Systematic Review and Meta-Analysis

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Thrombocytosis predicts poor prognosis of Asian patients with colorectal cancer

A systematic review and meta-analysis

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Abstract

Background: There is no study analyzing and evaluating the prognostic role of thrombocytosis in Asian patients with colorectal cancer (CRC).

Methods: A systematic search of articles (PubMed, Embase, and the Cochrane Library) was performed to identify studies using the terms Platelet count, Thrombocytosis, Thrombocytoses, Thrombocythemia or Thrombocythemias with colon, colonic, rectal, rectum, colorectal and prognostic, prognosis, survival or outcome.

Results: Thirteen eligible studies with 3964 patients were included. Thrombocytosis was associated with a poorer overall survival (HR of 1.88 [95% CI: 1.24–2.85; P = .003] with univariate analyses, HR of 2.07 [95% CI: 1.2–3.56; P = .008] with multivariate analyses), disease-free survival (HR of 2.58 [95% CI: 1.87–3.57; P < .00001] with multivariate analyses) and cancer specific survival (HR of 2.55 [95% CI: 1.68–3.85; P < .00001]) in Asian patients with CRC. Thrombocytosis had a significant association with female gender, tumor location in the colon, higher pathological T-stage, pathological positive N-stage, but not with lymphatic involvement and venous involvement.

Conclusion: The present meta-analysis demonstrates that thrombocytosis is a potentially useful tool for predicting poor survival in Asian patients with CRC, especially for overall survival.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, CSS = cancer specific survival, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, VTE = venous thromboembolism.

Keywords: colorectal cancer, meta-analysis, survival, thrombocytosis

1. Introduction

Thrombocytosis refers to a condition of high platelet (thrombocyte) count in the circulating blood and could occur in a variety of physiological stimuli, infections, inflammatory diseases, drug effects, malignant tumors, and some chronic myeloid diseases. Since Riess first reported the existence of thrombocytosis in malignant tumor patients in 1872,[1] the relationship between malignant tumor and thrombocytosis is attracting considerable attention. Recently, a growing number of studies have shown that thrombocytosis is closely related to the progression and prognosis of malignant tumors.[2–4] One study showed that about one-third of tumor patients have thrombocytosis,[5] and platelet concentration is inversely related to tumor progression and prognosis. Moreover, previous studies demonstrated that thrombocytosis could cause venous thromboembolism (VTE) and play an important role in tumor progression and metastasis.[6] Therefore, considering that platelet count is an inexpensive, rapid, and convenient laboratory test, it has been widely used as a prognostic predictor in lots of malignant diseases including renal cell carcinoma,[7] lung cancer,[8,9] gastrointestinal tract cancer,[10] and breast cancer.[11,12]Colorectal cancer (CRC) is a well-known primary malignant and poses serious threats to human health. To date, the most common therapeutic method for CRC is surgical intervention. However, surgical intervention often fails to completely remove the tumor and leads to postoperative recurrence and metastasis. Unfortunately, the 5-year survival rate of patients with CRC after resection is less than one-third.[13] Therefore, there is an urgent need for biomarkers that can identify patients at high risk of disease recurrence or poor survival. Several predictors of survival have been identified, including age, sex, tumor stage, weight loss, and carcinoembryonic antigen

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The datasets generated during and/or analyzed during the current study are publicly available.

Ethical approval was not necessary. As this article does not contain any studies with human or animal subjects performed by any of the authors, no ethical approval or patient consent was required.

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levels. Carcinoembryonic antigen is considered to be the most commonly used method for prognostic assessment of CRC patients, but it is also limited by the biological nature of tumor cells and other confounding factors. Recently, several studies have explored the potential association between thrombocytosis and CRC cancer prognosis. In addition, some studies were designed to be based on meta-analyses of related studies, showing that thrombocytosis predicts poor prognosis.[14,15] More importantly, the literature suggests that African Americans bear a higher risk of death with elevated platelets compared with Caucasians, indicating racial differences may lead to a major difference in survival.[16] Although according to the currently reported literature, there is a potential association between thrombocytosis and CRC, no systematic review and meta-analysis so far have assessed the prognostic role of thrombocytosis in Asian patients with CRC. Over the past decades, several randomized controlled trials on the prognostic value of thrombocytosis for survival in Asian CRC patients have been published. Hence, systematic evaluation of current research is needed, and the purpose of this meta-analysis is to review and analyze the prognostic value of thrombocytosis for survival in Asian patients with CRC.

2. Materials and Methods

2.1. Search strategy and study selection

Eligible studies regarding the prognostic utility of thrombocytosis for survival in Asian patients with CRC were recognized by searching PubMed, Embase, and the Cochrane Library from inception until January 1, 2021 using the following search terms: Platelet count, Thrombocytosis, Thrombocytoses, Thrombocythemia or Thrombocythemias with colon, colonic, rectal, rectum, colorectal and prognostic, prognosis, survival or outcome. The inclusion criteria of studies were as follows: provided clear information on survival in Asian patients with CRC; investigated the association between thrombocytosis and overall survival (OS), disease-free survival (DFS), cancer specific survival (CSS); and full-text articles in English. The major reasons for study exclusion were as follows: letters, reviews, expert opinions, case reports, or laboratory studies; studies with overlapping or duplicate data; or a lack of key information for evaluating the hazard ratio (HR) for further analysis.

2.2. Data extraction

Data were extracted independently by 2 reviewers. In case of disagreement, a third reviewer was consulted. For each relevant article, the following information was collected: author, year of publication, country, number of patients, cut-off value, clinical-stage, follow-up period, statistical method of the survival analysis, pretreatment, Newcastle-Ottawa Scale.

2.3. Statistical analysis

We evaluated the prognostic value of thrombocytosis for survival in Asian patients with CRC by examining the HR and 95% CI. Thrombocytosis was considered predictive of poor survival in Asian patients with CRC if HR > 1 and 95% CI did not cross 1. The I^2 and χ^2 were used to test the heterogeneity across studies, and significant heterogeneity was defined as I^2 > 50%. When I^2 > 50%, The random-effect model was used for analysis; otherwise, a fixed-effect model was used. Probable publication bias was estimated through a funnel plot by using Review Manager software version 5.3, and P < .05 was considered statistically significant.

3. Results

3.1. Search outcomes

A flow chart of the literature search was shown in Figure 1. We identified thirteen eligible studies[17–29] with 3964 patients according to the inclusion and exclusion criteria (8 studies for OS, 7 for DFS, and 3 for CSS). All of these articles were published in English. The characteristics of the included studies were summarized in Table 1. The number of patients in each study ranged from 50 to 636. The cut-off value was 400×10^9/L in 4 studies and 300×10^9/L in 5 studies, and their values ranged from 260×10^9/L to 450×10^9/L. Six of the eligible studies investigated the relationship between thrombocytosis and pathological features of CRC.[18,23,25–27,29] Finally, this study analyzed the following characteristics to determine their impact on survival: gender, tumor location, lymphatic involvement, venous involvement, and TNM classification.

3.2. Outcomes from eligible studies

3.2.1. The prognostic value of thrombocytosis for OS. As shown in Figures 2 and 3, the 8 studies evaluating OS were classified into 2 groups: 6 univariate studies with HRs and 95% CIs obtained from univariate analysis, and 6 multivariate studies with the same type of data from multivariate analysis (4 studies calculated HRs and 95% CIs by both multivariate and univariate analyses). Concerning OS, our results indicate that thrombocytosis was associated with shorter OS in Asian CRC patients, and a greater HR was observed both in univariate analysis (HR = 1.88, 95% CI: 1.24–2.85; $P_{\text{heterogeneity}}$ = .03, I^2 = 59%) and univariate analyses (HR = 2.07, 95% CI: 1.20–3.56; $P_{\text{heterogeneity}}$ = .0003, I^2 = 78%), respectively.

3.2.2. The prognostic value of thrombocytosis for DFS. As shown in Figures 4 and 5, the 7 studies evaluating DFS were classified into 2 groups: 5 studies for univariate analysis, and 3 studies for multivariate analysis (one study for both multivariate and univariate analyses). The combined HR

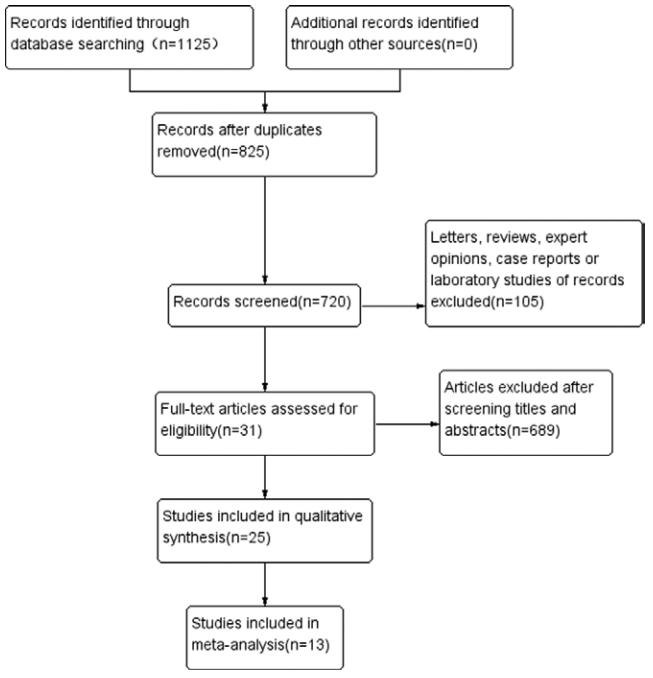

Figure 1. Flowchart of article selection.

Table 1

Major characteristics of the eligible studies.

Author (Ref)	Year	Country	No. of patients	Cut-off value	Clinical stage	Survival analysis	FT (mo)	Pretreatment	NOS score
Ishizuka et al[17]	2016	Japan	627	260	0–IV	OS	NR	Operation	7
Toiyama et al[18]	2015	Japan	89	300	I–III	OS, DFS	56 (2–147)	CRT	7
Shen et al[19]	2014	China	199	300	II–III	OS, DFS	31 (1–84)	CRT	8
Paik et al[20]	2014	Korea	600	400	I–IV	OS	27.4 (1–72)	RT	8
Huang et al[21]	2014	China	136	300	NR	OS	11 (1–65)	CT	5
Choi et al[22]	2014	Korea	105	400	I–IV	CSS	11 (1–65)	NR	5
Sasaki et al[23]	2012	Japan	636	370	I–IV	DFS, CSS	49.1	Operation	7
Kaneko et al[24]	2012	Japan	50	400	NR	OS, DFS	17 (0.77–61.6)	CT	7
Ishizuka et al[25]	2012	Japan	453	300	I–IV	OS	NR	Operation	5
Qiu et al[26]	2010	China	363	400	I–IV	OS	26 (3–50)	NR	6
Kim et al[27]	2015	Korea	314	370	NR	CSS, DFS	NR	CRT	6
Kawai et al[28]	2013	Japan	108	365	I–IV	DFS	NR	CRT	6
Lee et al[29]	2016	Korea	284	450	II	DFS	NR	Operation	7

CRT = chemoradiotherapy, CSS = cancer-specific survival, CT = chemotherapy, DFS = disease-free survival, FT = follow-up time (mouth) (median and range), NOS = Newcastle-Ottawa Scale., NR = not report, OS = overall survival, RT = radiotherapy.

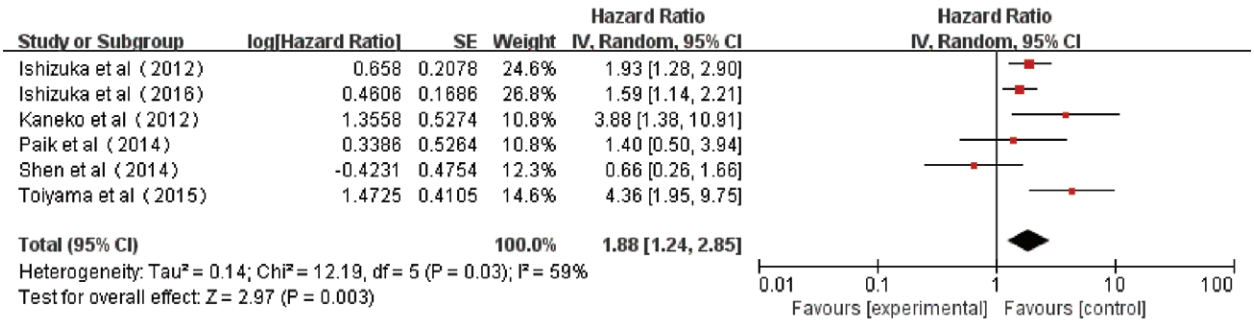

Figure 2. Forest plot of overall survival (univariate analysis). CI = confidence interval.

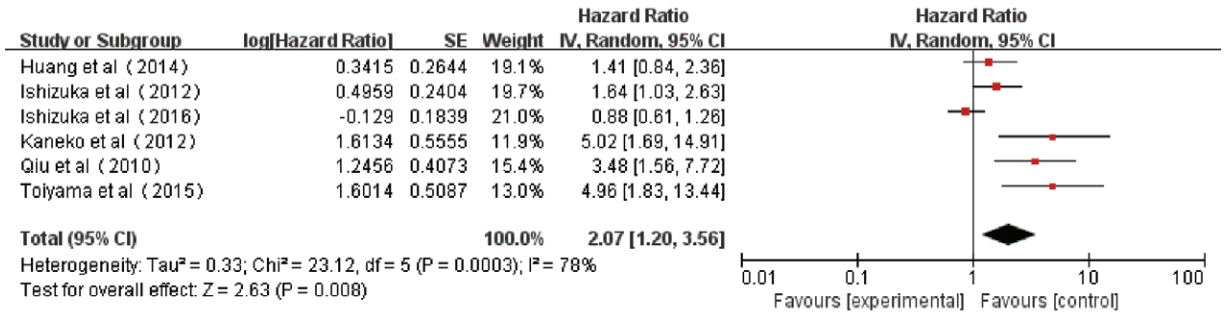

Figure 3. Forest plot of overall survival (multivariate analysis). CI = confidence interval.

revealed a significantly association between thrombocytosis and DFS in multivariate analyses (HR = 2.58, 95% CI = 1.87–3.57, $P_{\text{heterogeneity}} < .00001$, $I^2 = 0\%$). However, no significance was found in univariate analyses with a pooled HR of 1.47 (95% CI = 0.76–2.84; $P_{\text{heterogeneity}} = .02$, $I^2 = 67\%$).

3.2.3. The prognostic value of thrombocytosis for CSS. As shown in Figure 6, 3 studies were included to evaluate the association between thrombocytosis and CSS. The combined HR revealed an evident association between thrombocytosis and CSS with a pooled HR of 2.55 (95% CI = 1.68–3.85; $P_{\text{heterogeneity}} = .38$, $I^2 = 5\%$).

3.2.4. The association between thrombocytosis and clinical features. We performed a meta-analysis in 6 studies about the association between thrombocytosis and clinical features (such as gender, tumor location, TNM classification, and lymphatic and venous involvement). As shown in Table 2, thrombocytosis had a significant association with female gender, tumor location in the colon, higher pathological T-stage, pathological positive N-stage. Meanwhile, we found no significance in both lymphatic and venous involvement.

Following the criteria by the Cochrane Handbook for Systematic Reviews of Interventions, we did not analyze the publication bias because no group included more than 10 studies.

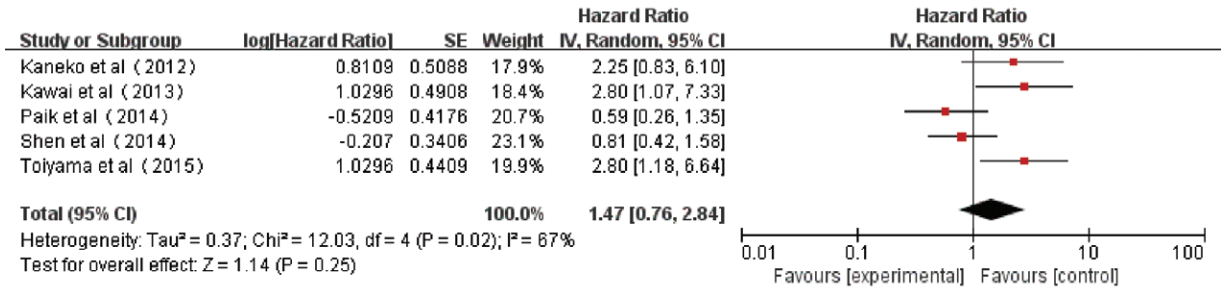

Figure 4. Forest plot of disease-free survival (univariate analysis). CI = confidence interval.

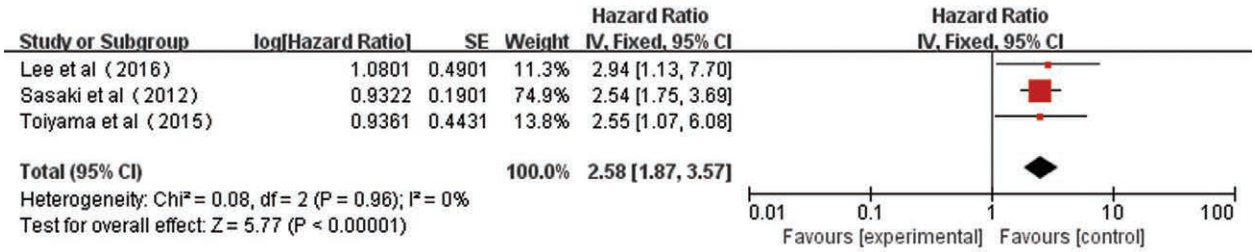

Figure 5. Forest plot of disease-free survival (multivariate analysis). CI = confidence interval.

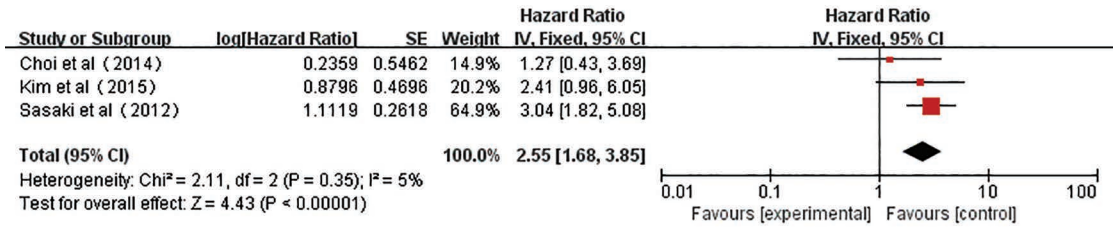

Figure 6. Forest plot of cancer-specific survival. CI = confidence interval.

4. Discussion

Several studies have shown that thrombocytosis is a potential prognostic biomarker for patients with CRC, but the prognostic value of thrombocytosis on survival in Asian CRC patients remains unclear. However, to the best of our knowledge, this is the first systematic review and meta-analysis to investigate the role of thrombocytosis in predicting survival in Asian patients with CRC.

Our meta-analysis of 13 independent studies with 3964 CRC cases unequivocally supported that thrombocytosis predicted a poorer survival of Asian CRC patients based on OS in both univariate and multivariate analyses and DFS and CSS in multivariate analysis. As shown in Table 2, the incidence of thrombocytosis was significantly associated with clinical features such as female gender, tumor location in the colon, higher pathological T-stage, pathological positive N-stage, but not with lymphatic involvement and venous involvement. This study was conducted strictly following the standards of "the preferred report item for systematic reviews and meta-analysis". Therefore, the results and conclusions of this meta-analysis could be credible and adopted in clinical practice.

Thrombocytosis is associated with patient prognosis in many cancers, although the underlying mechanism remains incompletely understood. Platelets are known to be directly involved in tumor progression, metastasis, and angiogenesis.[2–4] Currently three hypotheses for the relationship between thrombocytosis and cancers indicate that platelets may prevent circulating tumor cells from destruction by the host immune system[30,31] and mechanical damage[32,33] to facilitating the adhesion of cancer cells to the endothelium.[4] Moreover, the angiogenic and tumor growth factors secreted by platelets could enhance the promotion of tumor cell growth[2,3,34] and thrombocytosis could also be an epiphenomenon induced by the host response after tumor progression. In addition, recent studies support the hypothesis that the effect of platelets on cancer progression is mediated by lysophospholipids, which are released from activated platelets and exert key effects on the surrounding cells.[35–37] Furthermore, racial differences in immune responses may contribute to racial differences in survival, with African Americans bearing a higher risk of death with elevated platelets compared with Caucasians.

This meta-analysis provided strong evidence to support claims that thrombocytosis was an independent prognostic factor in predicting survival of Asian CRC patients. However, this meta-analysis had several limitations that should be carefully considered. First, the major limitation was the inconsistent of the cut-off value used or the definition of thrombocytosis in the included studies. As mentioned previously, the cut-off value of platelet count ranges from 260×10^9L to 450×10^9L, with most thrombocytosis defined as greater than 400×10^9/L. This may lead to heterogeneity between studies and affect the significance of the results. In addition, given that the included studies were limited to full-text articles published in English and were identified by searching the PubMed and Embase, publication bias cannot be excluded. Additionally, the number of the included studies was insufficient to perform further subgroup analysis.

Table 2

The association between thrombocytosis and clinical features.

Variable	Comparison	Number of studies	OR	95% CI	I^2	$P_{heterogeneity}$
Gender	Male vs female	6	0.69	0.54–0.87	11%	.35
Location	Colon vs rectum	4	1.49	1.13–1.98	28%	.25
Lymphatic involvement	Positive vs negative	3	1.26	0.73–2.20	56%	.10
Venous involvement	Positive vs negative	3	1.21	0.44–3.29	81%	.005
T	T0-2 vs T3-4	4	0.34	0.22–0.54	43%	.15
N	Positive vs negative	4	1.43	1.10–1.85	0%	1

CI = confidence interval.

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Author contributions

Conceptualization: Shijun Xia, Wenjiang Wu.
Data curation: Lijuan Ma, Linchong Yu, Shiwei Chen, Hao Wang.
Formal analysis: Shijun Xia.
Methodology: Shijun Xia.
Project administration: Shijun Xia.
Software: Hao Wang.
Writing – original draft: Shijun Xia.
Writing – review & editing: Shijun Xia.

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