The clinicopathological and prognostic role of thrombocytosis in patients with cancer: A meta-analysis

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Abstract. Previous studies have linked the presence of thrombocytosis with the progression and development of cancer; however, this trend requires further investigation. The present study aimed to derive an estimation of the degree of association between thrombocytosis and the 5-year overall survival rate of patients with cancer, as well as common clinicopathological features, by performing a meta-analysis of 20 (n=12,778) published studies. The PubMed and Embase databases were searched systematically for all relevant articles published in English. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using a fixed effects or random effects model to evaluate the degree of the observed associations. The results suggested that thrombocytosis (platelet count, >400x10^9/l) correlated with a decreased 5-year overall survival rate (OR=2.70, 95% CI=2.03-3.61) and an advanced tumor-node-metastasis stage (III + IV; OR=2.14, 95% CI=1.58-2.90). Furthermore, these associations remained robust following stratification of the data by cancer type and ethnicity. In addition, thrombocytosis (platelet count, >300x10^9/l) correlated with a decreased 5-year overall survival rate in patients with colorectal cancer (OR=3.49, 95% CI=1.44-8.46). Although certain biases were not able to be eliminated, the present meta-analysis suggested that thrombocytosis is a valuable indicator for the evaluation of pathological diagnosis and prognosis for patients with cancer. Further studies are required to investigate the effect of thrombocytosis on the prognosis of patients with cancer.

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Abbreviations: TNM, tumor node metastasis; OR, odds ratio; CI, confidence interval

Key words: thrombocytosis, cancer, prognosis, meta-analysis

Introduction

Despite improvements in early diagnosis, radical surgery and various novel treatments, the prognosis for patients with cancer remains poor (1). Esophageal cancer patients without detectable metastasis in the clinic at the time of diagnosis may still succumb to cancer recurrence following surgery (2). This suggests that certain metastasis of cancer may not be detected using conventional biochemistry testing, imaging or histopathological methods (2). Therefore, a novel biological marker that may enhance the ability to accurately predict patient treatment outcomes is required. In previous years, a number of studies have investigated potential prognostic factors in patients with cancer. Previous studies have demonstrated that certain preoperative alterations in hematological parameters may be associated with patient outcomes for several forms of solid tumors (3). In addition, it has been suggested that circulating platelet (PLT)-tumor cell aggregates may promote cancer metastasis (4).

Previous studies have investigated the association between thrombocytosis and tumor growth and development in various forms of malignancy (5-7); however, this trend requires further investigation. Yu *et al* (8) demonstrated, using a meta-analysis, that thrombocytosis (PLT count >400x10^9/l) may be associated with a poorer prognosis for patients with a gynecological malignancy. Therefore, the present meta-analysis was performed in order to assess the association between thrombocytosis, 5-year overall survival and tumor clinicopathological features in various types of cancer, excluding gynecological malignancies.

Materials and methods

Identification and eligibility of relevant studies. The PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Embase (https://www.elsevier.com/solutions/embase-biomedical-research) databases were searched with the following terms: 'Carcinoma' or 'cancer'; 'platelet count' or 'thrombocytosis'; 'prognosis' or 'survival' (the final search was performed on April 3rd, 2015). The associated reference articles were subsequently searched to identify any other relevant publications. Reference lists of all retrieved articles were also manually examined. If >1 article had been published using the same patient population, only the most recent or

complete study was selected. Studies included in the present meta-analysis were required to meet the following inclusion criteria: Study was written in the English language; the study defined thrombocytosis as PLT counts >300x10^9 platelets/l in patients with colorectal cancer and PLT counts >400x10^9 platelets/l for patients with other types of cancer; the study examined the association between thrombocytosis and the survival of patients with cancer and tumor clinicopathological features, including tumor differentiation, lymph node metastasis, and tumor node metastasis (TNM) stage which was measured in accordance with American Joint Commission for Cancer Staging (9).

The study exclusion criteria were as follows: The appropriate data was not able to be extracted from the published results; the study lacked information on clinicopathological features or survival; the study performed an evaluation of the association between thrombocytosis and forms of gynecological cancer.

Data extraction. Information was independently extracted from all eligible publications, according to the inclusion criteria. The primary aim was to assess the prognostic value of thrombocytosis, particularly regarding 5-year overall survival, in patients with cancer. The secondary aim was to evaluate the association between thrombocytosis and patient clinicopathological features. The following data were sought from each publication: The first author's last name, year and country of the study, cancer type, number of patients with and without thrombocytosis, 5-year overall survival and clinicopathological features, including tumor differentiation, lymph node metastasis, TNM stage and tumor location.

Statistical analysis. The degree of the association between thrombocytosis and the 5-year overall survival rate and tumor clinicopathological features in various types of cancer was evaluated by odds ratios (OR) with 95% confidence intervals (CI). The statistical significance of the pooled OR was determined using the z-test. The χ^2 test-based Cochran's Q-statistic was calculated to evaluate the heterogeneity between studies. If the between-study heterogeneity was significant, then the pooled ORs were analyzed using the random effects model (the DerSimonian and Laird method) (10); otherwise, the fixed effects model was selected (the Mantel-Haenszel method) (11). Subgroup analyses, in which studies were subdivided by cancer type and ethnicity, were adopted to minimize the influence of heterogeneity on the results. Funnel plots and Egger's linear regression test were used to evaluate potential publication bias. All analyses were performed using Stata software version 11.0 (StataCorp LP, College Station, TX, USA), and all tests were two sided. P<0.05 was considered to indicate a statistically significant difference.

Results

Identification of eligible studies. A total of 20 studies (7,12-30) that met the inclusion criteria were retrieved for analysis in the present study. The selection process of the included studies is presented in Fig. 1. The number of patients in each study ranged between 100 and 3,139 and the total number of patients included in the present study was 12,778, of whom 1,739 exhibited thrombocytosis at the time of initial diagnosis. The characteristics of each study are summarized in Table I, and 19/20 of the included studies provided data on the association between 5-year overall survival and thrombocytosis. The types of cancer examined by the 20 studies included in the meta-analysis were as follows: 4 gastric, 4 lung, 7 renal and 5 colorectal cancer.

Correlation between thrombocytosis and 5-year overall survival. The present meta-analysis indicated that thrombocytosis (defined as a PLT count of >400x10^9 platelets/l) was associated with a 2.70-fold increase in mortality, as compared with patients with normal PLT counts, when the 5-year overall survival rate was extracted from 15 eligible studies (OR=2.70; 95% CI=2.03-3.61). The random effects model was utilized for analysis due to the heterogeneity of the studies examined (I^2=69.6%). Upon stratification by cancer type, the pooled ORs for gastrointestinal, lung and renal cancer were 1.77 (95% CI=1.36-2.29), 3.21 (95% CI=1.75-5.92) and 3.11 (95% CI=2.03-4.77), respectively (Fig. 2). In addition, thrombocytosis (defined as a PLT count of >300x10^9 platelets/l) was associated with reduced 5-year survival rate (OR=3.49, 95% CI=1.44-8.46) in patients with colorectal cancer. When subdivided by ethnicity, the pooled ORs for Asian, African and European populations were 3.06 (95% CI=1.76-5.34), 1.71 (95% CI=1.17-2.49) and 2.72 (95% CI=1.91-3.90), respectively (Table II).

Correlation between thrombocytosis and tumor clinicopathological features. Analysis of the correlation between thrombocytosis (PLT >400x10^9/l) and the pooled clinicopathological feature data revealed that thrombocytosis was more frequently detected in patients with an advanced TNM stage (OR=2.14, 95% CI=1.58-2.90; I^2=54.1%). By contrast, no statistically significant association was identified between thrombocytosis and tumor differentiation (P=0.31), lymph node metastasis (P=0.097) or tumor location (P=0.24). Subgroup analyses were subsequently performed according to cancer type, and the pooled ORs for gastrointestinal, lung and renal cancer were 1.96 (95% CI=1.21-3.18), 1.96 (95% CI=1.23-3.12) and 3.16 (95% CI=3.16-8.32), respectively (Table II). In the subgroup analysis according to ethnicity, as there was no study investigating the association between thrombocytosis and advanced TNM stage in African patients, the pooled ORs for Asians and Europeans were 2.64 (95% CI=1.42-4.90) and 1.89 (95% CI=1.38-2.59), respectively (Fig. 3).

Heterogeneity and sensitivity analyses. The present meta-analysis detected significant between-study heterogeneity (5-year overall survival, $P_{heterogeneity}$<0.001; I^2=69.6%; TNM stage, $P_{heterogeneity}$=0.03; I^2=54.1%). However, stratification based on the type of cancer reduced the heterogeneity observed in the gastrointestinal cancer subgroups (5-year overall survival, $P_{heterogeneity}$=0.57, I^2=0.0%; TNM stage, $P_{heterogeneity}$=0.17, I^2=44.3%). In addition, there was no heterogeneity for studies investigating the association between thrombocytosis and 5-year overall survival in Africans (I^2=0%), and TNM stage in Europeans (I^2=30.6%). The source of heterogeneity was assessed for comparison of patient 5-year overall survival according to ethnicity, cancer type and sample size (>200 patients in

Table I. Characteristics of the eligible studies.

First author	Year	Country	Cancer type	Threshold level for thrombosis, x10^9/l	Total no. of patients	No. of patients with thrombocytosis
Li (7)	2014	China	Gastric	400	1,596	120
Hu (12)	2014	China	Gastric	400	313	71
Hwang (13)	2012	Egypt	Gastric	400	1,593	102
Wang (14)	2012	China	Gastric	400	100	21
Kim (15)	2014	Egypt	Lung	400	199	15
Maráz (16)	2013	Hungary	Lung	400	398	86
Tomita (17)	2007	Japan	Lung	400	244	14
Pedersen (18)	1996	Denmark	Lung	400	1,115	357
Venkatramani (19)	2015	India	Renal	400	320	33
Brookman-May (20)	2013	Germany	Renal	400	3,139	277
Wosnitzer (21)	2010	USA	Renal	400	958	91
Suppiah (22)	2006	USA	Renal	400	700	175
Göğüş (23)	2004	Turkey	Renal	400	151	21
Inoue (24)	2004	Japan	Renal	400	196	16
Symbas (25)	2000	USA	Renal	400	259	147
Kim (26)	2015	Egypt	Colorectal	370	314	69
Guo (27)	2014	Denmark	Colorectal	400	253	21
Lin (28)	2012	China	Colorectal	300	133	13
Cravioto-Villanueva (29)	2012	Mexico	Colorectal	350	163	13
Sasaki (30)	2012	Japan	Colorectal	370	636	77

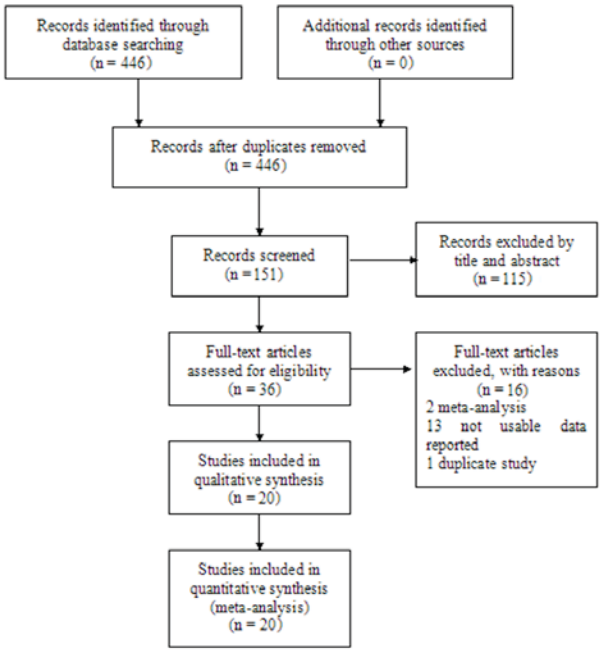

Figure 1. Flow diagram indicating the number of articles identified and selected using the criteria for inclusion and exclusion. A total of 20 studies were included in the present meta-analysis.

thrombocytosis and normal PLT count groups). The results revealed that none of these variables contributed a substantial proportion of the heterogeneity observed. Sensitivity analyses were performed following the sequential removal of each eligible study. Upon investigation of the thrombocytosis status and the 5-year overall survival rate of patients, the results suggested that the significance of the pooled ORs was not influenced by any individual study.

Table II. Stratified analyses of the association between thrombocytosis and 5-year overall survival and TNM stage.

	5-year overall survival				TNM stage			
Variables	Thrombocytosis cases/total	OR (95% CI)	P-value	I^2 (%)	Thrombocytosis cases/total	OR (95% CI)	P-value	I^2 (%)
Cancer types								
Gastrointestinal cancer	335/3853	1.77 (1.36-2.29)	0.570	0	214/2180	1.96 (1.21-3.18)	0.166	44.3
Lung cancer	472/1956	3.21 (1.75-5.92)	0.050	61.8	458/1753	1.96 (1.23-3.12)	0.090	58.0
Renal cancer	727/5403	3.11 (2.03-4.77)	0.006	69.5	182/581	3.16 (1.20-8.32)	0.070	69.5
Ethnicities								
Asian	519/5586	3.06 (1.76-5.34)	0.001	76.5	239/2470	2.64 (1.42-4.90)	0.017	70.6
African	117/1792	1.71 (1.17-2.49)	0.400	0	-	-	-	-
European	898/3934	2.72 (1.91-3.90)	0.040	54.7	615/2044	1.89 (1.38-2.59)	0.229	30.6

-, indicates that there were no studies investigating the association between thrombocytosis and advanced TNM stage in African patients. TNM, tumor-node-metastasis; OR, odds ratio; CI, confidence interval.

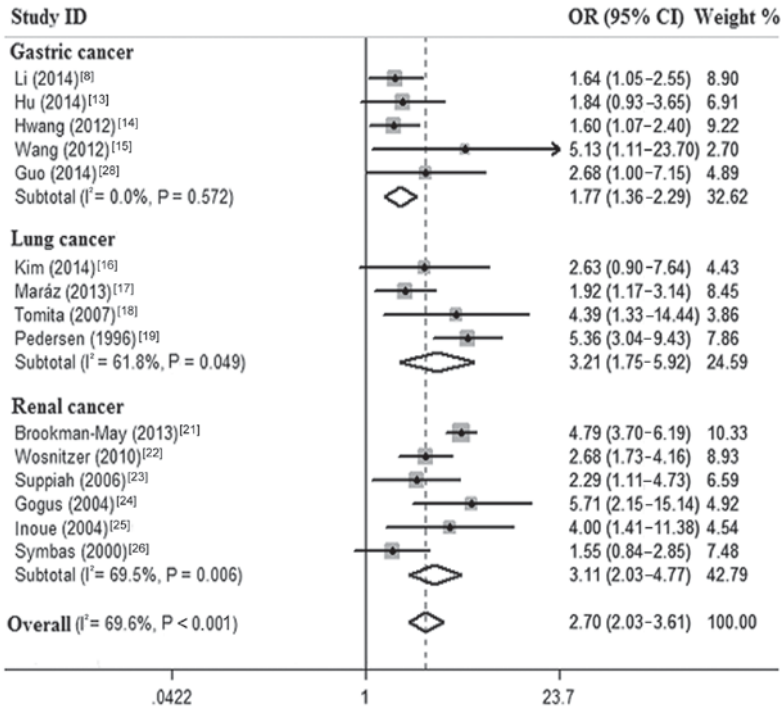

Figure 2. Forest plot of the associations between thrombocytosis and the 5-year overall survival of patients with cancer. OR, odds ratio; CI, confidence interval.

Publication bias. Begg's funnel plot and Egger's test were performed to assess publication bias. The funnel plots were not observed to indicate any marked asymmetry, which was subsequently supported by Egger's test revealing no statistical evidence of publication bias (Fig. 4).

Discussion

In the present study, thrombocytosis was defined as a PLT count of >400x10^9/l in patients with malignancies. However, only one study focusing on colorectal cancer was in accordance with this standard; therefore, studies which defined thrombocytosis as PLT counts >300x10^9 platelets/l were included. It was established that single studies alone are of limited value in predicting cancer progression (31). Therefore, the present study performed a meta-analysis, including 1,739 patients with thrombocytosis and 11,039 patients with normal PLT counts from 20 published studies, in order to investigate the association between thrombocytosis and 5-year overall survival and tumor clinicopathological features.

The results of the present meta-analysis revealed that the 5-year overall survival rate in the thrombocytosis group was significantly decreased, as compared with that of the normal PLT count group. Therefore, thrombocytosis may serve as a

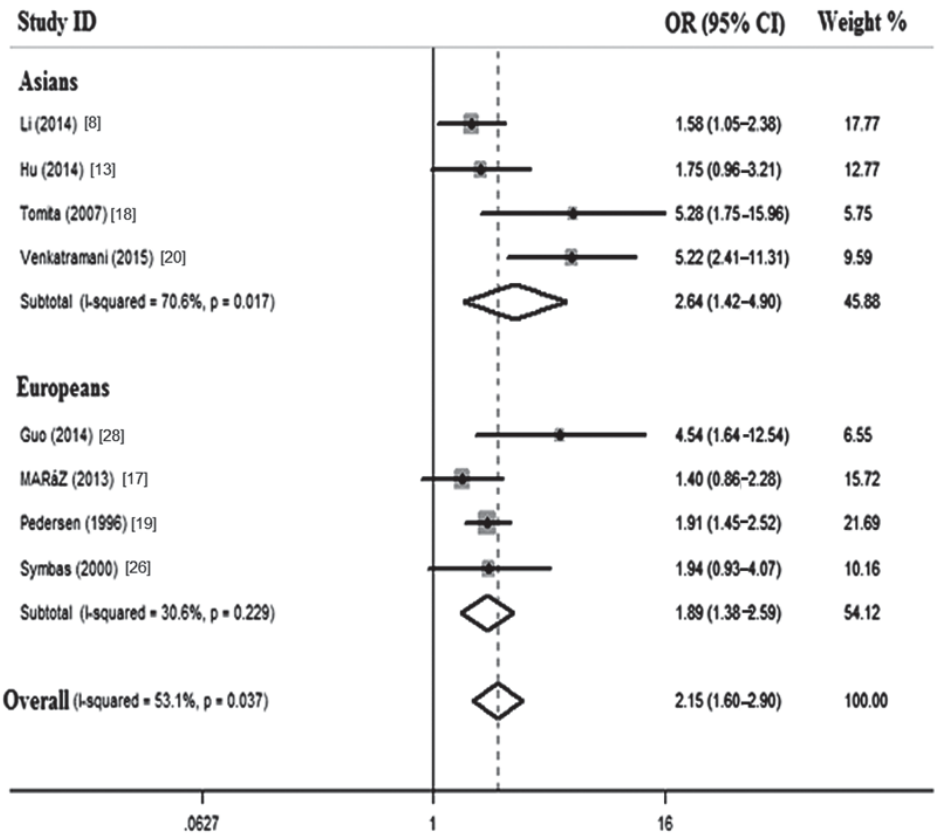

Figure 3. Forest plot of the associations between thrombocytosis and tumor-node metastasis stage of patients with cancer. OR, odds ratio; CI, confidence interval.

useful predictor of poor prognosis in patients with cancer. The present study also demonstrated that TNM stage, but not tumor differentiation, lymph node metastasis or tumor location, was an independent risk factor for thrombocytosis. In a subgroup analysis of the association between TNM and thrombocytosis, there were ≤3 studies, with limited sample sizes, for each type of cancer; therefore, the results are to be interpreted with caution. These results indicated that thrombocytosis may be important in cancer development and progression, as numerous complex molecular mechanisms underlie cancer cell-PLT interactions (32). The potential predictive value of the association between thrombocytosis and 5-year overall survival and TNM stage revealed by the present study may be advantageous for use in clinical decision-making during risk categorization in patients with cancer. In previous meta-analyses by Yu *et al* (8) and Men *et al* (33), thrombocytosis was associated with a poorer prognosis for patients with gynecological malignancies and renal cancer. Concordantly, in the present subgroup analysis, thrombocytosis exhibited an increased association with poor prognosis for gastrointestinal, lung and renal cancer. The aforementioned meta-analysis (8,33) did not investigate the association between thrombocytosis and clinicopathological

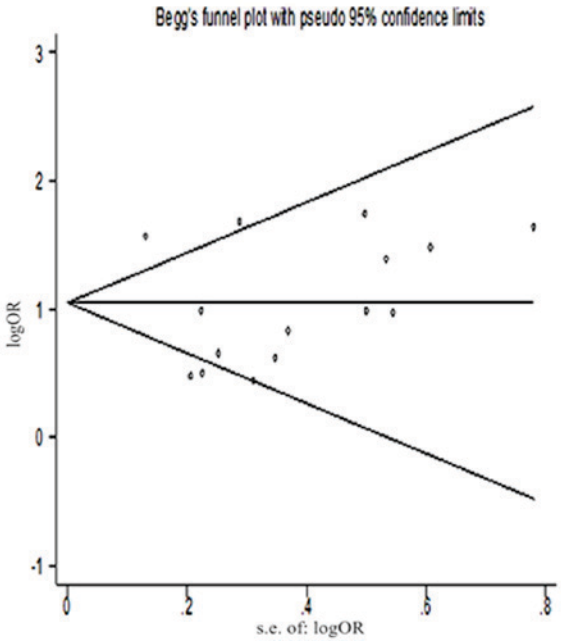

Figure 4. Funnel plots for the evaluation of potential publication bias in the impact of thrombocytosis on 5-year overall survival of patients with cancer. SE, standard error; OR, odds ratio.

features. Therefore, to the best of our knowledge, the current study is the first comprehensive meta-analysis to evaluate the association between clinicopathological features, 5-year overall survival and tumor-associated thrombocytosis in patients with cancer.

Previous studies have suggested that PLTs facilitate tumor cell survival, extravasation and angiogenesis; however, the mechanism underlying the thrombocytosis that develops in patients with malignant disease remains to be established (34,35). A number of mechanisms underlying tumor-induced PLT activation and PLT-induced cancer progression have been reported (36,37). Tumor-associated humoral factors, including interleukins 2 and 6, tumor growth factors (primarily vascular endothelial growth factor) and granulocyte colony-stimulating factor may have a role in promoting megakaryocyte growth and activating the coagulation cascade, resulting in activated PLT production (36). Tumor cell-induced PLT aggregation mediates the adhesion of PLTs to tumor cells and leukocytes, resulting in the formation of heteroaggregates, which enables the adhesion of cancer cells to the vascular endothelium and functions as physiological barrier, protecting tumor cells from the host immune system (38,39).

The present study possessed certain limitations. The results of the meta-analysis were based on unadjusted estimates, and a more precise analysis is required in order to provide an adjusted estimate by age and gender, in cases where detailed individual data is available. The number of published studies was not sufficiently large, limiting the statistical power of the present study, particularly for any given cancer site. Despite these limitations, the current meta-analysis also had certain advantages. To the best of our knowledge, the present study is the first meta-analysis to assess the association between thrombocytosis and the prognosis and clinicopathological characteristics of patients with cancer. Additionally, the quality of studies included in the current meta-analysis was satisfactory and met the set inclusion criteria.

In conclusion, the results of the present meta-analysis suggested that thrombocytosis was associated with poor survival and advanced TNM stage, particularly for gastric cancer, as well as lung and renal cancer. Further studies with larger sample sizes and including additional types of cancer are required to investigate these findings.

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