

Review Article

The preoperative platelet-to-lymphocyte ratio predicts clinical outcomes in patients with gastrointestinal stromal tumors: a meta-analysis

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Abstract: Background: The platelet-to-lymphocyte ratio (PLR) can predict clinical outcomes in multiple malignancies. The aim of this study was to assess the prognostic value of the PLR in gastrointestinal stromal tumors (GISTs). Methods: We searched MEDLINE, EMBASE and Cochrane databases to identify studies evaluating the prognostic significance of the preoperative PLR in GISTs. The end points were disease-free survival (DFS), recurrence-free survival (RFS), and clinicopathological parameters. Pooled hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed-effects/random-effects models. Results: A total of six studies comprising 1,735 patients with GISTs were included. The pooled analysis demonstrated that patients with elevated PLR had shorter DFS/RFS (HR: 1.46, 95% CI: 1.07-2.00, $p = 0.017$). The negative prognostic impact of high PLR on DFS/RFS outcome remained substantial in patients who received surgery, patients with $PLR \geq 150$, and studies with NOS score ≥ 7 . In addition, a high PLR was significantly related to the tumor size (> 5 cm), the mitotic index ($> 5/50$ HPF), and the NIH risk category (high/intermediate). Conclusions: Elevated preoperative PLR could be an unfavorable prognostic factor for clinical outcomes in patients with GIST.

Keywords: Platelet-to-lymphocyte ratio (PLR), gastrointestinal stromal tumors, biomarker, prognosis, meta-analysis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and represent approximately 0.1-3% of all GI malignancies [1]. They can occur anywhere along the alimentary tract, most commonly in the stomach with a frequency of about 60-70% [2]. GISTs are considered to arise from the interstitial cells of Cajal (ICC) or the pacemaker cells of the GI tract [3] and are the result of activating mutations in the KIT (CD117) proto-oncogene [4, 5]. According to the NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines, radical resection with negative microscopic margins (R0) is the most effective therapy for a primary localized GIST [6, 7]. Nevertheless, the postoperative recurrence rate for patients with localized GISTs can be high at 50% [8, 9]. Presently, many tumor-specific parameters such as size,

location, mitotic index, nuclear pleomorphism, and tumor necrosis have been identified as prognostic factors for GISTs [10-14]. However, only tumor size and mitotic index are the most widely used factors to predict the malignant potential of GISTs [15, 16].

Host inflammatory responses can largely influence tumor development and progression [17]. Several inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have been identified as prognostic indicators in a wide variety of solid tumors [18-21]. These tests are simple and inexpensive to perform, and they are readily available in daily oncological practice. PLR is a readily available, routinely measured, and inexpensive inflammatory biomarker, which can be easily applied into daily oncologic practice. Moreover, a high preoperative PLR, which also reflects the degree of systemic inflammation,

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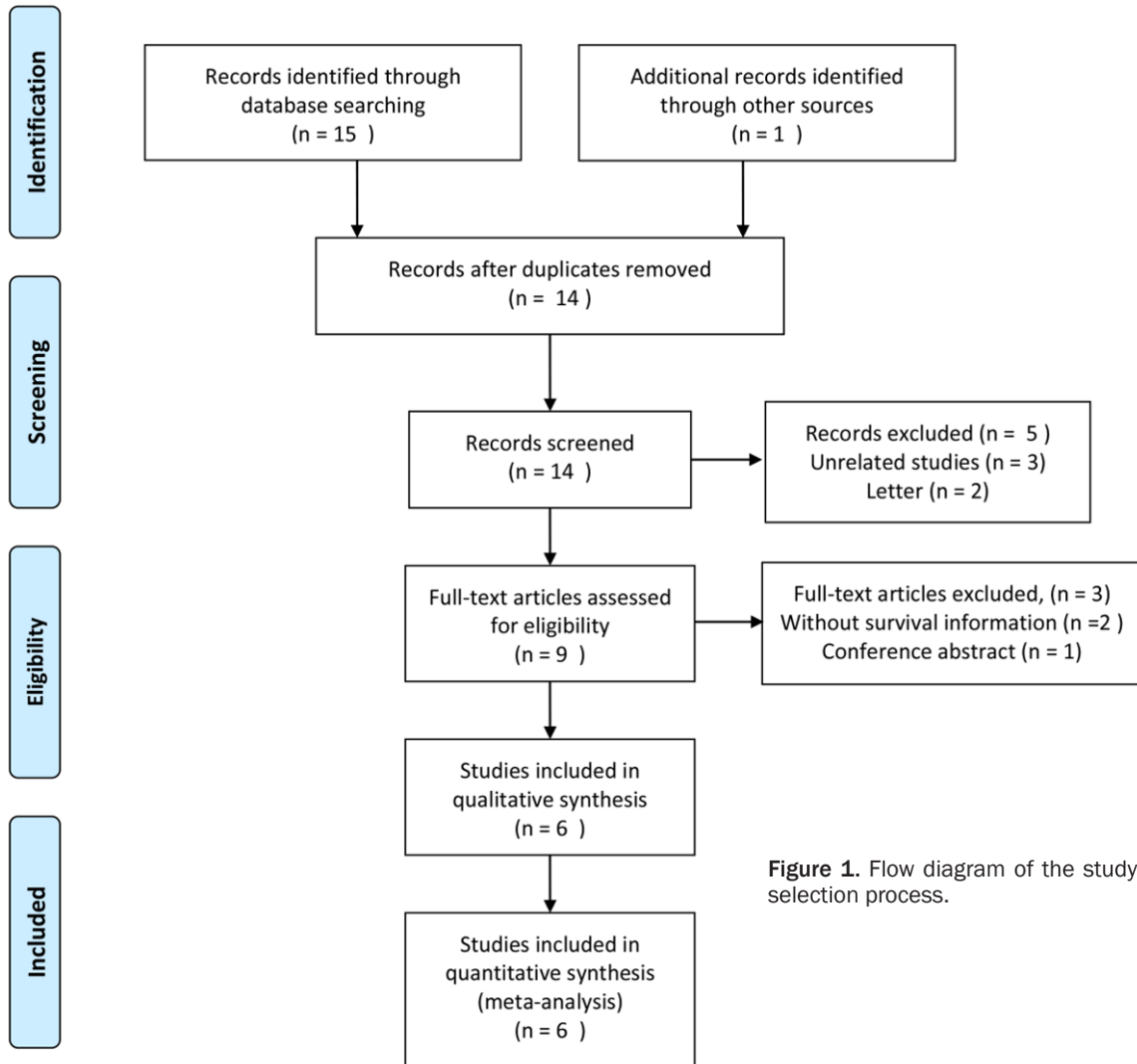


Figure 1. Flow diagram of the study selection process.

has been found to be linked to the prognosis in patients with a GIST [22, 23]. However, some studies failed to find the correlation between PLR and prognosis patients with a GIST [24, 25]. We therefore conducted a meta-analysis to assess the prognostic effect of preoperative PLR as well as associations between PLR and the clinicopathological features of patients with GISTs.

Materials and methods

Search strategies

A systematic literature search was performed using MEDLINE, EMBASE, and Cochrane databases from inception until March 2017. Search terms included “gastrointestinal stromal tumors” or “GIST”, “platelet lymphocyte ratio” or

“PLR”, “survival” or “prognostic” or “prognosis” or “recurrence” or “clinical outcome”. The bibliographies cited in selected articles were also examined to identify other relevant studies.

Study selection

The criteria for inclusion were as follows: (1) a GIST was pathologically confirmed; (2) studies assessed the prognostic value of preoperative PLR on OS, DFS/RFS, or CSS; (3) the cut-off value of PLR was reported; (4) studies supplied sufficient information for calculating hazard ratio (HR) and 95% confidence interval (CI). The exclusion criteria were as follows: (1) letters, case-reports, conference abstracts without original data; (2) reporting insufficient data for calculating an HR and 95% CI; and (3) overlapping or duplicate data.

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

Author	Year	Area	Study design	Follow-up (months)	Treatment	No. of patients	Stage	Cut-off value	Survival analysis	HR estimate	Analysis	NOS score
Yin	2017	China	Retrospective	128	Mixed (surgery & chemotherapy)	526	Non-metastatic	200	RFS	Reported	MV	7
Goh	2016	Singapore	Retrospective	43.5 (1.0-184.0)	Surgery	266	Non-metastatic	275	RFS	Reported	MV	6
Stotz	2016	Austria	Retrospective	57.6 (3-166.8)	Mixed (surgery & chemotherapy)	149	Mixed	180	OS/RFS	Reported	MV	6
Feng	2016	China	Retrospective	31.6 (2-83)	Surgery	274	Non-metastatic	141.3	DFS	Reported	UV	8
Xue	2016	China	Retrospective	NA	Surgery	448	Non-metastatic	127	RFS	Reported	UV	6
Racz	2015	Canada	Retrospective	39.1 (0-124.25)	Surgery	72	Non-metastatic	245.2	RFS	Reported	UV	7

Abbreviations: OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival, UV: univariate; MV, multivariate; NA, not available.

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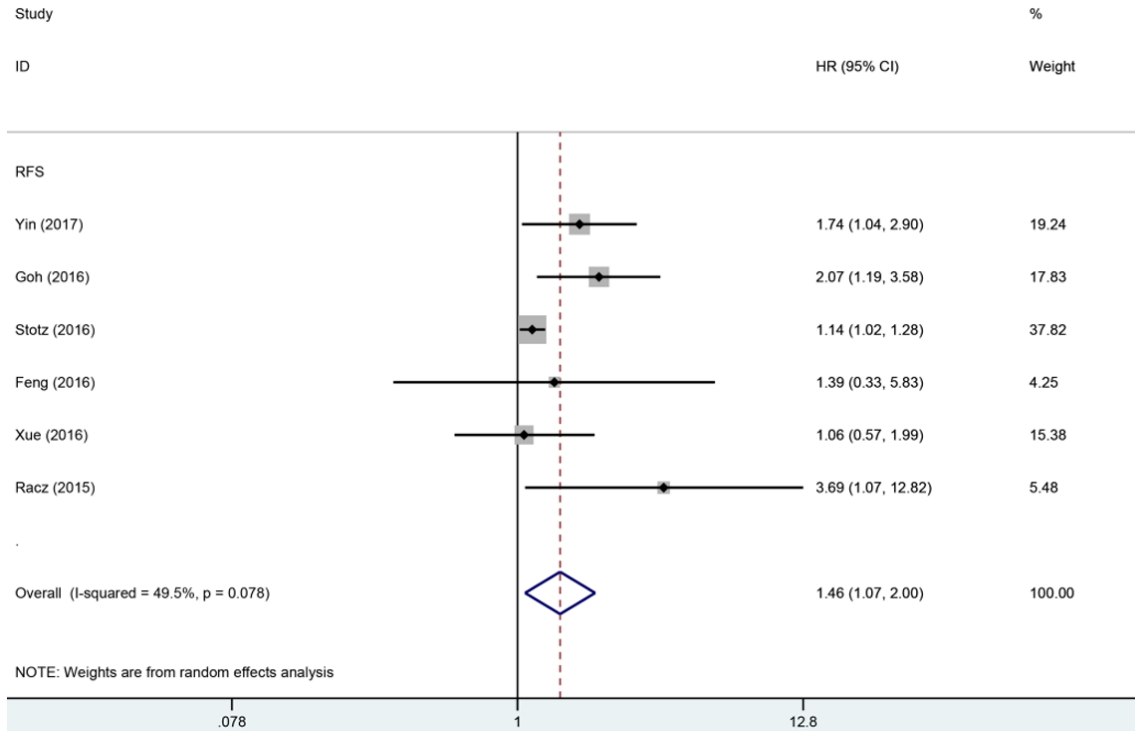


Figure 2. Forest plots for the association between PLR and DFS/RFS.

Table 2. Pooled hazard ratios (HRs) for DFS/RFS according to subgroup analyses

Subgroup	No. of studies	No. of patients	Effects model	HR (95% CI)	P value	Heterogeneity	
						I ² (%)	P _h
Overall	6	1,735	Random	1.46 (1.07-2.00)	0.017	49.5	0.08
Area							
Eastern	3	1,248	Fixed	1.42 (0.97-2.08)	0.07	0	0.48
Western	3	487	Random	1.70 (0.93-3.12)	0.09	74	0.02
Treatment							
Surgery	4	1,060	Fixed	1.66 (1.14-2.42)	0.009	30	0.23
Mixed (surgery & chemotherapy)	2	675	Random	1.30 (0.89-1.92)	0.18	60	0.12
Cut-off for PLR							
<150	2	722	Fixed	1.11 (0.63-1.96)	0.73	0	0.73
≥150	4	1,013	Random	1.65 (1.07-2.55)	0.02	69	0.02
Analysis method							
Univariate	3	749	Fixed	1.37 (0.81-2.29)	0.24	36	0.21
Multivariate	3	986	Random	1.49 (0.99-2.24)	0.05	69	0.04
NOS score							
<7	3	863	Random	1.30 (0.91-1.84)	0.15	54	0.11
≥7	3	872	Fixed	1.88 (1.20-2.95)	0.006	0	0.50

Data extraction and quality assessment

The two reviewers independently reviewed all eligible studies and extracted data. Any dis-

agreement was resolved by consensus. The following information was collected: first author's name, year of publication, study design, area of publication, number of patients, tumor stage,

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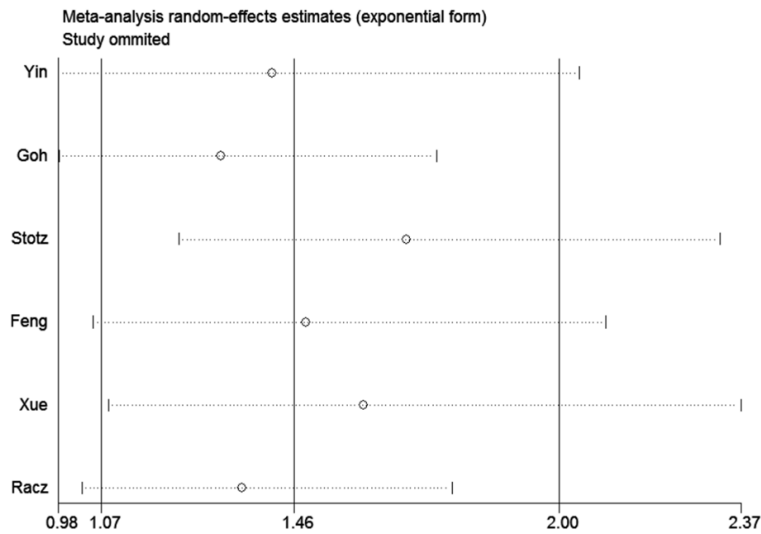


Figure 3. Sensitivity analysis of PLR on DFS/RFS in GIST patients.

survival analysis methods, cut-off values, time of follow-up, outcome measures (HRs for OS, DFS/RFS, as well as their 95% CIs), and clinicopathological features. HRs were extracted from multivariate or univariate analyses or estimated from Kaplan-Meier survival curves [26].

The study quality was assessed according to the Newcastle-Ottawa Scale (NOS) [27] by two reviewers. This scale included an assessment of subject selection, comparability of groups, and clinical outcomes. A total of nine items were extracted and each item scored 1. The maximum score is 9 and those studies with a NOS score ≥ 7 were considered as high-quality studies.

Statistical analysis

The meta-analysis was conducted by STATA 12.0 (College Station, TX, USA). Heterogeneity between studies was estimated using Cochran's Q test and Higgins' I-squared statistics [28]. The result was defined as heterogeneous when the I^2 was $> 50\%$ or the P -value was < 0.1 for the Q test. A fixed-effect model was used in the absence of significant heterogeneity, otherwise, a random-effect model was used. HRs and their 95% CIs were searched in the original articles or extrapolated using methods described by Tierney and Parmar [26, 29]. Associations between PLR and clinicopathologic features were expressed as odds ratios (ORs) and its 95% CIs. $P < 0.05$ was defined as statistically significant. Subgroup analyses

were conducted for: area of publication (Eastern, Western), treatment (surgery, chemotherapy, and mixed (surgery & chemotherapy)), analysis method (univariate, multivariate), NOS score (≥ 7 , < 7), and the cut-off value of PLR (≥ 150 , < 150). Sensitivity analyses were carried out to evaluate result stability excluding each study.

Results

Study characteristics

Our search strategy yielded 16 potentially relevant citations. Fourteen articles remained to be screened after exclusion of duplicated data. Of these, 5 were excluded through titles and abstracts, leaving 9 articles for further evaluation. Subsequently, 3 articles did not meet the inclusion criteria and were therefore excluded. As a result, 6 eligible studies, comprising a total of 1,735 patients, were included in the quantitative synthesis [22-25, 30, 31]. The selection process is shown in **Figure 1**.

All included studies were published between 2015 and 2017. Of the six studies, three studies were from China, one from Austria, one from Canada, and one from Singapore. The sample sizes ranged from 72 to 526. One study investigated the prognostic value of PLR on OS, and six studies explored the prognostic impact of PLR on DFS/RFS. The cut-off values for PLR ranged from 141.3 to 275, four studies used a PLR cut-off value ≥ 150 , while two studies used a PLR < 150 . HR and 95% CI were extracted directly from the six studies. For the methodological quality of studies, the overall NOS score ranged 6 to 8, with a median of 6.7. **Table 1** lists the detailed study characteristics.

Meta-analysis

Disease-free survival/recurrence-free survival

All included studies reported the data of PLR and DFS/RFS in GISTs. Overall, patients with elevated PLR had shorter DFS/RFS (HR: 1.46, 95% CI: 1.07-2.00, $p = 0.017$), with significant heterogeneity ($p = 0.08$, $I^2 = 49.5\%$; **Figure 2**).

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Table 3. Meta-analysis of the association between PLR and clinicopathological features of GIST

Characteristics	No. of studies	No. of patients	OR (95% CI)	p	Heterogeneity	
					I ² (%)	P _h
Gender (male vs. female)	3	667	1.29 (0.69-2.39)	0.43	65	0.06
Tumor location (stomach vs. non-stomach)	3	667	1.10 (0.25-4.91)	0.90	93	<0.001
Tumor size (> 5 cm vs. < 5 cm)	3	667	2.41 (1.71-3.41)	<0.001	27	0.26
Tumor rupture (yes vs. no)	2	574	1.68 (0.87-3.23)	0.12	0	0.56
Mitotic index, mitoses/50 HPF (> 5 vs. < 5)	3	667	2.21 (1.58-3.09)	<0.001	0	0.50
NIH risk category (high /intermediate vs. very low/low)	2	574	2.79 (1.90-4.08)	<0.001	0	0.70
Imatinib treatment (yes vs. no)	2	393	1.86 (0.99-3.50)	0.05	30	0.23

To detect potential heterogeneity, subgroup analyses were stratified by area of publication, treatment, analysis method, NOS score, and the cut-off value of PLR (**Table 2**). Exploratory subgroup analyses stratified by treatment methods, elevated PLR significantly predicted shorter DFS/RFS in patients that received surgery (HR = 1.66; 95% CI = 1.14-2.42; P = 0.009). The cut-off values ranged from 141.3 to 275. Stratified cut-off values were separated into two sub-groups: <150 and ≥150. Stratification by the cut-off value found that patients with PLR ≥150 had worse DFS/RFS (HR: 1.65, 95% CI: 1.07-2.55, p = 0.02), however, the prognostic effect disappeared in patients with PLR <150 (HR: 1.11, 95% CI: 0.63-1.96, p = 0.73). Pooled HRs for DFS/RFS were stratified by the NOS score, the negative effect of elevated PLR on DFS/RFS was observed in studies with NOS score ≥7 (HR: 1.65, 95% CI: 1.07-2.55, p = 0.02). When stratified by patients' area and analysis method, high PLR did not have a prognostic effect in all sub-groups. To assess the influence of single studies on the overall estimate, the sensitivity analysis was performed (**Figure 3**). The results showed that no study had a significant effect on the observed effect size (pooled HR), indicating the robustness of our findings.

PLR and clinicopathological features

In the meta-analysis, we identified 7 clinical factors to explore the impact of PLR on the clinical features in GIST. The pooled analysis revealed that a high PLR was significantly related to tumor size (> 5 cm vs. < 5 cm; HR = 2.41, 95% CI: 1.71-3.41, P <0.001), the mitotic index (> 5/50 HPF vs. < 5/50 HPF; HR = 2.21, 95% CI: 1.58-3.09, P <0.001), and NIH risk category (high/intermediate vs. very low/low; HR = 2.79, 95% CI: 1.90-4.08, P <0.001). Whereas no significant associations were found with gender

(male vs. female), tumor location (stomach vs. non-stomach), tumor rupture (yes vs. no) and imatinib treatment (yes vs. no). Correlation between PLR expression and clinicopathological parameters of GISTs is shown in **Table 3**.

Discussion

In the present study, we identified 6 studies involving 1,735 patients that investigated the clinical relevance and prognostic value of pre-operative PLR in patients with GIST. This meta-analysis showed that patients with elevated PLR had shorter DFS/RFS. Subgroup analyses revealed that the negative prognostic impact of high PLR on DFS/RFS remained substantial in patients who received surgery, patients with PLR ≥150, and studies with NOS score ≥7. Additionally, when we further analyzed the correlations between preoperative PLR and clinicopathologic features, we found that elevated PLR was significantly related to tumor size (> 5 cm), the mitotic index (> 5/50 HPF), and NIH risk category (high/intermediate). Therefore, preoperative PLR may serve as a promising prognostic biomarker for estimating GIST prognosis.

The actual mechanisms of the prognostic impact of PLR for a patient with a GIST are unclear. It has been suggested that cross-talk exists between the inflammatory response and tumor progression [17, 32, 33]. Platelets, as a critical sources of cytokines, binds VEGF, PDGF, FGF, and TGF-β family proteins, thus acting as a reservoir for secreted growth factors that regulate tumor angiogenesis, cell proliferation, migration, and metastasis [34-36]. Lymphocytes play critical roles in host immune response. They can inhibit the proliferative and metastatic ability of cancer cells via inducing cytotoxic cell death and cytokine production [37]. Tumor-

infiltrating lymphocytes (TILs), as representative components of the immune microenvironment, are implicated in several stages of tumor progression, and TIL phenotypes may be a predictor for favorable prognosis [38, 39]. Rusakiewicz et al. found that high densities of CD3+ tumor tissue infiltrating lymphocytes predicted progression-free survival of GISTs [40]. Conversely, low lymphocyte counts are thought to be responsible for an insufficient immunological response, which leads to inferior survival in multiple cancers [41, 42]. Taken together, PLR combined with the effects of platelet and lymphocyte may predict the prognosis for patients with GIST.

Nevertheless, our study has several limitations. First, excessive heterogeneity existed among studies. However, subgroup analyses showed that the heterogeneity diminished or disappeared in patients who received surgery and studies with NOS score ≥ 7 . Moreover, the stability of our results was confirmed by sensitivity analysis. Second, the cut-off value for PLR differed in each study. This might be significant contributors to substantial heterogeneity. Third, all included studies were retrospective, which was more susceptible to some biases.

In conclusion, our findings demonstrate that preoperative PLR could be a significant independent prognostic factor in patients with GIST.

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Disclosure of conflict of interest

None.

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