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Original Article

Pretreatment thrombocytosis, defined as platelet count ≥ 400 × 10^9/L, may predict prognosis of patients with colorectal cancer: a systematic review and meta-analysis

Jinrong Wang[1], Hui Li[2], Chunlian Wang[3]

[1]*Xijing University, Xi'an 710123, China;* [2]*Basic Medicine Department, Nursing School of Zhengzhou Sias University, Xinzheng 451000, China;* [3]*Noninfectious Chronic Disease Prevention and Control Department, Harbin Center for Disease Control and Prevention, Harbin 150056, China*

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Abstract: Background & aim: Numerous studies have reported that elevated pretreatment platelet counts are associated with prognosis of colorectal cancer (CRC). However, their cut-off values were different and results remain controversial. This meta-analysis was designed to analyze and evaluate the prognostic roles of preoperative or pretreatment thrombocytosis in patients with CRC. Methods: Databases, including PubMed, Embase, Cochrane Library, and Web of Science were searched up to April 2018. Hazard ratios (HR) with 95% confidence intervals (CI) were used to evaluate the relationship between platelet count and overall survival (OS), disease free survival (DFS), and cancer specific survival (CSS). Analysis was performed and assessed using Review Manager 5.2. This work was in accord with the standards of Preferred Reporting Items for Meta-analysis and Meta-Analyses (PRISMA) Guidelines. Results: A total of 12 studies, including 4,522 patients, were included in this systematic review. Analysis results showed that pretreatment thrombocytosis had a close relationship with OS, DFS, and CSS of CRC, with pooled HRs of 1.86 (95% CI 1.58-2.18; $P < 0.00001$), 1.60 (95% CI 1.19-2.16; $P = 0.002$), and 1.59 (95% CI 1.05-2.42; $P = 0.03$) respectively. Conclusion: The present meta-analysis indicates that colorectal cancer patients with pretreatment thrombocytosis, defined as platelet count ≥ 400 × 10^9/L, may experience worse survival.

Keywords: Thrombocytosis, platelet count, prognosis, colorectal cancer

Introduction

Platelets have been well studied for many decades. Its increase and decrease significantly influence patient conditions and outcomes. Recently, new effectiveness for platelets has been reported by many studies. For instance, thrombocytopenia may be used as one of the indicators to guide therapeutic options and strategies for patients in the Intensive Care Unit (ICU) [1]. In addition, thrombocytosis has been reported as a prognostic indicator for many patients with malignant tumors.

Colorectal cancer (CRC), an increasingly common malignancy, is currently raging throughout many countries. It has been reported that the incidence rate of CRC is in third place now, as one of the most common cancers [2]. According to statistics in 2010, incidence of CRC in men and women was 12.3% and 13.1%, respectively, in Europe [3]. Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer deaths in the United States. In 2015, an estimated 93,090 new cases of colon cancer and approximately 39,610 cases of rectal cancer will occur. During the same year, an estimated 49,700 people will die of colon and rectal cancer combined [4]. Despite observed improvements in overall colorectal cancer incidence rate, a retrospective cohort study of colorectal cancer registry found that incidence of colorectal cancer in patients younger than 50 years has increased. The authors estimate that incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively [5]. Though radical operation, resecting the lesions, is the optimal

option for colorectal cancer at present, prognosis of colorectal cancer remains very poor. Approximately half of the patients die within 5 years after diagnosis [6]. Therefore, appropriate biomarkers are needed to predict CRC patient post-treatment prognosis.

In recent decades, many studies have reported that elevated platelet counts or pretreatment thrombocytosis may be associated with poor prognosis of colorectal cancer [7-11]. However, their results have remained inconsistent. In addition, cut-off values of platelet counts in these studies were varied. One meta-analyses, which studied the association between pretreatment thrombocytosis and prognosis of CRC, comprehensively analyzed various cut-off values [12]. Comparing studies about the association between platelet counts and prognosis of CRC, it was found that most supported the prognostic value of platelet count ≥ 400 × 10^9/L for CRC. Therefore, the current meta-analysis was designed, including studies with cut-off values of platelet count ≥ 400 × 10^9/L, aiming to analyze and evaluate the prognostic roles of pretreatment thrombocytosis for patients with colorectal cancer.

Methods and materials

Inclusion and exclusion criteria

Inclusion criteria: (1) Prospective and observational retrospective studies; (2) Patients included in studies were diagnosed with colorectal cancer; (3) Circulating platelet counts of patients before they received therapies could be obtained; and (4) Overall survival, disease free survival, cancer specific survival, the number of participants, and the cut-off value of platelet counts were reported or can be obtained.

Exclusion criteria: (1) Non-human researches or trials on animals; (2) Articles were abstracts, letters, editorials, expert opinions, reviews, case reports, or laboratory studies; (3) Patients having other primary tumors which affected their survival; (4) Studies without sufficient data; (5) The cut-off value of platelet count was not 400 × 10^9/L; and (6) Duplicate studies.

Search strategy

Databases, including PubMed, Embase, Cochrane Library and Web of Science, were searched up to April 2018. Researchers also hand-searched the citation lists of included studies and previously identified systematic reviews to identify further relevant trials. Search terms and procedures were as follows: (1) “platelet count”; (2) “colorectal cancer”, “rectal cancer”, “colon cancer”; (3) “prognosis”, “survival”, “outcome”; (1) AND (2) AND (3). Databases were searched with these terms in English, including references of some studies. Two investigators, independently, screened the titles and abstracts of each study. Once studies meeting the inclusion criteria were found, full texts were obtained for further evaluation.

Quality assessment and data extraction

Two investigators, independently, evaluated the quality of all included studies using the 9-star Newcastle-Ottawa Scale (NOS) [13]. Total scores of each study are displayed in the characteristics table. Scores were judged according to the three aspects of NOS of evaluation: Selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study), comparability (comparability of cohorts on the basis of the design or analysis), and outcomes (assessment of outcomes, was follow-up long enough for outcomes to occur, adequacy of follow up of cohorts). A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. Studies with scores ≥ 6 were defined as high-quality studies.

Data were extracted, independently, by two reviewers and disagreements were resolved by discussion. In addition, extracted content included study demographics, published years, country, trial design, cancer location, follow-up time, and outcomes, using a standardized form. Data were input into RevMan 5.2 software for analysis [14].

Statistical analysis

In this meta-analysis, the influence of platelet counts on CRC patient prognosis was measured by estimating hazard ratios (HR) between experiment groups and control groups. Associated 95% confidence intervals (CI) were also measured. Heterogeneity between studies

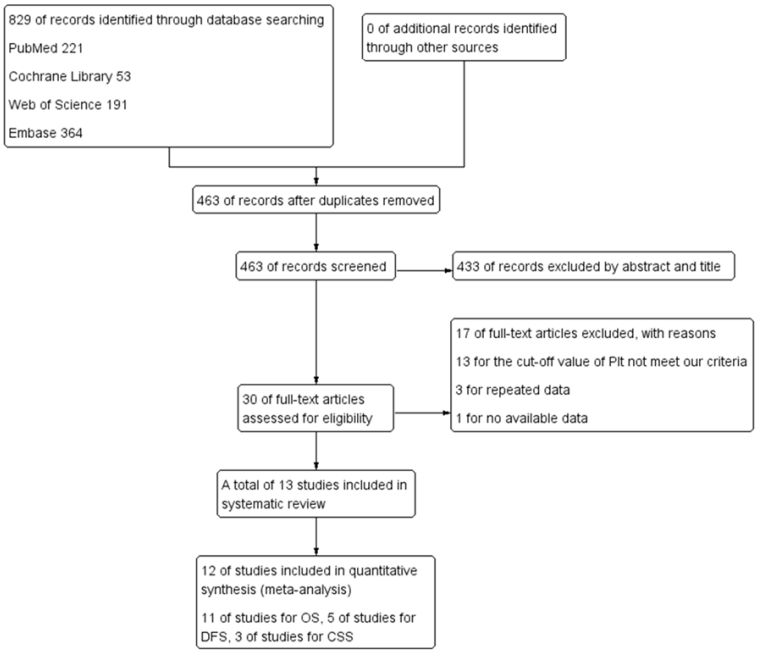

Figure 1. Flow diagram of the search strategy for circulating pretreatment platelet count ≥ 400 × 10^9/L of colorectal cancer.

was evaluated by Chi-squared-based *Q* statistical test [15], with *P*-values and I^2 statistic ranging from 1 to 100%, to quantify the effects of heterogeneity. $P \leq 0.10$ was deemed to represent significant heterogeneity [16, 17] and pooled HR was estimated using a random-effects model (DerSimonian and Laird method [18]). In contrast, if statistical study heterogeneity was not observed ($P \geq 0.10$), a fixed-effects model (Mantel-Haenszel method [19]) was used. Effects of platelet counts on OS, DFS, and CSS of CRC were statistically significant if HRs 95% CI did not overlap with 1.

Subgroup analysis was conducted for the association between platelet counts and OS according to therapy methods (surgical resection vs. chemo-radiotherapy), NOS scores (5, 6 vs. 7 vs. 8 scores), study design (prospective vs. retrospective), and sample (> 300 vs. < 300). Sensitivity analysis was performed to examine the stability of pooled results. Finally, publication bias was assessed by contour-enhanced funnel plots. If the shape of funnel plots revealed no obvious evidence of asymmetry, there was no obvious publication bias.

This work was in accord with standards of the Preferred Reporting Items for Meta-analysis and Meta-Analyses (PRISMA) Guidelines.

Results

Retrieval results and study characteristics

After removing duplicate studies from the primary retrieval results, 463 results were initially obtained. Screening the titles and abstracts of these studies, 433 studies were excluded further and 30 of full-text articles were obtained for further assessment. After 17 full articles were excluded (13 studies for the cut-off value or defining of platelet count did not meet our criteria, 1 study for lack of available data, and 3 studies for repeated data from same or similar population), a total of 12 studies [20-31], including 4,522 patients, were included in this systematic review. Eleven studies were used to evaluate the association between platelet counts and OS of CRC patients. Five studies were about DFS and three were about CSS.

Details of the search process and a summary of studies are shown in the study flow diagram (**Figure 1**). Other study characteristics are shown in **Table 1**.

Prognostic value of platelet count ≥ 400 × 10^9/L for OS

Of the eleven studies estimating the association between circulating pretreatment platelet count ≥ 400 × 10^9/L and overall survival (OS) of colorectal cancer patients, ten provided available data evaluating the prognostic value of platelet count ≥ 400 × 10^9/L with univariate analysis (UVA), while five used multivariate analysis (MVA).

Analysis results showed that colorectal cancer patients with circulating pretreatment platelet count ≥ 400 × 10^9/L experienced poor OS, compared with patients with normal platelet counts, with pooled HRs of 1.86 (95% CI 1.58-2.18; $P < 0.00001$) with univariate analysis (**Figure 2**) and 2.20 (95% CI 1.64-2.95; $P < 0.00001$) with multivariate analysis (**Figure 3**),

Table 1. Characteristics of included studies for the meta-analysis

Author/Year	Country	Study design	N/n	Location	Clinical stage	*P* value	Pretreatment	FT (month)	NOS score	Outcome
Neal et al. 2015	UK	Pro	276/26	Colorectum	NR	NR	Operation	29.7 (4-96)	6	OS
Josa et al. 2015	Hungary	Retro	336/45	Colorectum	I-IV	NR	Operation	46.0	8	OS
Paik et al. 2014	Korea	Pro	600/43	Colorectum	I-IV	0.402	Radiotherapy	27.4 (1-72)	8	OS
Guo et al. 2014	USA	Retro	310/25	Colorectum	I-IV	NR	Operation	NR	5	OS
Choi et al. 2014	Korea	Retro	105/14	Colorectum	I-IV	NR	NR	44 (2-81)	5	CSS
*Baranyai et al. 2014	Hungary	Retro	336/45	Colorectum	I-IV	NR	Operation	36.1	6	OS, DFS
*Baranyai(m) et al. 2014	Hungary	Retro	118/6	mCRC	IV	NR	Operation	36.1	6	OS, DFS
Wan et al. 2013	USA	Retro	1513	Colorectum	0-IV	0.0001	Operation	46.7 (19.6-84.7)	7	OS
Kaneko et al. 2012	Japan	Retro	50/7	Colorectum	NR	NR	Chemotherapy	17.0 (0.77-61.6)	7	OS, DFS
Qiu et al. 2010	China	Retro	363/30	NR	I-IV	0.001	NR	26 (3-50)	6	OS
Neal et al. 2009	UK	Pro	168/6	mCRC	-	-	Operation	NR	7	OS, DFS
Kandemir et al. 2005	Turkey	Retro	198/24	Colon	NR	NR	Operation	47 (19-100)	6	OS, DFS
Leitch et al. 2007	UK	Pro	149/32	Colorectum	I-IV	0.001	Operation	48 (36-73)	8	OS, CSS

*They were from the same study; N, total number of eligible patients; n, number of patients with thrombocytosis; NOS, Newcastle-Ottawa Scale; OS, overall survival; DFS, disease free survival; CSS, cancer specific survival; mCRC, metastatic colorectal cancer; FT, follow-up time (month) (median and range); CRT, chemo-radiotherapy; Retro, retrospective; Pro, prospective; NR, not report.

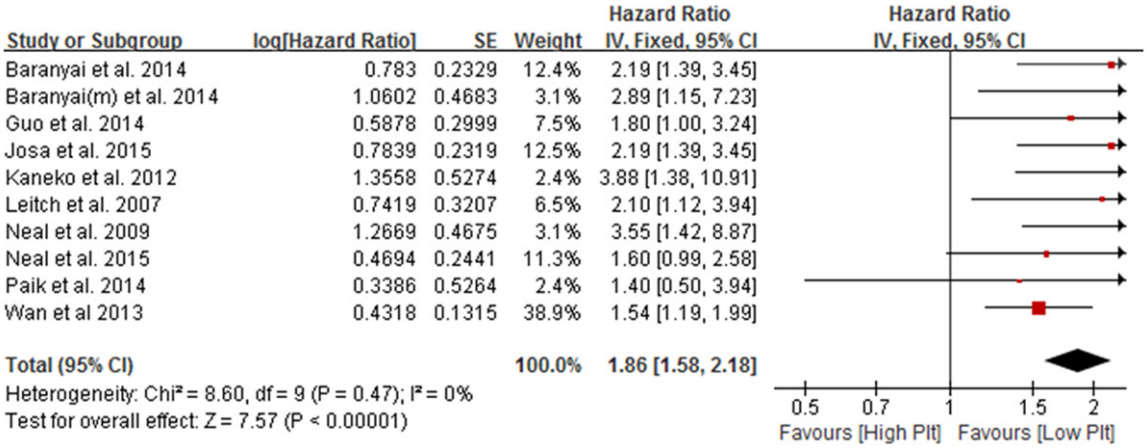

Figure 2. Forest plot of the association between circulating pretreatment platelet count ≥ 400 × 10^9/L and overall survival (UVA).

respectively. Both, univariate and multivariate analyses, were estimated using fixed-effect models because no significant heterogeneity (P = 0.47, I^2 = 0% and P = 0.23, I^2 = 28%, respectively) between studies was found.

Prognostic value of platelet count ≥ 400 × 10^9/L for DFS

There were five studies providing available data evaluating the prognostic value of circulating pretreatment platelet count ≥ 400 × 10^9/L for disease free survival (DFS) of colorectal cancer patients. Because of no significant heterogeneity between studies (I^2 ≥ 46% and P ≤ 0.12), a fixed-effects model was used to estimate pooled HRs of DFS with univariate analyses. The combined HR revealed an evident association between platelet count ≥ 400 × 10^9/L and DFS, with a pooled HR of 1.60 (95% CI 1.19-2.16; P = 0.002) with univariate analysis (**Figure 4**).

Prognostic value of platelet count ≥ 400 × 10^9/L for CSS

Three studies were included to evaluate the association between circulating pretreatment platelet count ≥ 400 × 10^9/L and cancer specific survival (CSS). Despite the small number of eligible studies, obvious significance was found for CSS, with a pooled HR of 1.59 (95%

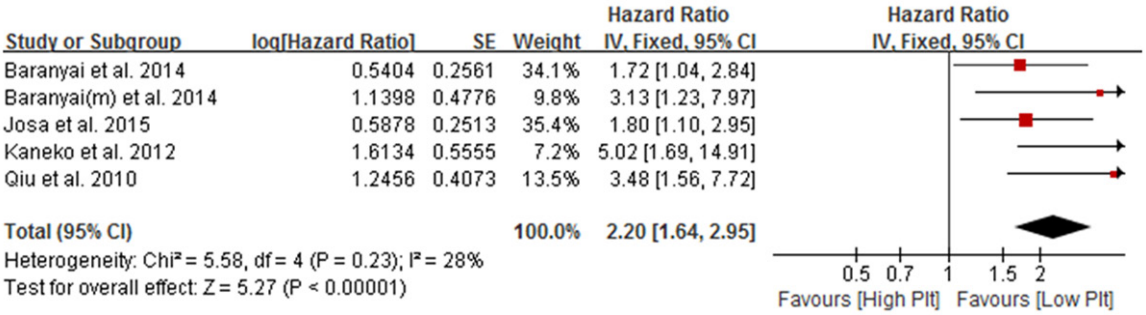

Figure 3. Forest plot of the association between circulating pretreatment platelet count ≥ 400 × 10^9/L and overall survival (MVA).

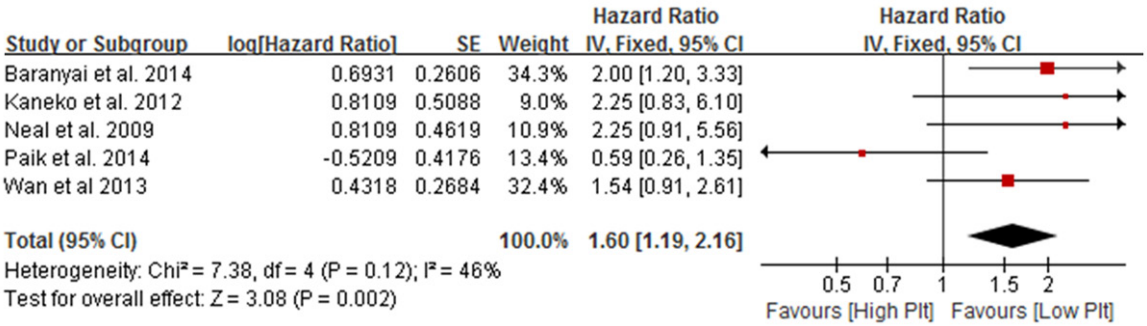

Figure 4. Forest plot of the association between circulating pretreatment platelet count ≥ 400 × 10^9/L and disease-free survival (UVA).

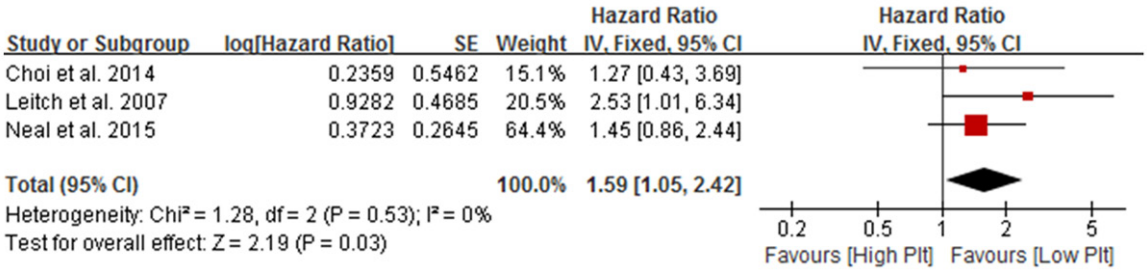

Figure 5. Forest plot of the association between circulating pretreatment platelet count ≥ 400 × 10^9/L and cancer-specific survival (UVA).

CI 1.05-2.42; P = 0.03). Because there was no significant heterogeneity between studies (I^2 = 0% and P = 0.53), a fixed-effects model was used (**Figure 5**).

Subgroup analysis, sensitivity analysis, and publication bias

Subgroup analysis was performed to study the prognostic effects of platelet count ≥ 400 × 10^9/L on OS. As shown in **Table 2**, statistically significant effects were observed in all subgroups, according to therapy methods (surgical resection vs. chemo-radiotherapy), NOS scores (5, 6 vs. 7 vs. 8 scores), study design (prospective vs. retrospective), and samples (> 300 vs. < 300). In addition, there was good homogeneity among all subgroups, as no significant heterogeneity between studies was found. Thus, a fixed-effects model was used to estimate pooled effects, except the subgroup of NOS score = 7 (I^2 = 64%, P = 0.06). Sensitivity analysis showed that all pooled results of OS, DFS, and CSS had high stability by omitting any sin-

Table 2. Pooled results of subgroups for the association between platelet count ≥ 400 × 10^9/L and OS

Subgroups	Number of studies	Number of participants	Pooled results			Heterogeneity		
			HR	95% CI	*P* value	I^2	*p* value	Analytical effect model
NOS score								
5, 6	5	1403	2.06	1.59, 2.67	< 0.00001	0%	0.48	Fixed effects model
7	3	1731	2.41	1.21, 4.80	0.01	64%	0.06	Random-effect model
8	3	1085	2.06	1.45, 2.91	< 0.0001	0%	0.74	Fixed effects model
Study design								
Prospective	2	1193	1.89	1.36, 2.64	0.0002	0%	0.44	Fixed effects model
Retrospective	9	3026	1.91	1.60, 2.28	< 0.00001	26%	0.23	Fixed effects model
N (sample)								
> 300	6	3458	1.82	1.52, 2.18	< 0.00001	11%	0.34	Fixed effects model
< 300	5	761	2.18	1.60, 2.98	< 0.00001	6%	0.37	Fixed effects model
Therapy								
Surgical resection	7	3206	1.84	1.56, 2.17	< 0.00001	0%	0.50	Fixed effects model
Chemo-radiotherapy	2	650	2.33	1.12, 4.84	0.02	46%	0.17	Fixed effects model

NOS, Newcastle-Ottawa Scale; HR, hazard ratio; CI, confidence intervals.

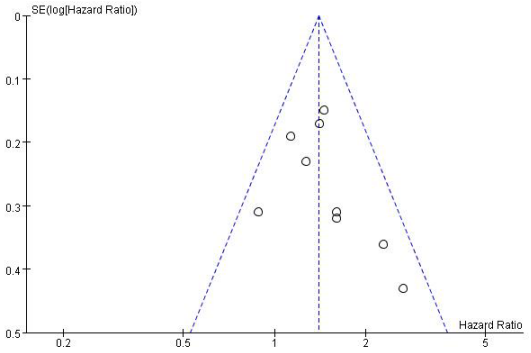

Figure 6. Funnel plot for detecting publication bias.

gle study. No single study significantly affected pooled results and heterogeneity between studies. Funnel plots were conducted for assessment of publication bias of included studies. Publication bias was roughly assessed by seeing whether their shapes showed any obvious asymmetry. The funnel plot showed no clear evidence of publication bias (**Figure 6**).

Discussion and conclusion

The function of platelets has been studied for many decades. It has been demonstrated that thrombocytopenia often complicates critical illness and is associated with increased morbidity and mortality. Approaching thrombocytopenia is challenging in the ICU because of the multifactorial pathogenesis of this disorder. Interpretation of the platelet count course after ICU admission is helpful in narrowing down the cause of thrombocytopenia [32, 33].

Many studies have reported the prognostic roles of elevated platelet counts for patients with malignancies. Similar results have been found in colorectal cancer. Resent analysis demonstrated that elevated platelet counts or thrombocytosis have a significant association with prognosis of colorectal cancer. However, the cut-off values of platelet count in these studies had a large range. The mechanisms or precise correlations between platelet counts and prognosis of patients with tumors have not been studied thoroughly. It has been reported that platelet counts might protect tumor cells from cytolysis, promoting metastasis by surface shielding them from immune system detection. This seems to be the main mechanism of platelet protection [34]. In addition, angiogenesis regulatory proteins have been implicated in tumor growth and invasion. In colorectal cancer patients, levels of platelet derived growth factor, platelet factor 4, and vascular endothelial growth factor are elevated in platelets. Thus, elevated levels of these proteins have been correlated with cancer state [35]. Platelets could stimulate angiogenic vessel growth and prevent hemorrhages from the angiogenic vessels, which are promoted by the adhesion function of platelets, as mediated by glycoprotein Ibα. These processes could stimulate and potentiate tumor cells to form distant metastases [36]. Additionally, T-factor could

reveal that platelets may assist tumor cells in invading adjacent tissues. Thrombocytosis is strongly correlated with the progression of T-factor.

Additionally, some studies have found a significant relationship between post-operation platelet counts and survival of colorectal cancer patients receiving surgical resections [21]. Besides, some analysis and studies have shown neutrophils-to-lymphocytes ratios and platelet-to-lymphocytes ratios to have an association with prognosis of colorectal cancer [37, 38]. However, the cut-off values of platelet-counts that they used were different. Thus, after checking related studies, cut-off value of platelet count $\geq 400 \times 10^9$/L were studied in most studies in which significant results were demonstrated. The current meta-analysis was performed with an aim of comprehensively demonstrating the relationship between circulating pretreatment platelet count $\geq 400 \times 10^9$/L and prognosis of colorectal cancer receiving operation. This study eventually included 12 studies, including 4,522 patients, for review. Eleven studies were included for estimating OS of colorectal cancer and 5 studies for DFS. In addition, three studies were included for evaluating the association between platelet count and CSS. Present results statistically support the conclusion that circulating pretreatment platelet count $\geq 400 \times 10^9$/L has association with poor prognosis of colorectal cancer. Present results are consistent with previous conclusions in gastric cancer, lung cancer, and gynecologic malignancies [39-41].

There were several limitations to the present meta-analysis. The greatest limitation was the variation of clinical stages of patients. Clinical stage, especially TNM stage of tumors, is one of the main factors of tumor patient prognosis and is most commonly used as the predictor for prognosis of tumor patients. Moreover, incidence of high platelets was associated with clinical stages and increased to 12.2% and 20.6% in patients with stage III and IV disease, respectively [23]. Current analysis also found significant association between and TNM stage. As Guo TH et al. reported, platelet count $\geq 400 \times 10^9$/L has association with poor prognosis in patients with stage I to stage III colorectal cancer, but not in patients with stage IV disease, presumably because of poor prognosis regardless of the platelet count. In addition, Sasaki K suggested that the prognostic significance of platelet count was found only in patients at stage III for cancer-specific survival and at stages II and III [42]. The second limitation was the time of measuring platelet counts prior to treatment or operation. This might be an important factor concerning incidence of high platelet counts. In included studies, the time ranged from one week to one month and many studies did not report it, as shown in **Table 1**. Finally, platelet count and prognosis of patients are influenced by multiple other factors, such as age, follow-up time, adjuvant therapy, and tumor size, histological type, and venous involvement. These factors should be taken into consideration.

Considering limitations from the nature of retrospective studies, more prospective studies should be conducted, aiming to demonstrate the association between platelet count and prognosis of colorectal cancer. There are only a few prospective studies included in the current analysis. Further studies are necessary to clarify the significance of high platelet counts in different clinical stages. Despite many limitations and influencing factors, current results suggest that patients with pretreatment thrombocytosis, defined as platelet count $\geq 400 \times 10^9$/L, may experience worse survival.

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Disclosure of conflict of interest

None.

Address correspondence to: Chunlian Wang, Noninfectious Chronic Disease Prevention and Control Department, Harbin Center for Disease Control and Prevention, No. 30 Weixing Road, Daowai District, Harbin 150056, Heilongjiang Province, China. E-mail: biannn1026@163.com

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