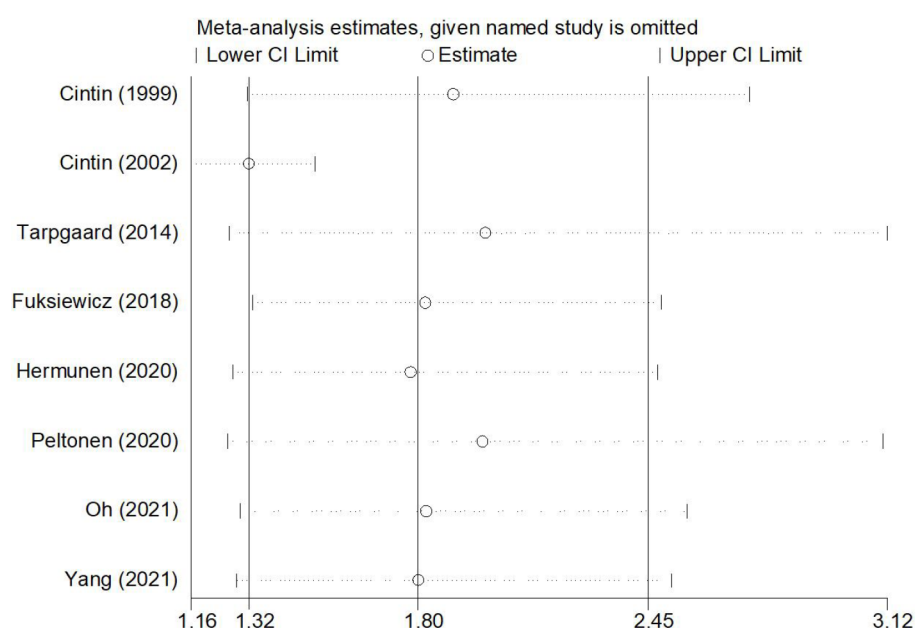


Figure 4 Sensitivity analysis about the association between YKL-40 and overall survival.

## CONCLUSION

In overall, elevated serum/plasma concentration of YKL-40 or positive expression in tumor cells was related with poor survival of colorectal carcinoma patients. YKL-40 might serve as a novel and reliable indicator for the evaluation of prognosis in colorectal cancer.

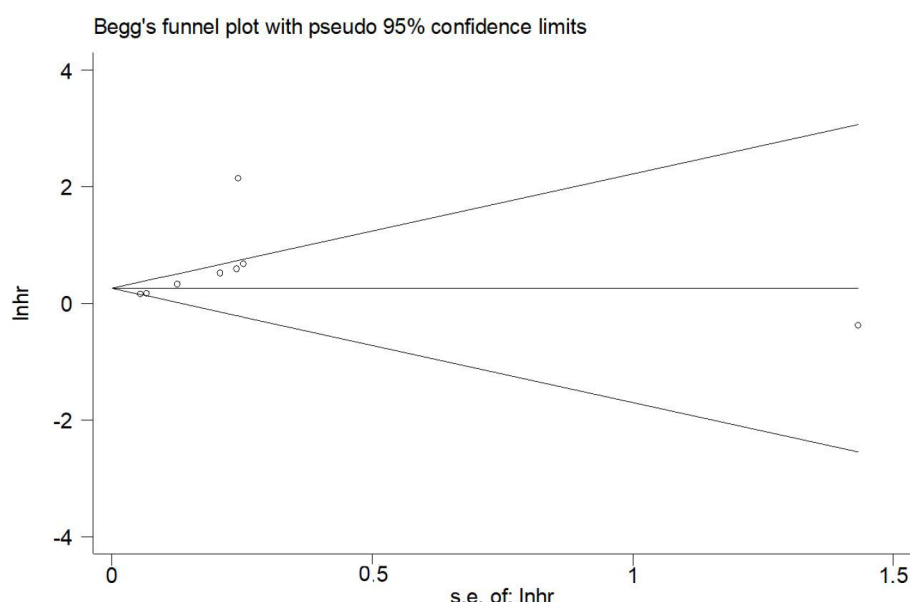


Figure 5 Begg's funnel plot.

## ARTICLE HIGHLIGHTS

### Research background

The predictive role of YKL-40 for long-term survival in colorectal cancer patients has been gradually investigated in recent years.

### Research motivation

Whether it is a reliable and valuable prognostic indicator in patients with colorectal carcinoma has not been certified.

### Research objectives

To verify the prognostic value of serum/plasma concentration of YKL-40 or expression status of YKL-40 in tumor cells in colorectal carcinoma.

### Research methods

Several electronic databases were searched to identify relevant articles. The hazard ratio with 95% confidence interval was combined to evaluate the association between YKL-40 and overall survival (OS) and progression-free survival (PFS).

### Research results

YKL-40 was significantly associated with poor OS ( $P < 0.001$ ) and PFS ( $P = 0.001$ ). Subgroup analysis stratified by the treatment, tumor type and source of YKL-40 showed similar results.

### Research conclusions

Elevated serum/plasma concentration of YKL-40 or positive expression in tumor cells was related with worse prognosis of colorectal carcinoma patients.

### Research perspectives

YKL-40 might serve as a novel and reliable indicator for the evaluation of prognosis in colorectal cancer.

## FOOTNOTES

**Author contributions:** Ding L made the substantial contributions to the conception and design of the work; Wang J and Qi S searched, selected materials and extracted data, wrote this manuscript; Zhu YB revised the paper carefully and also contributed to the statistical analysis; Wang J and Qi S contributed equally to this work; all authors have read and approved the final manuscript.

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