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META-ANALYSIS

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Prognostic Value and Clinicopathologic Features of Platelet Distribution Width in Cancer: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The association between platelet distribution width (PDW) and cancer has been evaluated by a few studies, but the influence of PDW on cancer prognosis is unclear. Therefore, we conducted the present meta-analysis.

Material/Methods: We identified relevant research using identical search strategies. The influence of PDW level on cancer prognosis, as well as clinical characteristics, was analyzed.

Results: A total of 11 studies comprising 2625 cancer patients were included in our meta-analysis. The results suggested that high PDW level was obviously related to poor OS (HR=1.54, 95%CI 1.18–2.00), especially for breast cancer (HR=1.21, 95%CI 1.07–1.36) and pharyngolaryngeal cancer (HR=3.06, 95%CI 1.68–5.57). Furthermore, high PDW was obviously related to poor OS both in older and younger subgroups, with combined HR estimates of 1.58 (95%CI 1.15–2.16) and 1.64 (95%CI 1.19–2.26), respectively. High PDW level was notably related to poor OS in the cut-off value ≥16% subgroup (HR=1.84, 95%CI 1.01–3.40). Moreover, high PDW level was obviously associated with lymph node metastasis (OR=1.43, 95%CI 1.04–1.99).

Conclusions: The findings of this study suggest that PDW is an effective and convenient indicator of cancer prognosis. Furthermore, high PDW level is obviously associated with lymph node metastasis.

MeSH Keywords: **Blood Platelets • Meta-Analysis • Prognosis**

Abbreviations: **PDW** – platelet distribution width; **HR** – hazard ratio; **OR** – odds ratio; **CI** – confidence interval; **PAR** – protease activated receptor; **MMP** – matrix metalloproteinase; **VEGF** – vascular endothelial growth factor; **PDGF** – platelet-derived growth factor; **NOS** – Newcastle-Ottawa quality assessment scale

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Background

Cancer is one of the major causes of morbidity and mortality in the world [1]. Although drug treatments and surgical methods develop rapidly, the survival of most tumors is still disappointing [1]. Therefore, it is of great importance to find effective and convenient indicators for predicting prognosis of cancer [2].

Platelets play an important role in cancer progression and metastases [3]. The interactions between platelets and cancer cells lead to tumor growth, abnormal angiogenesis, and tumor metastasis [4,5]. It is speculated that tumor cells can escape from shear-induced damage by binding with platelets, which facilitates tumor colonization [6]. Platelet distribution width (PDW) a platelet index indicating variation in platelet size [7]. In addition, PDW has been reported to be a marker of platelet morphology and activation [7]. The relationship between PDW level and prognosis of cancer is not clear. Recently, several studies have reported that high PDW level was associated with unfavorable prognosis for various types of tumors, including breast cancer, colorectal cancer, and laryngeal cancer [8–10], but other studies found that PDW is not associated with progression of gastric cancer [11].

Therefore, we performed this meta-analysis to investigate the possible association between PDW level and overall survival of cancer patients and determine whether PDW could an effective and convenient indicator of cancer prognosis.

Material and Methods

Literature search strategies

We searched PubMed, Web of Science, and EMBASE databases for relevant articles using the keywords "Platelet distribution width", "PDW", ''cancer'', ''tumor'', and "malignancy" with all combinations. To find additional relevant studies, we also manually searched bibliographies, reviews, and a few related articles. The last update was conducted on June 30, 2018.

Selection criteria

In our meta-analysis, the inclusion criteria for choosing articles were as follows: (1) studies should evaluate the value of PDW in the blood; (2) studies should assess the relationship between PDW and prognostic value or clinical characteristics of cancer patients; (3) studies should provide abundant information for estimating HR of OS, or OR of clinical characteristics; (4) papers should be published in English.

Due to insufficient data needed to properly evaluate review articles, case reports, and conference reports, these were not included in our meta-analysis [12]. In case of duplication, we only included the most complete article when studies included the same patient population.

Data extraction

Two researchers (Wen-Jie Xia and Jiang-Feng Tu) individually checked each related article and gathered relevant information. Disagreements were arbitrated by researcher Wu-Zhen Chen. Basic information was obtained from each article, such as name of first author, publication year, patient population, cancer types, cut-off value of PDW, and HR data [2].

Quality evaluation

The Newcastle-Ottawa quality assessment scale (NOS) was utilized for assessing the quality of each study in our meta-analysis [2,13]. This scale was used to evaluate each study, with 8 items on methodology from 3 dimensions: selection, comparability, and exposure [2]. The studies with scores of 6 or higher were qualified for our meta-analysis [2]. Two investigators each evaluated all studies and scored them, and disagreements were settled by researcher Wu-Zhen Chen.

Statistical analysis

Hazard ratio (HR) with 95% confidence interval (CI) was obtained from each included study for the pooled analysis of survival: when the information on HR was given in the study, it was obtained directly; otherwise, we calculated relevant HR information with the use of data given in the papers by means described by Parmar and Jayne [2,14,15]. The influence of PDW level on cancer prognosis was estimated by the combined HR and 95%CI. The relationship between PDW level and clinical parameters, such as age, sex, differentiation, and lymph node metastasis, was evaluated by combined odds ratio (OR) and its 95% CI. We performed this meta-analysis with the use of STATA v12.0 (Stata Corporation, Collage Station, Texas, USA). Heterogeneity in the analysis was estimated by using the chi-square-based Q statistical test and I^2 test [2,16,17]. We used a fixed-effects model when analysis did not show significant heterogeneity (I^2 value <50%) [18]; otherwise, we used a random-effects model for pooling data [19]. We used Begg's test for estimating publication bias [20], which was identified as p value of Begg's test <0.05 [21].

Results

Study selection and description

Totally 347 published studies were retrieved from databases using the information retrieval strategies described in Figure 1.

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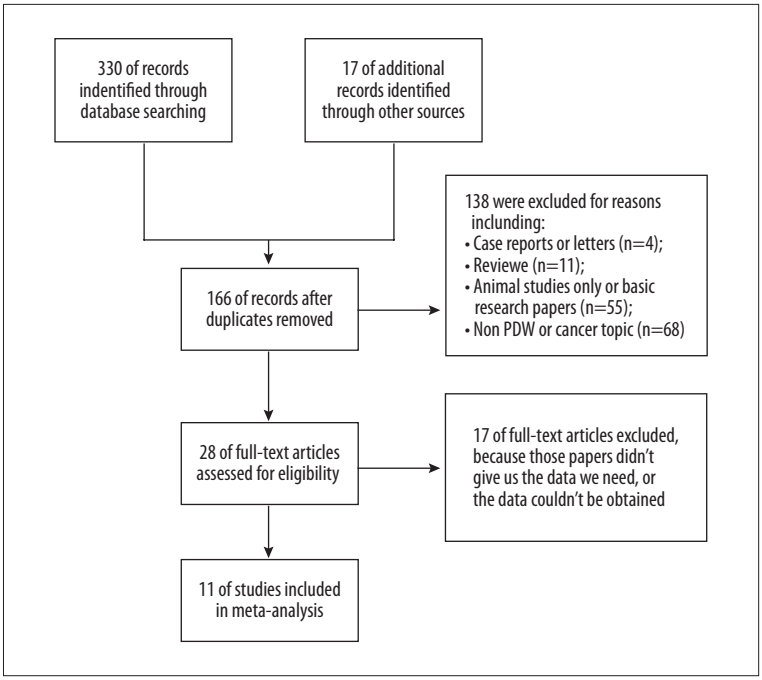

Figure 1. Flow diagram of study selection procedure.

After duplicates were removed, 166 studies in total were included in preliminary screening. We excluded 138 because they were, for instance, fundamental experimental studies, reviews, not focussed on PDW or cancer; 28 studies were checked with full text, and 17 were excluded due to insufficient data to assess the relationship between PDW and prognostic value or clinicopathologic features of cancer patients.

Finally, 11 eligible studies met our requirements and were included in our meta-analysis [8–11,22–28], and their basic characteristics are described in Table 1. In the aggregate, 2625 cancer patients were involved in the meta-analysis. The median population size was 239 (range, 168–379). Eight studies assessed patients from China and 3 studies assessed patients from Western countries. All the included studies passed methodological evaluation and were qualified for analysis.

Influence of PDW level on OS of cancer

Ten studies estimated the relationship between PDW and OS of cancer using HR data, suggesting that compared with low PDW level, high PDW level substantially raised the mortality risk of cancer patients, with a combined HR estimate of 1.54 (95%CI: 1.18–2.00, I^2=89.5%) (Figure 2). Sensitivity analysis was conducted, in which individual studies were sequentially omitted (Figure 3). The result showed no clear variation in the combined HR and the result was robust.

In addition, subgroup analysis was also performed by cancer type, study location, median age, cut-off value, and length of follow-up (Table 2). Showing significant correlations between high PDW level and poor prognosis for breast cancer (HR=1.21, 95%CI: 1.07–1.36) and pharyngolaryngeal cancer (HR=3.06, 95%CI: 1.68–5.57), but not for gastrointestinal cancer (HR=1.13, 95%CI: 0.68–1.87). High PDW was obviously related to worse OS both in older and younger subgroups, with a combined HR estimate of 1.58 (95%CI: 1.15–2.16) and 1.64 (95%CI: 1.19–2.26), respectively. Furthermore, high PDW level was notably related to worse OS in the shorter follow-up subgroup (HR=1.82, 95%CI: 1.03-3.20) and cut-off value ≥16% subgroup (HR=1.84, 95%CI: 1.01–3.40). Other subgroups did not show significant correlations between PDW and overall survival.

Relation between PDW level and clinical parameters

Six studies were included that evaluated the relationship between PDW level and clinical parameters of cancer patients. High PDW was strongly associated with lymph node metastasis (OR=1.43, 95%CI: 1.04-1.99, I^2=33%) (Table 3), suggesting PDW is an effective and convenient indicator of cancer metastasis. However, PDW was not closely associated with age (OR=0.87, 95%CI 0.67–1.13, I^2=10%), sex (OR=1.15, 95%CI: 0.87–1.52, I^2=13%), tumor differentiation (OR=1.01, 95%CI: 0.72–1.44, I^2=0%), or tumor stage (OR=1.18, 95%CI: 0.75-1.85, I^2=65%) (Table 3).

Publication bias

Begg's test indicated that after assessing the funnel plot for included studies, there was no noteworthy publication bias in this meta-analysis (Figure 4).

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Table 1. Basic characteristics of the included studies.

First author	Year	Country	Patients	Median age (year)	Cancer type	Follow up (months)	Cut-off value	HR estimation	NOS score
Hideya T	2017	US	275	64.5	Breast cancer	45	15.3%	HR for OS	7
Cheng S	2017	China	227	NA	Gastric cancer	61	11.5%	HR for OS	8
Xie X	2017	China	168	49	Nasopharyngeal carcinoma	65.2	16.3%	HR for OS	7
Zhang H	2017	China	241	57.8	Laryngeal cancer	60	16.70%	HR for OS	8
Li N	2017	China	220	56.3	Melanoma	60	17.20%	HR for OS	8
Yun ZY	2017	China	379	55.6	Gastric cancer	NA	NA	NA	6
Zhang X	2017	China	294	56	Gastric cancer	60	16.80%	HR for OS	7
Song X	2017	China	206	57	Colorectal cancer	52	17.35%	HR for OS	7
Gunaldi M	2016	Turkey	269	59.4	Gastric cancer	14.04	16.65%	HR for OS	7
Wang L	2015	China	168	61	Pancreatic adenocarcinoma	48	14.15%	HR for OS	7
Okuturlar Y	2015	Turkey	178	53.8	Breast cancer	NA	NA	HR for OS	6

HR – hazard ratio; OS – overall survival; NOS – Newcastle-Ottawa quality assessment scale; NA – not available.

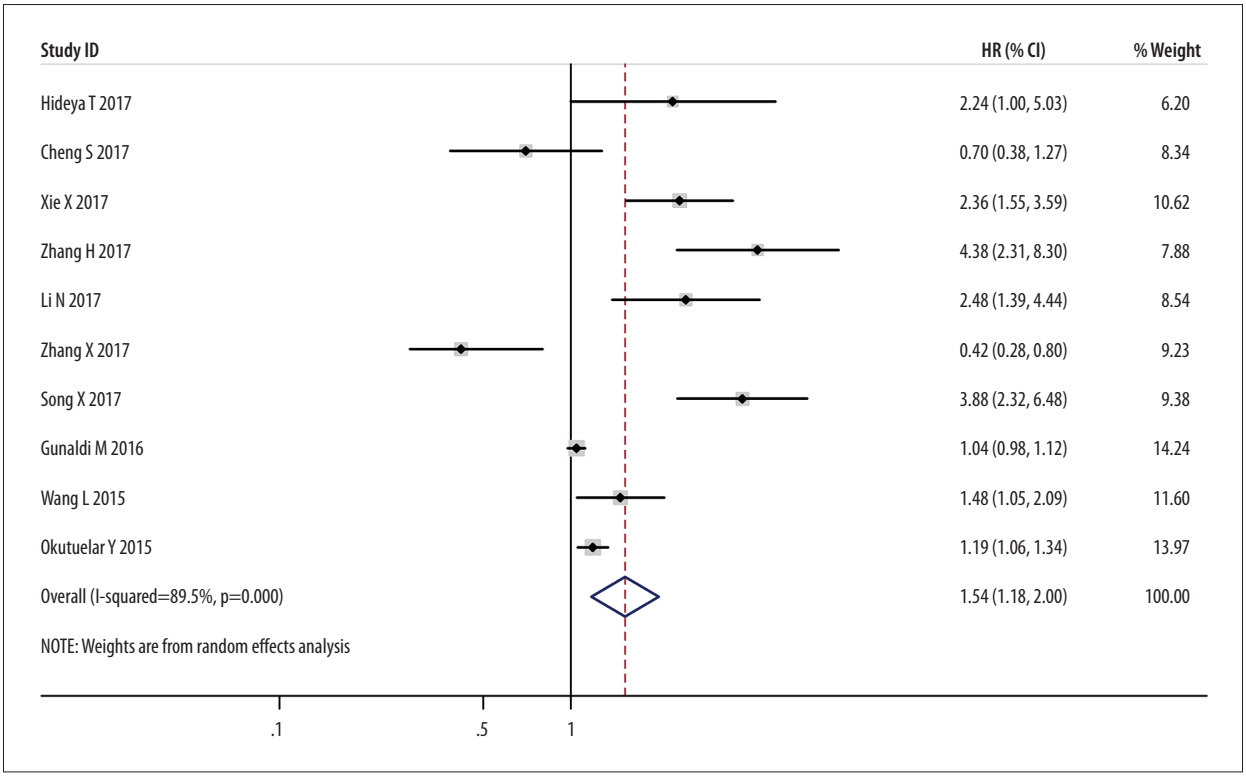

Figure 2. Forest plot of hazard ratio (HR) and 95%CI for the correlation between PDW level and overall survival (OS). HR >1 indicates worse survival for the group.

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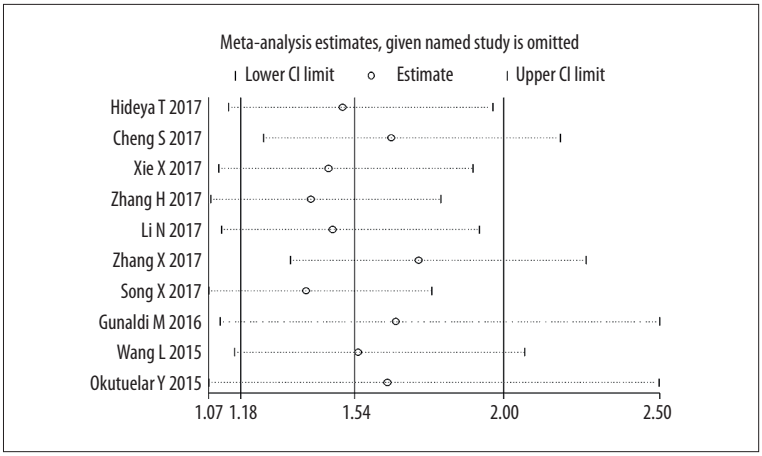

Figure 3. Forest plot of sensitivity analysis for influence of PDW level on OS with HR and 95%CI. HR >1 indicates worse survival for the group.

Table 2. Stratified analysis of pooled hazard ratios for cancer patients with PDW.

Stratified analysis	Number of studies	Number of patients	Pooled HR (95%CI)
Cancer type			
Breast cancer	2	453	1.21 (1.07–1.36)
Pharyngolaryngeal cancer	2	409	3.06 (1.68–5.57)
Gastrointestinal cancer	5	1164	1.13 (0.68–1.87)
Median age			
≥60	2	443	1.58 (1.15–2.16)
<60	7	1576	1.64 (1.19–2.26)
Follow up (months)			
≥60	5	1150	1.49 (0.65–3.43)
<60	4	918	1.82 (1.03–3.20)
Study location			
Asian	7	1524	1.71 (0.95–3.07)
Non-Asian	3	722	1.14 (0.97–1.33)
Cut-off value			
≥16%	6	1398	1.84 (1.01–3.40)
<16%	3	670	1.29 (0.72–2.31)

Table 3. Relationship between PDW level and clinicopathological features.

Clinical features	Pooled OR	Low value of 95%CI	High value of 95%CI	I square	Model used
Lymphatic metastasis	1.43	1.04	1.99	33%	Fixed effect model
Differentiation (poor *vs.* well)	1.01	0.72	1.44	0%	Fixed effect model
Sex (Male *vs.* Female)	1.15	0.87	1.52	13%	Fixed effect model
Age (older *vs.* younger)	0.87	0.67	1.13	10%	Fixed effect model
Tumor stage (T3+T4 *vs.* T1+T2)	1.18	0.75	1.85	65%	Random effect model

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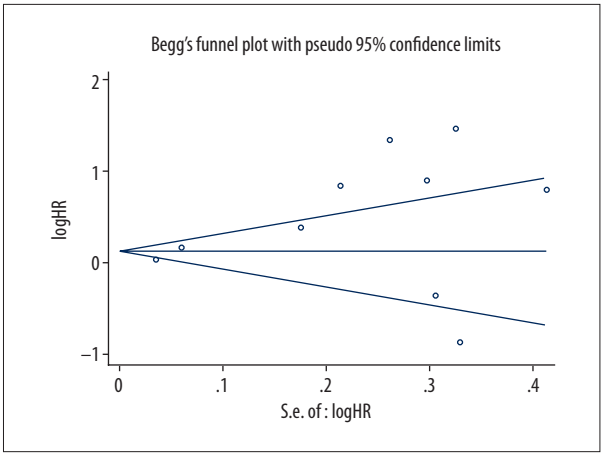

Figure 4. Begg's funnel plot indicated there was no significant publication bias for studies evaluating the impact of PDW level on OS.

Discussion

Despite rapid development of drug treatments and surgical methods, the survival of most cancers is still very poor [1]. Complicated interactions between platelets and cancer cells lead to tumor growth, abnormal angiogenesis, and metastasis [29]. Platelets are reported to play an important role in the inflammatory response, and can influence the tumor microenvironment and promote tumor growth [30,31]. Tumor cells can secrete many mediators, such as thrombin, which interact with platelet surface receptors via PAR-1, PAR-4, and P2Y12 receptors [32]. Tumor cells can also secrete matrix metalloproteinases (MMPs) and interleukin-6, which activate platelets and promote tumor growth [32–34]. In addition, it was reported that by degranulation, activated platelets can release tumor growth factors, such as vascular endothelial growth factor (VEGF), which promote tumor growth and abnormal angiogenesis [35]. Moreover, platelet-derived growth factor (PDGF) was confirmed to inhibit the cell-killing effects of NK cells [36]. Compared with platelet count, which changes rapidly, PDW was revealed to be a better indicator to reflect the characteristics of activated platelets [37]. A few researches assessed the association between PDW and cancer, but the influence of PDW on cancer prognosis was not clear.

To the best of our knowledge, the present study is the first to show the influence of PDW on cancer prognosis and the association with clinical characteristics.

In this meta-analysis, 10 studies in total estimated the relationship between PDW and OS of cancer, and 6 estimated the relationship between PDW and clinical parameters. Eventually, we found that high PDW level strongly predicts poor OS of cancer patients. The sensitive analysis suggests our results are robust**.** Thus, PDW appears to be an effective and convenient indicator of cancer prognosis. All the blood samples collected in the included studies were obtained before surgery; thus, the time of collecting blood samples was not a factor affecting the results in our analysis.

Subgroup analysis was conducted by cancer type, study location, median age, cut-off value, and follow-up. High PDW level was obviously related to worse OS for breast cancer and pharyngolaryngeal cancer, suggesting PDW has a better prognostic value in these tumors. Furthermore, high PDW was notably related to poor OS both in older and younger subgroups, indicating PDW could be an efficient predictor of prognosis, regardless of patient age. High PDW seemed to be related to unfavorable OS in the cut-off value ≥16% subgroup, suggesting PDW has a better prognostic value with cut-off values in this range. Moreover, significant correlations were found between PDW level and lymph node metastasis, suggesting PDW is an effective and convenient indicator of cancer metastasis.

There were a few limitations in our study. First of all, the patient populations of the included studies were undersized, and we could not evaluate the prognostic value of PDW in each cancer separately, mainly because some studies only provided average level of PDW, which we could not use, rather than assessing it as high or low. Second, the cut-off values in the included studies were various, which could lead to heterogeneity between studies. Subgroup analysis showed PDW might have a better prognostic value with cut-off value ≥16%.

Conclusions

High PDW level was obviously related to poor OS, especially for breast cancer and pharyngolaryngeal cancer, and high PDW was strongly associated with poor OS in the older and younger subgroups. Furthermore, high PDW was notably related to poor OS in the cut-off value ≥16% subgroup, and high PDW was obviously associated with lymph node metastasis. Therefore, the results of our meta-analysis suggest PDW is an effective and convenient indicator of cancer prognosis and lymph node metastasis.

Conflicts of interest

None.

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