

RESEARCH ARTICLE

Poor Prognosis Significance of Pretreatment Thrombocytosis in Patients with Colorectal Cancer: a Meta-Analysis

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Abstract

Background: Recently, several studies have reported that elevated platelet counts may be associated with the poor prognosis of colorectal cancer. However, conclusions remain controversial. This meta-analysis was therefore designed to analyze and evaluate the prognostic role of preoperative or pretreatment thrombocytosis in patients with colorectal cancer. **Materials and Methods:** We searched PubMed, EMBASE, the Cochrane Library and Web of Science to March 29th, 2015. The citation lists of included studies were also hand-searched to identify further relevant trials. To investigate the association between thrombocytosis and prognosis of colorectal cancer, the 1-year, 3-year and 5-year survival of each studies were obtained. The odds ratio (OR) with its 95% confidence interval (CI) was used to evaluate the relation of overall survival (OS) between thrombocytosis and normal platelet counts (PLT). Likewise, disease free survival (DFS) was obtained and evaluated. The analysis was performed and assessed using Review Manager 5.2. **Results:** A total of 14 studies (N=5,566 participants, 11 including 4,468 for OS, 6 including 1,533 for DFS) were included in this meta-analysis, of which seven (N=3810) defined thrombocytosis as a platelet count $\geq 400 \times 10^9/L$, and 375 (9.8%) patients exhibited pretreatment thrombocytosis. Thrombocytosis have a close relationship with the poor OS of colorectal cancer compared with normal PLT, with the pooled ORs of 1-year, 3-year and 5-year survival being 0.41 [95% CI 0.34-0.51; $P < 0.001$], 0.28 [95% CI 0.21-0.38; $P < 0.001$] and 0.26 [95% CI 0.20-0.34; $P < 0.001$], respectively. For DFS, the same results were showed as the pooled ORs of 1-year, 3-year and 5-year survival respectively being 0.34 [95% CI 0.24-0.50; $P < 0.001$], 0.31 [95% CI 0.23-0.43; $P < 0.001$] and 0.25 [95% CI 0.18-0.34; $P < 0.001$]. **Conclusions:** This meta-analysis indicated that thrombocytosis may predict poor prognosis for patients with colorectal cancer, and platelet counts may be a cost-effective and noninvasive marker.

Keywords: Thrombocytosis - prognosis - colorectal cancer - meta-analysis

Asian Pac J Cancer Prev, 17 (9), 4295-4300

Introduction

According to the report from Wanqing Chen, the incidence rate of malignancies was 264.85/100,000 (289.30/100,000 in males, 239.15/100,000 in females) (Chen et al., 2016). The colorectal cancer (CRC) is one of the increasingly common malignancies worldwide. The incidence of the disease is 12.3% in men and 13.1% in women in Europe (Kanavos et al., 2010). What is more, in North America, CRC is the third most common cause of cancer-related deaths (Canadian Cancer Statistics 2013). Despite surgical resection is the optimal option for the patients with colorectal cancer, at least about half of patients die within 5 years after their diagnosis (Aranda et al., 2015). Thus, appropriate prognostic markers were

needed to predict patients' postoperative prognosis and the survival of patients at high risk of recurrence, and to guide patients to choose additional treatment.

Hopefully, in recent years, several reviews have reported that elevated platelet counts may be associated with the poor prognosis of gastric cancer, lung cancer, renal cancer and gynecologic malignancies (Yu et al., 2012; Zhang et al., 2015; Zhang et al., 2015; Men et al., 2015). Besides, breast cancer, esophageal cancer and pancreatic cancer have been also reported to have association with thrombocytosis (Suzuki et al., 2004; Alcindor et al., 2008; Campos Gomez et al., 2014; Wang et al., 2015; Ilhan-Mutlu et al., 2015; Gu et al., 2015). Likewise, the association between thrombocytosis and the survival of colorectal cancer had also been published

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in some studies (Monreal et al., 1998; Padilla et al., 2004; Shwaiki et al., 2004; Kandemir et al., 2005; Nyasavajjala et al., 2010; Qiu et al., 2010; Cravioto-Villanueva et al., 2012; Ishizuka et al., 2012; Lin et al., 2012; Sasaki et al., 2012; Ishizuka et al., 2013; Juan Castillo-Perez et al., 2013; Kawai et al., 2013; Wan et al., 2013; Baranyai et al., 2014; Guo et al., 2014; Toiyama et al., 2015; Josa et al., 2015; Josa et al., 2015; Al-Saeed et al., 2015). However, fallaciously, their results still remained inconsistent, with several studies drawing inverse conclusions (Guo et al., 2014; Kawai et al., 2013; Nyasavajjala et al., 2010; Yu et al., 2016). Therefore, we designed a meta-analysis based on relevant studies to analyze and evaluate the prognostic role of preoperative or pretreatment thrombocytosis in patients with colorectal cancer.

Materials and Methods

Including and excluding criteria

The including criteria of this meta-analysis were as follows: (1) Both randomized, controlled trials (RCTs) and observational retrospective studies were included; (2) Included people with a diagnosis of colorectal cancer; (3) Included patients received operation; (4) Overall survival, the number of participants, preoperative platelet counts and definition of thrombocytosis were reported or can be obtained; (5) The incidence of preoperative or pretreatment thrombocytosis was given.

Excluding criteria were as follows: (1) Trials on animals; (2) abstracts, letters, editorials, expert opinions, reviews, case reports; (3) Patients having other primary tumors; studies without sufficient data.

Search strategy

We searched PubMed, EMBASE, The Cochrane Library and Web of Science to March, 29th 2015. We also hand searched the citation lists of included studies and previously identified systematic reviews to identify further relevant trials. We searched the databases with the terms “thrombocytosis”, “platelet count*”, “colorectal

cancer”, “rectal cancer”, “colonic cancer”, “prognosis” and “survival” and other related terms in English, including references of some literatures we read. Two assessors independently screened the titles and abstracts of each study. Once relevant studies became certain, the full texts were obtained for further evaluation.

Data extraction and conversion

Data for the analysis were extracted independently by two reviewers, and disagreement was resolved by their discussion. In addition, the extracted contents included study demographics, published years, country, trial design, cancer location, OS and DFS, using a standardized form. When the incidence of thrombocytosis and events were only presented with percentages or Kaplan-Meier curves, the specific number of people was obtained via converting and calculating from the graphical survival plots.

Data collected were input into RevMan 5.2 software for analysis (Review Manager.Version 5.2 et al., 2012).

Statistical analysis

In this meta-analysis, the impact of thrombocytosis on patients' survival was measured by estimating the odds ratio (OR) between the thrombocytosis group and normal platelet counts group. The associated 95% confidence intervals (CI) were also measured. The heterogeneity between studies was evaluated with P value and I^2 . $I^2 \geq 50\%$ or $P \leq 0.05$ was deemed to represent significant heterogeneity (Higgins J and G.S et al., 2014; University of York Centre for Reviews and Dissemination et al., 2009), and pooled OR was estimated using a Random-effect model. On the contrary, if statistical study heterogeneity was not observed ($I^2 \leq 50\%$ and $P \geq 0.05$), a fixed effects model was used. Subgroup analysis was used in this meta-analysis when the outcomes or intervening measures were significantly different.

Finally, publication bias was assessed by Begg's and Egger's test, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using standard statistical procedures provided in RevMan 5.2 (Review Manager.Version 5.2 et al., 2012).

Table 1. Characteristics of the Included Studies

Year	Author	Country	Location	No.	no. of thrombocytosis	Cut-off value	Clinical Stage	Study design
2015	Toiyama	Japan	Rectum	89	19	300×109/L	I-III	retrospective study
2015	Josa	Hungary	Colorectum	336	45	400×109/L	I-IV	retrospective study
2014	Guo	USA	Colorectum	310	25	400×109/L	0-IV	retrospective study
2013	Wan	USA	Colorectum	1513	153	400×109/L	0-IV	retrospective study
2013	Kawai	Japan	Rectum	108	22	365×109/L	I-IV	retrospective study
2012	Sasaki1*	Japan	Colorectum	636	77	370×109/L	I-IV	retrospective study
	Sasaki2*	Japan	Colorectum	636	47	400×109/L	I-IV	retrospective study
	Sasaki3*	Japan	Colorectum	636	19	450×109/L	I-IV	retrospective study
2012	Ishizuka	Japan	Colorectum	453	226	300×109/L	I-IV	retrospective study
2012	Adrian	Mexico	Rectum	163	13	350×109/L	0-III	retrospective study
2010	Qiu	China	Colorectum	363	30	400×109/L	null	retrospective study
2010	Nyasavajjala	UK	Colorectum	627	51	450×109/L	I-IV	retrospective study
2005	Kandemir	Turkey	Colon	198	24	400×109/L	null	retrospective study
2014	Baranyal1*	Hungary	Colorectum	336	45	400×109/L	I-IV	retrospective study
	Baranyal2*	Hungary	mCRC	118	6	400×109/L	I-IV	retrospective study
2015	JosaV	Hungary	mCRC	166	11	380×109/L	null	retrospective study
2012	Mao	China	Colorectum	150	30	300×109/L	I-IV	retrospective study

*they are from the same study

Results

Included studies and study characteristics

After 47 studies were excluded (40 studies for no defining of thrombocytosis, 6 studies for lack of available data, 1 studies for just review), A total of 14 studies (N=5566 participants) were included in this meta-analysis, of which 11 studies including 4468 participants were included for estimating OS (Kandemir et al., 2005; Sasaki et al., 2012; Lin et al., 2012; Ishizuka et al., 2012; Cravioto-Villanueva et al., 2012; Wan et al., 2013; Baranyai et al., 2014; Guo et al., 2014; Toiyama et al., 2015; Josa et al., 2015; Josa et al., 2015) and 6 studies including 1533 participants were included for DFS

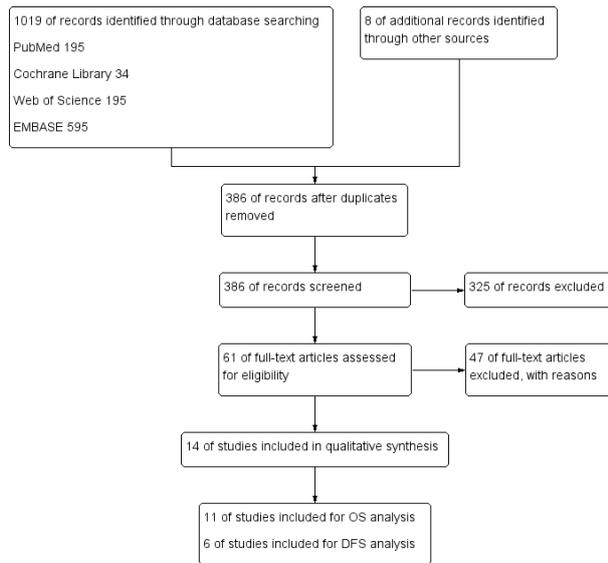


Figure 1. Flow Diagram of the Search Strategy for Pretreatment Thrombocytosis as a Prognostic Role in Patients with Colorectal Cancer

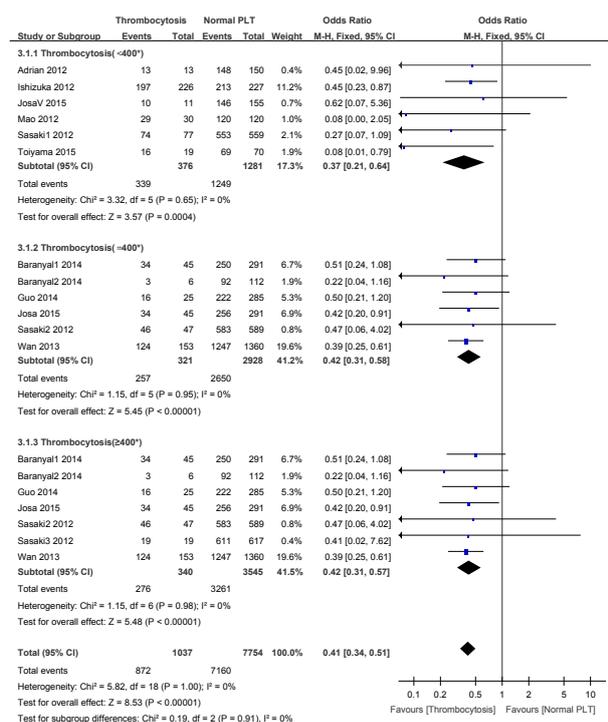


Figure 2. Forest Plot Comparing the Association of 1-year OS between Thrombocytosis and Normal PLT

(Kandemir et al., 2005; Sasaki et al., 2012; Kawai et al., 2013; Baranyai et al., 2014; Toiyama et al., 2015; Josa et al., 2015). Seven studies (N=3810) defined thrombocytosis as platelet counts $\ge 400 \times 10^9/L$, and 375 patients (9.8%) exhibited pretreatment thrombocytosis. There were six studies with cut-off values less than $400 \times 10^9/L$. All of the 14 studies included were observation retrospective studies.

The detail search process and summary of studies were showed in study flow diagram (Figure 1). The other study characteristics were showed in Table 1.

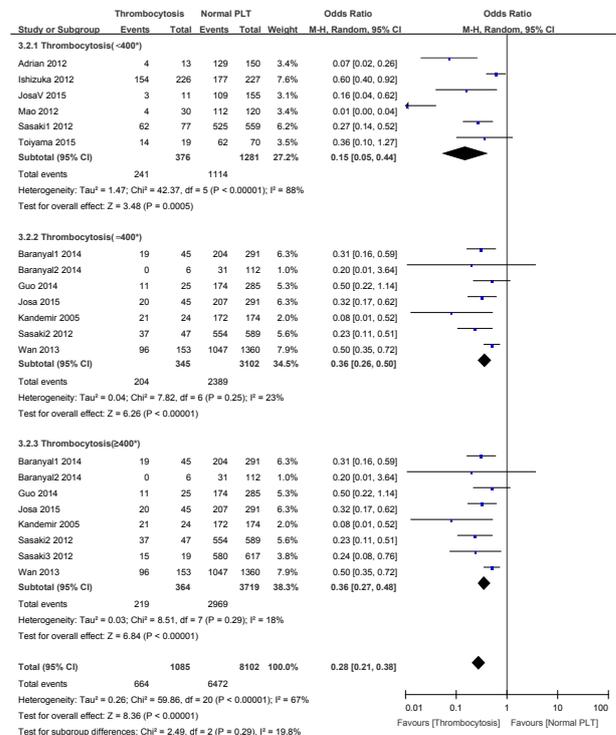


Figure 3. Forest Plot Comparing the Association of 3-year OS between Thrombocytosis and Normal PLT

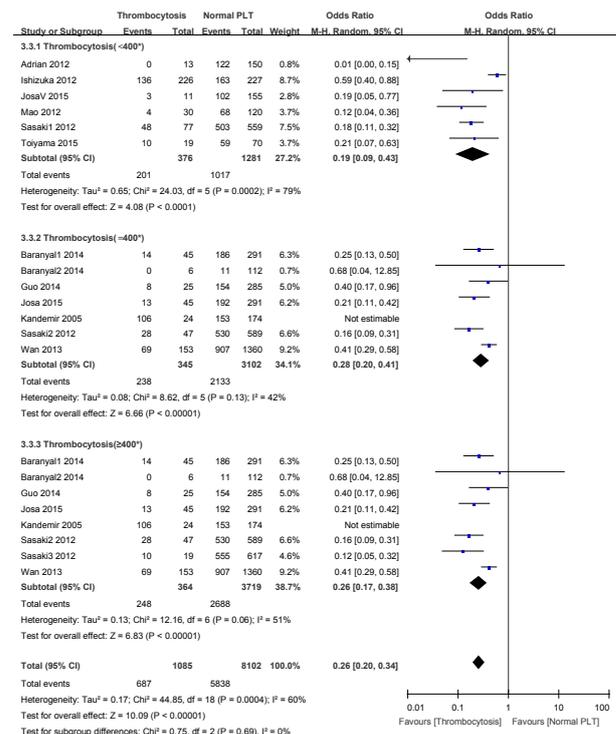


Figure 4. Forest Plot Comparing the Association of 5-year OS between Thrombocytosis and Normal PLT

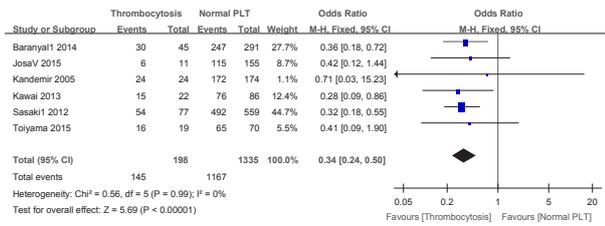


Figure 5. Forest plot comparing the association of 1-year DFS between thrombocytosis and normal PLT

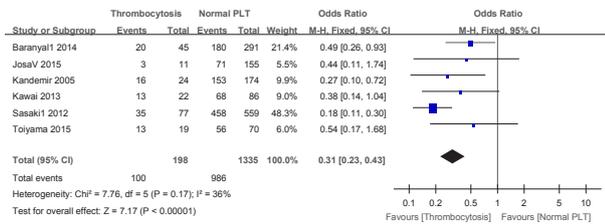


Figure 6. Forest plot comparing the association of 3-year DFS between thrombocytosis and normal PLT

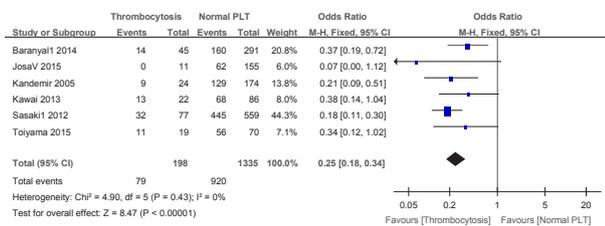


Figure 7. Forest Plot Comparing the Association of 5-year DFS between Thrombocytosis and normal PLT

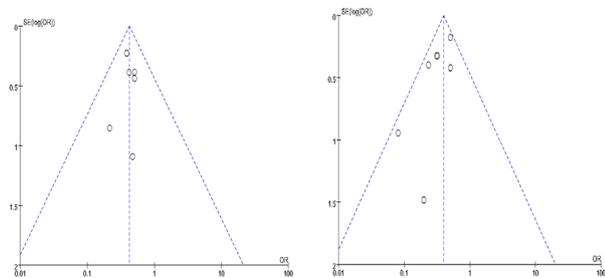


Figure 8. Funnel Plots for Detecting Publication Bias Cut-off value equal to 400×10⁹/L: A: 1-year OS; B: 3-year OS

Prognostic value of thrombocytosis to OS

Of the 11 studies included for estimating OS, 10 studies provided the available data for evaluating the prognostic value between preoperative thrombocytosis and the 1-year survival of patients with colorectal cancer, and 11 studies for 2-year and 3-year survival.

As displayed in Fig.2, for 1-year OS, meta-analysis comparing elevated PLT group to normal PLT group showed significant correlation, with the pooled OR being 0.41 [95% CI 0.34–0.51; P<0.00001]. For subgroup analyses, the pooled OR of cut-off values less than 400×10⁹/L was 0.37 [95% CI 0.21–0.64; P=0.0004]. The pooled OR of cut-off values equal to 400×10⁹/L was 0.42 [95% CI 0.31–0.58; P<0.00001] and cut-off values equal to or more than 400×10⁹/L was 0.42 [95% CI 0.31–0.57; P<0.00001].

For 3-year OS, as the significant heterogeneity between studies ($I^2 \geq 50\%$, $P \leq 0.05$), a random effect model was used to estimate the pooled OR. The combined OR indicated that thrombocytosis had a distinct association with the survival of patients with colorectal cancer [OR=0.28, 95% CI 0.21–0.38; P<0.00001] (Fig.3). Significant results were also showed for subgroup analysis. The pooled ORs of cut-off values less than 400×10⁹/L and equal to 400×10⁹/L were 0.15 [95% CI 0.05–0.44; P=0.0005] and 0.36 [95% CI 0.26–0.50; P<0.00001], respectively. The pooled OR of cut-off values equal to or more than 400×10⁹/L was 0.36 [95% CI 0.27–0.48; P<0.00001] (Fig.3).

A random effect model revealed an evident association between thrombocytosis and 5-year OS. The pooled OR with numerical significant heterogeneity indicated that thrombocytosis had an obvious association with the 5-year survival [OR=0.26, 95% CI 0.20–0.34; P<0.00001] (Fig.4). Similarly, as Fig.4 showed, The pooled ORs of cut-off values less than 400×10⁹/L and equal to 400×10⁹/L were 0.19 [95% CI 0.09–0.43; P=0.0001] and 0.28 [95% CI 0.20–0.41; P<0.00001], respectively. The pooled OR of cut-off values equal to or more than 400×10⁹/L was 0.26 [95% CI 0.17–0.38; P<0.00001].

The prognostic value of thrombocytosis to DFS

There were 6 studies providing the available data for evaluating the prognostic value between pretreatment thrombocytosis and disease free survival (DFS). The cut-off values ranged from more than 300×10⁹/L to more than 400×10⁹/L. Because of the small number of eligible studies, no subgroup analysis was performed.

As no significant heterogeneity between studies ($I^2 \leq 50\%$ and $P \geq 0.05$), a fixed effect model was used to estimate the pooled OR of DFS. The combined OR revealed an evident association between thrombocytosis and 1, 3 and 5-year DFS, with the pooled OR being 0.34 [95% CI 0.24–0.50; P<0.00001], 0.31 [95% CI 0.23–0.43; P<0.00001] and 0.25 [95% CI 0.18–0.34; P<0.00001], respectively (Figure 5, Figure 6 and Figure 7).

Publication bias

Funnel plots were conducted for assessing the publication bias of included literatures and we could roughly assess the publication bias by seeing whether their shapes were of any obvious asymmetry. The funnel plots of the cut-off value equal to 400×10⁹/L for 1 and 3-year OS did not reveal any obvious evidence of asymmetry and this indicated that there was no obvious publication bias for them (Figure 8). However, significant bias were found in the cut-off value less than or more than 400×10⁹/L for OS and DFS, especially for 5-year OS (figures were not given) and the analysis of causes were offered in discussion.

Discussion

Recently, great interest has been given in the prognostic role of thrombocytosis for patients with malignancies as previously mentioned. However, the mechanism or precise association between thrombocytosis and malignancies have not been clarified. There were

several possible explanations for the association between thrombocytosis and poor prognosis of malignancies. First, Thrombocytosis might protect tumor cells from cytolysis, thereby promoting metastasis, by surface shielding them from immune system detection and this seems to be the main mechanism of platelet protection (Nieswandt et al., 1999). Secondly, angiogenesis regulatory proteins are implicated in tumor growth and invasion. In colorectal cancer patients, the levels of PDGF, PF4 and VEGF are elevated in platelets, and the elevated levels of all three proteins correlated with the cancer state (Peterson et al., 2012). Platelets could stimulate angiogenic vessel growth and prevent hemorrhage from the angiogenic vessels, which was promoted by the adhesion function of platelets, as mediated by glycoprotein (GP) Iba α , and these processes could stimulate and potentiate tumor cells to form distant metastases (Kisucka et al., 2006). Additionally, T-factor could reveal that platelets may assist tumor cells in invading to adjacent tissues, and thrombocytosis is just right strongly correlated with the progression of T-factor.

We perform this meta-analysis for purpose of demonstrating the relation between thrombocytosis and prognosis of cancer in spite of the unclear mechanism. This review found 11 eligible studies for OS and 6 available studies for DFS. The cut-off values of platelet counts varied from 300 \times 10⁹/L to 450 \times 10⁹/L in the included studies, of which the cut-off values of 7 studies were 400 \times 10⁹/L (Kandemir et al., 2005; Qiu et al., 2010; Sasaki et al., 2012; Wan et al., 2013; Baranyai et al., 2014; Guo et al., 2014; Josa et al., 2015) and 3 studies were 300 \times 10⁹/L (Ishizuka et al., 2012; Lin et al., 2012; Toiyama et al., 2015) as displayed in Table 1. Our results statistically supported the conclusions that thrombocytosis has association with the poor prognosis in colorectal cancer, which was consist with the conclusions in gastric cancer, lung cancer and gynecologic malignancies (Yu et al., 2012; Zhang XJ et al., 2015; Zhang X et al., 2015).

Nevertheless, there were several limitations for this meta-analysis. The greatest limitation was the discordance of the platelet count cut-off values or the definition of thrombocytosis used in the included studies. As what mentioned before, the cut-off values of platelet counts varied from 300 \times 10⁹/L to 450 \times 10⁹/L, and most thrombocytosis was defined as more than 400 \times 10⁹/L. This discordance may lead to between-study heterogeneity and affect the significance of results. For example of the study by Sasaki et al (2012), the significant difference in survival was found only in the cut-off values of platelet counts equal to 370 \times 10⁹/L, but not in the cut-off values of platelet counts equal to 400 \times 10⁹/L or 450 \times 10⁹/L. However, our subgroup analyses stratified by the cut-off values did not find substantial affection to prognostic value of thrombocytosis. What's more, even though the various definitions of thrombocytosis, no significant difference in subgroups was found according to the pooled analysis, and sensitivity analysis did not draw any different conclusions as well. The second limitation is the variation of the clinical stages. The incidence of thrombocytosis was associated with clinical stages and increased to 12.2% and 20.6% in patients with stage III and IV disease respectively (Guo et al., 2014). As 2014

Tianhua Guo reported, thrombocytosis has association with poor prognostic significance in patients with stage I to stage III colorectal cancer, but not in patients with stage IV disease, presumably because of poorly regardless of the platelet count. In addition, Sasaki K suggested that the prognostic significance of thrombocytosis was found only in patients at stage III for cancer-specific survival and at stages II and III (Sasaki et al., 2012). Moreover, the time of measuring platelet count before treatment or surgery might be an important factor. Finally, platelet count was also influenced by multiple other factors, such as age, adjuvant therapy, and tumor size, histological type, venous involvement should also be taken into consideration. The last important limitation was the publication bias. As mentioned before, there were obvious publication bias for the cut-off value less than or more than 400 \times 10⁹/L for OS and DFS, especially for 5-year OS, but not for the cut-off value equal to 400 \times 10⁹/L. The factors impacting publication bias were various. In my opinion, apart from the factors like no publication of negative results, termination of publication and language limitation, the research period was the main influence. Compared to 1-year survival, there is more difficulty for 5-year survival, and so many studies might come to an end after obtain the 1 and 3-year survival. Thus the publication bias for 5-year survival were obviously higher. Therefore, the prognostic value of thrombocytosis for 5-year survival might remain consideration.

Taking into account such factors, further researches need to clarify the suitable definition of thrombocytosis. Besides, patients with different stages should be studied to clear the influence of clinical stages in thrombocytosis and studies with negative results were needed to publish for analysis. Despite many difference and influencing factors, we could cautiously draw a conclusion that thrombocytosis have a close association with worse survival in colorectal cancer patients, with consideration of the evident statistical significance. Thrombocytosis may predict poor prognosis for patients with colorectal cancer, and platelet counts may be a cost-effective and noninvasive marker.

Acknowledgements

The authors declare no conflicts of interest.

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