



The prognostic roles of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in gastrointestinal stromal tumours: a meta-analysis

Zhe-Wei Wei^{1,2#}, Wei-Bin Huang^{1,2#}, Dong-Jie Yang^{1,2}, Yu-Jie Yuan^{1,2}, Yu-Long He^{1,2,3}, Chang-Hua Zhang³

¹Department of Gastrointestinal Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; ²Gastric Cancer Center, Sun Yat-sen University, Guangzhou, China; ³Department of Digestive Diseases, the Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, China

Contributions: (I) Conception and design: YL He, CH Zhang; (II) Administrative support: ZW Wei, WB Huang; (III) Provision of study materials or patients: WB Huang, DJ Yang; (IV) Collection and assembly of data: DJ Yang, WB Huang; (V) Data analysis and interpretation: YJ Yuan, ZW Wei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Chang-Hua Zhang, MD, PhD. Department of Digestive Diseases, the Seventh Affiliated Hospital of Sun Yat-sen University, 628 Zhenyuan Road, Shenzhen, Guangdong 518000, China. Email: zhchangh@mail.sysu.edu.cn; Yu-Long He, MD, PhD. Gastric Cancer Center, Sun Yat-sen University, 58 Zhongshan 2nd Road, Guangzhou, Guangdong 510080, China. Email: heyulong@mail.sysu.edu.cn.

Background: The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have been found to be associated with prognosis in several solid tumours. However, the prognostic roles of PLR and NLR in gastrointestinal stromal tumours (GISTs) remain controversial. The aim of this meta-analysis was to assess the prognostic roles of PLR and NLR in GISTs.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library for relevant articles. A systematic review was performed to calculate pooled hazard ratios (HRs) for disease-free survival (DFS) and overall survival (OS) by fixed-effects/random-effects models.

Results: Fourteen studies containing 3,151 subjects were finally enrolled in this meta-analysis. Eight studies including 2,560 patients investigated the prognostic effect of PLR, and thirteen studies with 2,751 subjects explored the prognostic effect of NLR. Both elevated PLR (HR: 1.29, 95% CI: 1.10–1.52, P=0.002) and NLR (HR: 1.37, 95% CI: 1.15–1.63, P=0.0005) were significantly associated with decreased DFS. The pooled HR for PLR was not significantly different from that for NLR. High PLR and NLR correlated with increased tumour sizes, more advanced tumour stages and mitotic index (>5/50 HPF). In addition, elevated PLR was related to adjuvant tyrosine kinase inhibitor (TKI) therapy.

Conclusions: Elevated preoperative PLR and NLR are associated with poor outcomes in patients with GISTs.

Keywords: Gastrointestinal stromal tumours (GISTs); platelet-to-lymphocyte ratio (PLR); neutrophil-to-lymphocyte ratio (NLR); prognosis; meta-analysis

Submitted Feb 14, 2020. Accepted for publication Aug 05, 2020.

doi: 10.21037/tcr-20-1037

View this article at: <http://dx.doi.org/10.21037/tcr-20-1037>

Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract and account for approximately 0.2% of all GI

malignancies (1). They are deemed to arise from the interstitial cells of Cajal (ICC) and are composed of predominantly spindle or epithelioid cells (2,3). GISTs are found primarily in the stomach (60–70%) and the small intestine (30%) but may also occur in the colon, rectum,

and oesophagus (4). The tumorigenesis and progression of GISTs are partially attributed to gain-of-function mutations in the KIT proto-oncogene or platelet-derived growth factor receptor alpha (PDGFR α) gene, which serve as therapeutic targets for targeted therapy (5). R0 resection is the first treatment option for localized GISTs (6-9). However, some patients still develop recurrent disease even after R0 resection (10). It is critical to identify factors that predict the treatment response and survival of GIST patients.

Presently, most of the well-established prognostic factors of GISTs rely heavily on the results of tissue biopsy, including the mitotic index, tumour size, location of the primary tumour and tumour rupture (11,12). However, there is a gap between estimated recurrence rates by risk-stratification models and the exact recurrence rates (13). Therefore, it is critical to develop novel criteria or supplement the current stratification systems with new parameters.

Over the past decade, it has been elucidated that systemic inflammation could promote tumour metastasis by inducing angiogenesis or inhibiting apoptosis (14,15). Inflammation-based biomarkers, such as the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), have been demonstrated to be independent prognostic factors in several types of tumours (16-19). Recently, several studies have been performed to assess the prognostic value of PLR and NLR in GISTs. One meta-analysis suggested that NLR is an independent prognostic factor in patients with GISTs (20). Based on their results, the prognostic effects of PLR and NLR in GISTs remain inconsistent. Therefore, we performed this systematic analysis to assess the prognostic effects of PLR and NLR in GISTs. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-1037>).

Methods

Search strategy

We performed a comprehensive search in MEDLINE, EMBASE and the Cochrane Library. The protocol for this systematic review was registered on PROSPERO (ID: CRD42020168505) and is available in full on the University of York website. The following terms were searched: “gastrointestinal stromal tumors” or “GISTs”, “PLR” (or “platelet-lymphocyte ratio”) or “NLR” (or “neutrophil-lymphocyte ratio”), “survival” or “prognostic”

or “prognosis” or “recurrence” or “clinical outcome” (Figure 1).

Study selection

The inclusion criteria included the following: (I) all patients had been diagnosed with GIST by pathological examination; (II) the association between PLR and overall survival (OS) and/or disease-free survival (DFS)/recurrence-free survival (RFS) or between NLR and OS and/or DFS/RFS was evaluated; and (III) all blood samples were obtained before treatment. The following types of studies were excluded: (I) case reports, reviews, conference abstracts and letters; (II) studies with insufficient data to calculate an HR and 95% CI; and (III) overlapping or duplicate publications. If multiple studies were reported by the same team from the same institute or were performed at the same time, only the latest article was included.

Data extraction

Data were reviewed and extracted independently by two authors (ZW Wei and WB Huang). The following information was recorded from each study: first author, study design, year of publication, country, number of subjects, NIH risk categories, PLR and NLR cut-off values, time of follow-up, outcome measures (HRs for OS and DFS/RFS and their 95% CIs), and clinicopathological characteristics. Hazard ratios were provided by the original studies or could be estimated from Kaplan-Meier survival curves (21).

Quality assessment

Study quality assessment was performed independently by two investigators according to the Newcastle-Ottawa Scale (NOS) (22). The range of total scores was from 0 to 9. High-quality trials scored more than 6.

Statistical analysis

The log HR and standard error (SE) were used to pool the survival results (21,23). Cochran's Q test and the I^2 statistic were used to evaluate the heterogeneity of the pooled outcomes. A P value <0.1 for the Q-test or I^2 >50% suggested significant heterogeneity among the included studies, and a random-effects model was used. A fixed-effects model was used to estimate the effect

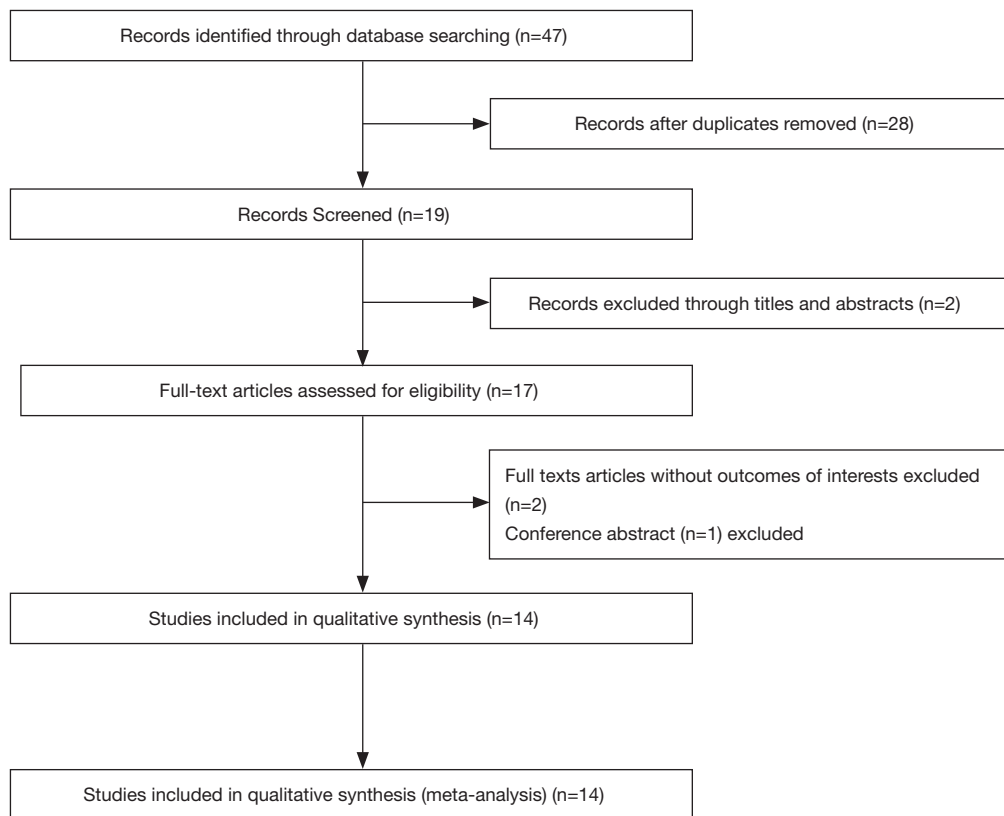


Figure 1 Systematic search and selection strategy.

magnitude when inter-study heterogeneity was absent. Subgroup analyses were performed according to the area of publication, sample size, treatment, analysis method, cut-off value of PLR and NOS score. Publication bias was analysed by assessing the symmetry of the funnel plot and performing Egger's test. The effect of potentially unpublished studies was investigated using the trim and fill procedure. Statistical analysis was performed with Review Manager Version 5.2 (Nordic Cochrane Centre, the Cochrane Collaboration), Stata version 14 and the R software environment.

Results

Description of studies

The initial search strategy identified 47 articles, and 28 articles were excluded after removing duplicate articles (Figure 1). Fourteen studies published between 2013 and 2019 including 3151 GIST patients were enrolled in this meta-analysis (Table 1) (13,24-36). Eight studies assessed the prognostic impact of both PLR and NLR, and five of the

enrolled studies investigated only NLR.

The number of subjects in each study varied from 67 to 510. Seven studies were from China, 2 were from Poland, 1 was from Singapore, 1 was from Canada, 1 was from Turkey, 1 was from the USA and 1 was from Austria. Thirteen studies determined DFS, and only 2 studies reported OS. Nine of the studies had ≥ 200 patients, and the other five had < 200 patients (Table 1).

Prognostic impact of PLR and NLR

A total of 9 studies including 2,860 patients investigated the association between PLR and DFS. Significant heterogeneity was detected among the 9 studies ($I^2=64\%$, $P=0.002$) (Figure S1A). The heterogeneity seemed to be attributed to the study by Goh *et al.* After excluding this study, the heterogeneity decreased ($P=0.38$, $I^2=7\%$), and DFS was still significantly worse for the high PLR group than for the low PLR group, with a pooled HR of 1.29 (95% CI: 1.10–1.52, $P=0.002$; Figure 2A).

Twelve studies reported the impact of NLR on DFS/RFS

Table 1 The characteristics of the studies included in this study

Author	Year	Country	Study type	Follow-up [months]	Treatment	Sample size	Stage	Models	Cutoff value	Outcome	Analysis	HRs	NOS score
Perez <i>et al.</i>	2013	USA	R	27 [6–59]	Surg ± TKIT	335	Non-metastasis	NLR	NLR: 2.7	RFS	UV	Reported	6
Atila <i>et al.</i>	2014	Turkey	R	49 [1–110]	Surg	67	Non-metastasis	NLR	NLR: 1.92	DFS	UV	Reported	8
Jiang <i>et al.</i>	2016	China	R	NA	Surg ± TKIT	129	Non-metastasis	NLR	NLR: 2.07	OS	MV	Reported	6
Xue <i>et al.</i>	2017	China	R	NA	Surg ± TKIT	510	Non-metastasis	PLR & NLR	PLR: 127; NLR: 2.0	RFS	MV	Reported	6
Racz <i>et al.</i>	2015	Canada	R	39.1 [0–124.25]	Surg ± TKIT	93	Non-metastasis	PLR & NLR	PLR:245; NLR: 2.04	RFS	UV	Reported	7
Goh <i>et al.</i>	2016	Singapore	R	43.5 [1.0–184.0]	Surg ± TKIT	300	Non-metastasis	PLR & NLR	PLR:275; NLR: 3.0	RFS	MV	Reported	6
Feng <i>et al.</i>	2016	China	R	31.6 [2–83]	Surg	274	Non-metastasis	PLR & NLR	PLR:141.29; NLR: 2.24	DFS	UV	Reported	8
Yin <i>et al.</i>	2017	China	R	44 [16–134]	Surg ± TKIT	400	Non-metastasis	PLR	PLR:153.075	RFS	MV	Reported	7
Yin <i>et al.</i> [2]	2017	China	R	NA	Surg ± TKIT	363	Non-metastasis	PLR & NLR	PLR:200; NLR: 1.245	RFS	MV	Reported	7
Stotz <i>et al.</i>	2016	Austria	R	57.6 [3–166.8]	Surg ± TKIT	149	Mixed	PLR & NLR	PLR:NA; NLR: 2.7	RFS, OS	MV	Reported	6
Rutkowski <i>et al.</i>	2018	Poland	R	55	TKIT	385	Metastasis	NLR	NLR:2.7	PFS	MV	Reported	7
Sobczuk <i>et al.</i>	2019	Poland	R	70.1 [64–104.5]	TKIT	146	Metastasis	NLR	NLR:2.4	PFS	MV	Reported	7
Shi <i>et al.</i>	2019	China	R	44.3	Surg ± TKIT	340	Non-metastasis	PLR & NLR	PLR:148.6; NLR: 2.03	RFS	UV	Reported	6
Sun <i>et al.</i>	2019	China	R	NA	Surg ± TKIT	431	Non-metastasis	PLR & NLR	PLR: 203.2; NLR: 2.18	RFS	MV	Reported	7

NOS, Newcastle-Ottawa Scale; ;R, retrospective; Surg, surgery; TKIT, tyrosine kinase inhibitors therapy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; PFS, progression-free survival; UV, univariate; MV, multivariate; NA, not available.

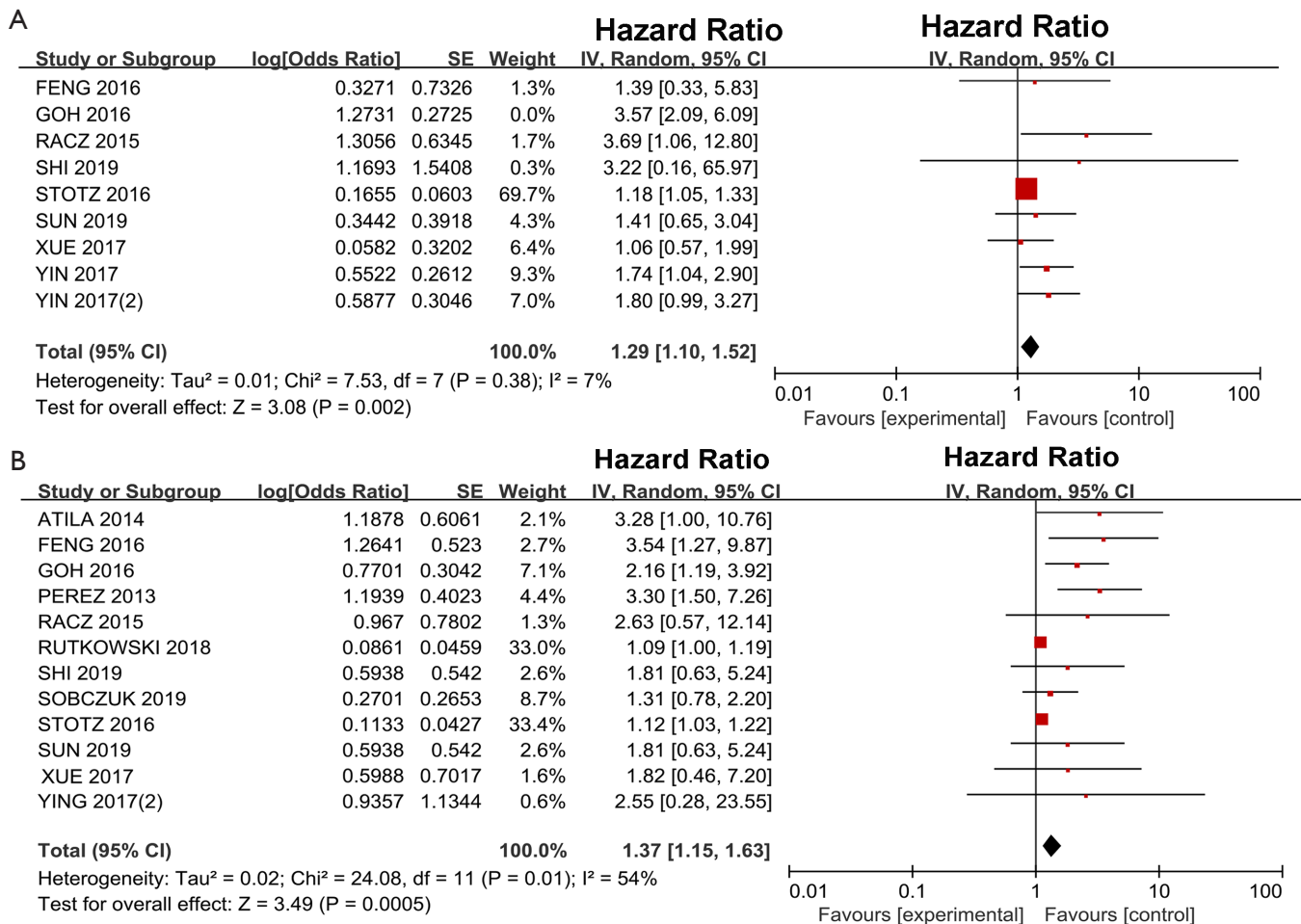


Figure 2 Forest plots of (A) platelet-to-lymphocyte ratio (PLR) and (B) neutrophil-to-lymphocyte ratio (NLR) in predicting disease-free survival.

in GISTs. As shown in *Figure 2B*, the pooled analysis of the 12 studies showed that the DFS of patients with a high NLR was significantly inferior to that of patients with a low NLR (HR =1.37, 95% CI: 1.15–1.63; P=0.0005).

In addition, only two studies with 278 patients explored the prognostic effect of NLR on OS. The OS of the high NLR group seemed worse, but the difference was not significant (HR =1.74; P=0.29) (*Figure S1B*). Only Stotz *et al.* (29) investigated the association between PLR and OS and revealed that high PLR is an unfavourable predictor of OS.

Subgroup analysis of PLR for DFS

In addition, we performed meta-regression and subgroup analyses by area, sample size, analysis method, PLR cut-off value and NOS score, as shown in *Table 2*. Elevated

PLR was correlated with poor DFS in studies performed in Eastern countries (HR =1.52, 95% CI: 1.13–2.04; P=0.006). In the subgroup analysis by sample size, a high PLR was associated with inferior DFS in studies with sample sizes ≥ 200 (HR =1.80, 95% CI: 1.27–2.57; P=0.001). The prognostic impact of high PLR was significant regardless of the analysis method (univariate or multivariate). The cut-off values of PLR ranged from 127 to 275. According to the cut-off value of PLR, studies were stratified into two subgroups: < 200 and ≥ 200 . Stratification based on the cut-off value showed that a high PLR was associated with poor DFS in studies with cut-off values ≥ 200 (HR =2.08, 95% CI: 1.04–4.15; P=0.040). Moreover, subgroup analysis suggested that elevated PLR significantly predicted decreased DFS in studies with NOS scores ≥ 7 (HR =1.76, 95% CI: 1.27–2.44; P=0.0007).

Table 2 Pooled hazard ratios (HRs) for DFS/RFS according to subgroup analyses based on the platelet-to-lymphocyte ratio (PLR)

Subgroup	No. of studies	No. of patients	Effects model	HR (95% CI)	P value	Heterogeneity	
						I ² (%)	P
Overall	9	2,860	Fixed	1.29 (1.10–1.52)	0.002	7	0.38
Area							
Eastern	7	2,618	Fixed	1.52 (1.13–2.04)	0.006	0	0.83
Western	2	242	Random	2.30 (0.91–5.81)	0.080	89	<0.001
Sample size							
≥200	7	2,618	Fixed	1.80 (1.27–2.57)	0.001	38	0.14
<200	2	242	Random	1.75 (0.60–5.07)	0.290	69	0.07
Analysis method							
Univariate	4	1,092	Fixed	1.19 (1.06–1.33)	0.003	20	0.20
Multivariate	5	1,768	Fixed	2.02 (1.41–2.91)	<0.001	32	0.20
Cut-off value of PLR							
≥200	4	1,187	Random	2.08 (1.04–4.15)	0.040	87	<0.001
<200	4	1,524	Fixed	1.44 (0.99–2.11)	0.060	0	0.64
NOS score							
≥7	5	1,561	Fixed	1.76 (1.27–2.44)	<0.001	0	0.77
<7	4	1,299	Random	1.67 (0.86–3.23)	0.130	82	0.001

NOS, Newcastle-Ottawa Scale.

Subgroup analysis of NLR for DFS

Among all the studies on NLR, 5 studies were performed in Eastern countries, and 7 studies were conducted in Western countries (Table 3). Subgroup analysis suggested that the correlations between NLR and DFS were still significant in both the Eastern countries (HR =2.22, 95% CI: 1.30–3.81; P=0.004) and Western countries (HR =1.28, 95% CI: 1.07–1.53; P=0.006) (Table 3). The results of the pooled analysis of 8 studies with sample sizes greater than 200 revealed that an elevated NLR was associated with poor survival (HR =1.96, 95% CI: 1.24–3.08; P=0.004). Concerning the analysis method, the prognostic impact of NLR on DFS was still significant according to univariate and multivariate analyses. Subgroup analyses stratified by NOS score showed that high NLR was correlated with shorter DFS regardless of NOS score.

Associations between PLR, NLR and clinicopathological features

The present meta-analysis explored the effect of PLR on 7

clinical factors previously identified in GISTs. The pooled analysis demonstrated that elevated PLR was correlated with larger tumour size (>5 vs. <5 cm; OR =2.46, 95% CI: 1.87–3.22; P<0.001), mitotic index (>5/50 HPF vs. <5/50 HPF; OR =2.09, 95% CI: 1.61–2.71; P<0.001), adjuvant tyrosine kinase inhibitor (TKI) therapy (yes vs. no; OR =5.05, 95% CI: 1.07–23.75; P=0.04), and NIH risk category (high/intermediate vs. very low/low; OR =2.72, 95% CI: 2.03–3.64; P<0.001). Meanwhile, no significant association was found for sex (male vs. female), primary tumour site (stomach vs. non-stomach) or cellular type (spindle vs. non-spindle). The correlations between PLR and the clinicopathological features of GISTs are shown in Table S1.

As shown in Table S2, the correlations between NLR and clinicopathological features were also investigated. Similarly, a high NLR can predict the prognosis of patients with GISTs larger than 5 cm (OR =1.91, 95% CI: 1.48–2.47; P<0.001) and those in the high/intermediate risk groups (OR =2.41, 95% CI: 1.49–3.89; P<0.001). Moreover, elevated NLR was correlated with male sex and mitotic index (>5/50 HPF vs. <5/50 HPF; OR =1.80; P=0.006).

Table 3 Pooled hazard ratios (HRs) for DFS/RFS according to subgroup analyse based on neutrophil-to-lymphocyte ratio (NLR)

Subgroup	No. of studies	No. of patients	Effects model	HR (95% CI)	P value	Heterogeneity	
						I ² (%)	P
Overall	12	3,393	Fixed	1.37 (1.15–1.63)	0.0005	54	0.01
Area							
Eastern	5	1,918	Fixed	2.22 (1.30–3.81)	0.004	0	0.88
Western	7	1,475	Random	1.28 (1.07–1.53)	0.006	64	0.010
Sample size							
≥200	8	2,938	Random	1.96 (1.24–3.08)	0.004	64	0.007
<200	4	455	Fixed	1.31 (0.93–1.83)	0.12	35	0.20
Analysis method							
Univariate	5	1,109	Fixed	2.92 (1.83–4.65)	<0.001	0	0.90
Multivariate	7	2,284	Fixed	1.12 (1.05–1.19)	<0.001	16	0.31
NOS score							
≥7	7	1,759	Fixed	1.61 (1.09–2.38)	0.02	46	0.08
<7	5	1,634	Random	1.80 (1.08–3.00)	0.02	68	0.01

Comparison between PLR and NLR

Presently, PLR and NLR are the two most widely available markers in GISTs (25). Seven and four studies reported the HR for PLR and NLR in univariate and multivariate analyses, respectively. The pooled HR for PLR was not significantly different from that for NLR (Table S3).

Publication bias

Funnel plots of PLR and NLR were used to evaluate publication bias, as shown in Figure 3. Then, the asymmetry of the funnel plots was further tested by Egger's test. No evidence of obvious publication bias was detected by Egger's test (P=0.072) for PLR. For NLR, significant publication bias was found by Egger's test (P<0.001). Then, a trim and fill analysis was performed to investigate the potential effect of publication bias. After incorporating 7 hypothetical studies, the funnel plots were shown to be symmetrical (Figure 4). The adjusted pooled analysis with the 7 additional studies showed that the DFS of patients with a high NLR was still worse than that of patients with a low NLR (HR =1.19, 95% CI: 1.01–1.42).

Discussion

Emerging evidence has demonstrated that inflammation-

based factors, including PLR and NLR, which are representative of the inflammatory response, are associated with worse outcomes in several malignant tumours (37). Several studies demonstrated that PLR and NLR are independent prognostic factors in GISTs, while some other studies did not find similar results. A meta-analysis performed by Luo *et al.* suggested that an elevated preoperative NLR is associated with unfavourable outcomes in patients with GISTs (20). However, the prognostic role of PLR and NLR in GISTs remains controversial. We enrolled 14 studies involving 3,151 patients that investigated the prognostic roles of PLR and NLR in patients with GISTs. This meta-analysis aimed to identify the effects of elevated PLR and NLR on prognosis in patients with GISTs.

In the present meta-analysis, we demonstrated that elevated PLR and NLR are associated with worse DFS in GISTs. Although the specific mechanism remains unclear, our results are consistent with other studies that demonstrated that PLR or NLR was predictive of poorer prognosis in multiple types of malignancies, including colorectal cancer, hepatocellular carcinoma, and oesophageal tumours (38–42). PLR and NLR indicate the levels of systematic inflammation, which play vital roles in tumour progression (43,44). Platelets can release a variety of cytokines and chemokines to promote tumour metastasis (45). Labelle *et al.* reported that platelets recruit

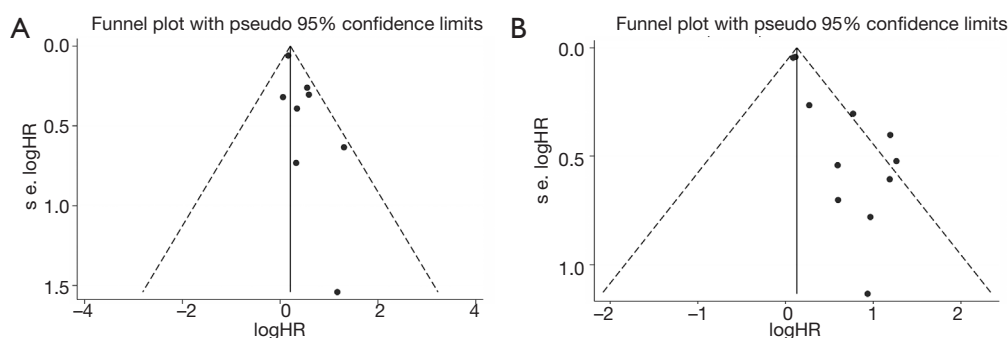


Figure 3 Funnel plots of DFS for (A) platelet-to-lymphocyte ratio (PLR) and (B) neutrophil-to-lymphocyte ratio (NLR).

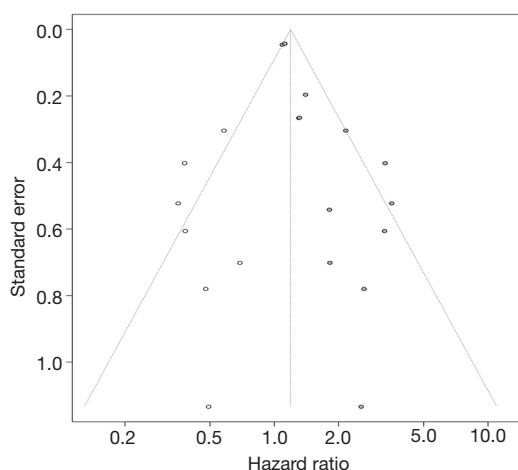


Figure 4 Funnel plots with trim-and-fill analysis for neutrophil-to-lymphocyte ratio (NLR).

granulocytes and facilitate the formation of premetastatic niches, which are critical for metastasis (46). Moreover, there is increasing evidence suggesting crosstalk between platelets and tumour cells that contributes to tumour growth and progression (47). Lymphocytopenia and the suppression of lymphocyte activity induced by the systemic inflammatory response may result in the impairment of innate cellular immunity, leading to inferior survival (48). Given their important roles, elevated PLR combined with the effects of thrombocytosis and lymphocytopenia may be associated with the prognosis of GISTs. Moreover, it is well established that neutrophils act as key regulators of tumour-associated inflammation and the immune response (49). Neutrophils, especially tumour-associated neutrophils, are recruited into the tumour microenvironment by cytokines and chemokines to regulate

inflammation, immunosuppression and tumour growth (50). Moreover, neutrophils counteract the function of immune cells to facilitate tumorigenesis via reactive oxygen species (ROS) and arginase-I (ARG) (51). Thus, NLR, as a marker of neutrophilia and lymphocytopenia, is correlated with poor prognosis in GISTs.

Subgroup analysis revealed that elevated PLR and NLR remain significant prognostic factors of DFS/RFS for GISTs in studies with sample sizes ≥ 200 . The nonsignificant associations between PLR, NLR and DFS may be due to the limited number of studies with fewer than 200 subjects. Given that the cut-off values of PLR varied among the included studies, we performed subgroup analysis to assess the effects of different cut-off values on the prognostic impact of PLR and demonstrated that patients with elevated PLR suffer worse prognosis than those with low PLR in studies with cut-off values ≥ 200 . Subgroup analysis of PLR for DFS revealed that no differences could distinctly be observed in Western countries. However, the limited sample size, with only 242 subjects from Western countries, might be responsible for this result. For NLR, significant differences were detected in both Eastern and Western countries. Moreover, elevated PLR and NLR predicted worse DFS/RFS in patients with GISTs, regardless of the analysis method.

PLR and NLR reflect the systemic inflammatory status, which is a hallmark of tumours. Yang *et al.* reported that PLR is elevated with TNM stage in colon cancers (52). Our data suggested that patients with high PLR tend to fall into the NIH high- and intermediate-risk categories. Liu *et al.* reported that elevated NLR is associated with increased tumour size in thyroid cancer (53). Consistent with the studies mentioned above, the present meta-analysis demonstrated that GISTs larger than 5 cm seem to correlate

with high PLR and NLR. The innate immune system in early-stage tumours can recognize and eliminate tumour cells, and afterwards, with the progression of tumours, tumour cells can evade immune surveillance, leading to more advanced tumours (54). Hence, high PLR and NLR, indicators of systemic inflammation, correlate with advanced tumour stages in GISTs.

For GISTs, PLR and NLR are currently the two most widely available inflammatory markers. Racz *et al.* demonstrated that only PLR but not NLR is associated with prognosis in GISTs by univariate analysis (24). Goh *et al.* concluded that both PLR and NLR are independent prognostic factors in GISTs (25). Herein, we attempted to compare the prognostic influence of PLR and NLR, and no significant difference was observed.

Nevertheless, several limitations need to be addressed in the current meta-analysis. First, significant heterogeneity existed among the studies. The difference in cutoff values may be the major reason for the heterogeneity. Second, all the included studies were retrospective, and there were no randomized controlled trials (RCTs). Given the retrospective nature of the enrolled studies, the magnitude of any confounding factors would have been further amplified, and original articles supplied only summarized but not original data, which may have increased the heterogeneity. Third, HRs and their 95% CIs were extracted from univariable analysis in five studies. Consequently, the prognostic effect of PLR and NLR might be overestimated.

Conclusions

The current meta-analysis demonstrated that elevated preoperative PLR and NLR play significant roles in the prognosis of patients with GISTs. Additionally, PLR and NLR are cost-effective markers that may serve as potential prognostic biomarkers for GISTs in clinical practice. More well-designed and high-quality multicentre clinical trials are warranted to validate the impact of PLR and NLR in risk stratifications.

Acknowledgments

Funding: This study was supported by the National Natural Science Foundation of China (81702325) and natural Science Foundation of Guangdong Province (2017A030310565).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-1037>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-1037>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Schrage Y, Hartgrink H, Smith M, et al. Surgical management of metastatic gastrointestinal stromal tumour. *Eur J Surg Oncol* 2018;44:1295-300.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors. *Gastroenterol Clin North Am* 2013;42:399-415.
- Mei L, Smith SC, Faber AC, et al. Gastrointestinal Stromal Tumors: The GIST of Precision Medicine. *Trends Cancer* 2018;4:74-91.
- De Vogelaere K, Van Loo I, Peters O, et al. Laparoscopic resection of gastric gastrointestinal stromal tumors (GIST) is safe and effective, irrespective of tumor size. *Surg Endosc* 2012;26:2339-45.
- Mei L, Du W, Idowu M, et al. Advances and Challenges on Management of Gastrointestinal Stromal Tumors. *Front Oncol* 2018;8:135.
- Koh YX, Chok AY, Zheng HL, et al. A systematic review and meta-analysis comparing laparoscopic versus open gastric resections for gastrointestinal stromal tumors of the stomach. *Ann Surg Oncol* 2013;20:3549-60.
- Goh BK, Chow PK, Kesavan SM, et al. Outcome

- after curative resection of large (>OR =10 cm) gastric gastrointestinal stromal tumors: how frequent is adjacent organ involvement and is concomitant distal pancreatectomy necessary? *J Gastrointest Surg* 2010;14:607-13.
8. Chok AY, Koh YX, Ow MY, et al. A systematic review and meta-analysis comparing pancreaticoduodenectomy versus limited resection for duodenal gastrointestinal stromal tumors. *Ann Surg Oncol* 2014;21:3429-38.
 9. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. *Gastric Cancer* 2016;19:3-14.
 10. Hølmekjær T, Hompland I, Bjerkehagen B, et al. Recurrence-Free Survival After Resection of Gastric Gastrointestinal Stromal Tumors Classified According to a Strict Definition of Tumor Rupture: A Population-Based Study. *Ann Surg Oncol* 2018;25:1133-9.
 11. Yanagimoto Y, Takahashi T, Muguruma K, et al. Re-appraisal of risk classifications for primary gastrointestinal stromal tumors (GISTs) after complete resection: indications for adjuvant therapy. *Gastric Cancer* 2015;18:426-33.
 12. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol* 2012;13:265-74.
 13. Xue A, Gao X, Fang Y, et al. Incorporation of NLR into NIH stratification system increases predictive accuracy for surgically resected gastrointestinal stromal tumors. *Acta Biochim Biophys Sin (Shanghai)* 2017;49:179-85.
 14. Shalpour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J Clin Invest* 2015;125:3347-55.
 15. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014;15:e493-503.
 16. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. *Surg Oncol* 2014;23:31-9.
 17. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol* 2009;27:3437-44.
 18. Zhou X, Du Y, Huang Z, et al. Prognostic value of PLR in various cancers: a meta-analysis. *PLoS One* 2014;9:e101119.
 19. Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106:dju124.
 20. Luo XF, Zhou LH. Prognostic significance of neutrophil to lymphocyte ratio in patients with gastrointestinal stromal tumors: A meta-analysis. *Clin Chim Acta* 2018;477:7-12.
 21. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.
 22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
 23. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
 24. Racz JM, Cleghorn MC, Jimenez MC, et al. Predictive Ability of Blood Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Gastrointestinal Stromal Tumors. *Ann Surg Oncol* 2015;22:2343-50.
 25. Goh BK, Chok AY, Allen JC Jr, et al. Blood neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are independent prognostic factors for surgically resected gastrointestinal stromal tumors. *Surgery* 2016;159:1146-56.
 26. Feng F, Tian Y, Liu S, et al. Combination of PLR, MLR, MWR, and Tumor Size Could Significantly Increase the Prognostic Value for Gastrointestinal Stromal Tumors. *Medicine (Baltimore)* 2016;95:e3248.
 27. Yin XN, Tang SM, Yin Y, et al. [Associations of Preoperative Platelet-to-lymphocyte Ratio and Derived Neutrophil-to-lymphocyte Ratio with the Prognosis of Gastrointestinal Stromal Tumor]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2017;48:239-43.
 28. Yin Z, Gao J, Liu W, et al. Clinicopathological and Prognostic Analysis of Primary Gastrointestinal Stromal Tumor Presenting with Gastrointestinal Bleeding: a 10-Year Retrospective Study. *J Gastrointest Surg* 2017;21:792-800.
 29. Stotz M, Liegl-Atzwanger B, Posch F, et al. Blood-Based Biomarkers Are Associated with Disease Recurrence and Survival in Gastrointestinal Stroma Tumor Patients after Surgical Resection. *PLoS One* 2016;11:e0159448.
 30. Shi WK, Zhang XH, Zhang J, et al. Predictive ability of prognostic nutritional index in surgically resected gastrointestinal stromal tumors: a propensity score matching analysis. *Jpn J Clin Oncol* 2019;49:823-31.
 31. Sun J, Mei Y, Zhu Q, et al. Relationship of prognostic nutritional index with prognosis of gastrointestinal stromal

- tumors. *J Cancer* 2019;10:2679-86.
32. Perez DR, Baser RE, Cavnar MJ, et al. Blood neutrophil-to-lymphocyte ratio is prognostic in gastrointestinal stromal tumor. *Ann Surg Oncol* 2013;20:593-9.
 33. Atila K, Arslan NC, Derici S, et al. Neutrophil-to-lymphocyte ratio: could it be used in the clinic as prognostic marker for gastrointestinal stromal tumor? *Hepatogastroenterology* 2014;61:1649-53.
 34. Jiang C, Hu WM, Liao FX, et al. Elevated preoperative neutrophil-to-lymphocyte ratio is associated with poor prognosis in gastrointestinal stromal tumor patients. *Oncotargets Ther* 2016;9:877-83.
 35. Sobczuk P, Teterycz P, Lugowska I, et al. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio in patients with advanced gastrointestinal stromal tumors treated with sunitinib after imatinib failure. *Oncol Lett* 2019;18:3373-80.
 36. Rutkowski P, Teterycz P, Klimczak A, et al. Blood neutrophil-to-lymphocyte ratio is associated with prognosis in advanced gastrointestinal stromal tumors treated with imatinib. *Tumori* 2018;104:415-22.
 37. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2014;23:1204-12.
 38. Yodying H, Matsuda A, Miyashita M, et al. Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis. *Ann Surg Oncol* 2016;23:646-54.
 39. Szkandera J, Pichler M, Absenger G, et al. The elevated preoperative platelet to lymphocyte ratio predicts decreased time to recurrence in colon cancer patients. *Am J Surg* 2014;208:210-4.
 40. Dell'Aquila E, Cremolini C, Zeppola T, et al. Prognostic and predictive role of neutrophil/lymphocytes ratio in metastatic colorectal cancer: a retrospective analysis of the TRIBE study by GONO. *Ann Oncol* 2018;29:924-30.
 41. Zhang Y, Brodin NP, Ohri N, et al. Association between neutrophil-lymphocyte ratio, socioeconomic status, and ethnic minority with treatment outcome in hepatocellular carcinoma. *Hepato Int* 2019;13:609-17.
 42. Ishibashi Y, Tsujimoto H, Hiraki S, et al. Prognostic Value of Preoperative Systemic Immunoinflammatory Measures in Patients with Esophageal Cancer. *Ann Surg Oncol* 2018;25:3288-99.
 43. Grinberg-Bleyer Y, Ghosh S. A Novel Link between Inflammation and Cancer. *Cancer Cell* 2016;30:829-30.
 44. Dong CH, Wang ZM, Chen SY. Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: A systematic review and meta-analysis. *Clin Biochem* 2018;52:131-6.
 45. Tesfamariam B. Involvement of platelets in tumor cell metastasis. *Pharmacol Ther* 2016;157:112-9.
 46. Labelle M, Begum S, Hynes RO. Platelets guide the formation of early metastatic niches. *Proc Natl Acad Sci U S A* 2014;111:E3053-61.
 47. Lonsdorf AS, Kramer BF, Fahrleitner M, et al. Engagement of alphaIIb beta3 (GPIIb/IIIa) with alphanubeta3 integrin mediates interaction of melanoma cells with platelets: a connection to hematogenous metastasis. *J Biol Chem* 2012;287:2168-78.
 48. Schalk E, Zeremski V, Fischer T. Impact of lymphopenia on prognosis of patients with primary central nervous system lymphoma. *Eur J Cancer* 2017;75:280-3.
 49. Masucci MT, Minopoli M, Carriero MV. Tumor Associated Neutrophils. Their Role in Tumorigenesis, Metastasis, Prognosis and Therapy. *Front Oncol* 2019;9:1146.
 50. Shaul ME, Fridlender ZG. Cancer-related circulating and tumor-associated neutrophils - subtypes, sources and function. *FEBS J* 2018;285:4316-42.
 51. Zhang X, Xu W. Neutrophils diminish T-cell immunity to foster gastric cancer progression: the role of GM-CSF/PD-L1/PD-1 signalling pathway. *Gut* 2017;66:1878-80.
 52. Yang L, He W, Kong P, et al. Clinical baseline and prognostic difference of platelet lymphocyte ratio (PLR) in right-sided and left-sided colon cancers. *BMC Cancer* 2017;17:873.
 53. Liu CL, Lee JJ, Liu TP, et al. Blood neutrophil-to-lymphocyte ratio correlates with tumor size in patients with differentiated thyroid cancer. *J Surg Oncol* 2013;107:493-7.
 54. Milette S, Fiset PO, Walsh LA, et al. The innate immune architecture of lung tumors and its implication in disease progression. *J Pathol* 2019;247:589-605.

Cite this article as: Wei ZW, Huang WB, Yang DJ, Yuan YJ, He YL, Zhang CH. The prognostic roles of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in gastrointestinal stromal tumours: a meta-analysis. *Transl Cancer Res* 2020;9(9):5128-5138. doi: 10.21037/tcr-20-1037

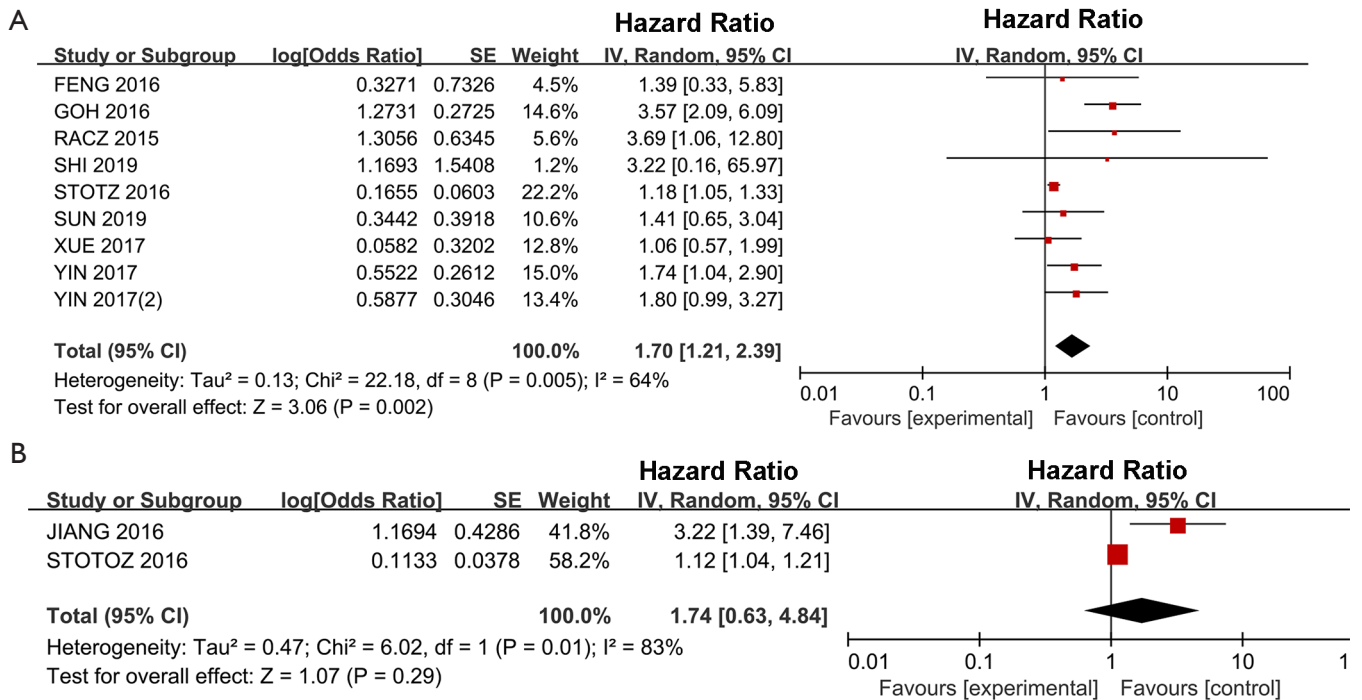


Figure S1 Forest plots of (A) platelet-to-lymphocyte ratio (PLR) in predicting DFS including the study of Goh *et al.* and (B) neutrophil-to-lymphocyte ratio (NLR) in predicting OS.

Table S1 Meta-analysis of the association between platelet-to-lymphocyte ratio (PLR) and clinicopathological features of gastrointestinal stromal tumours (GISTs)

Characteristics	No. of studies	No. of patients	OR (95% CI)	P	Heterogeneity	
					I ² (%)	P
Gender (male vs. female)	5	1,407	1.14 (0.76–1.71)	0.52	54	0.09
Tumor size (>5 vs. <5 cm)	5	1,406	2.46 (1.87–3.22)	<0.001	0	0.65
Primary tumor site (stomach vs. non-stomach)	5	1,407	0.85 (0.27–2.66)	0.78	93	<0.001
Mitotic index (>5 vs. <5)	5	1,402	2.09 (1.61–2.71)	<0.001	0	0.73
Cellular type (spindle vs. non-spindle)	1	274	0.68 (0.25–1.85)	0.45	–	–
Adjuvant TKI therapy (yes vs. no)	4	1,133	5.05 (1.07–23.75)	0.04	91	<0.001
NIH risk category (high/intermediate vs. very low/low)	4	1,314	2.72 (2.03–3.64)	<0.001	0	0.91

Mitotic index, per 50 high-power field (HPF). OR, odds ratio; TKI, tyrosine kinase inhibitors.

Table S2 Meta-analysis of the association between neutrophil-to-lymphocyte ratio (NLR) and clinicopathological features of gastrointestinal stromal tumours (GISTs)

Characteristics	No. of studies	No. of patients	OR (95% CI)	P	Heterogeneity	
					I ² (%)	P
Gender (male vs. female)	8	2,514	2.05 (1.75–2.41)	<0.001	80	<0.001
Tumor size (>5 vs. <5 cm)	7	2,074	1.91 (1.48–2.47)	<0.001	44	0.11
Primary tumor site (stomach vs. non-stomach)	9	2,452	0.82 (0.60–1.13)	0.23	68	0.002
Mitotic index (>5 vs. <5)	8	2,117	1.80 (1.18–2.74)	0.006	78	<0.001
Cellular type (spindle vs. non-spindle)	3	841	1.16 (0.74–1.81)	0.52	38	0.20
Adjuvant TKI therapy (yes vs. no)	6	1,968	1.13 (0.87–1.47)	0.28	20	0.35
NIH risk category (high/intermediate vs. very low/low)	6	1,881	2.41 (1.49–3.89)	<0.001	83	<0.001

Mitotic index, per 50 high-power field (HPF). OR, odds ratio; TKI, tyrosine kinase inhibitors.

Table S3 Comparison of relative risk of HR between platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR)

	Studies	Pooled HR for PLR (95% CI)	Pooled HR for NLR (95% CI)	Subgroup difference P
PLR vs. NLR (univariate)	7	2.568 (1.385–4.760)	2.409 (1.725–3.365)	0.858
PLR vs. NLR (multivariate)	4	1.892 (1.282–2.792)	2.307 (1.432–3.716)	0.528