ORIGINAL RESEARCH

Pretreatment hematologic markers as prognostic predictors of gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis

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Background: Systemic inflammation can be reflected by peripheral hematologic parameters and combined index like the lymphocyte count, neutrophil count, platelet count, neutrophil-to-lymphocyte (NLR), and platelet-to-lymphocyte ratio (PLR). This systematic review and meta-analysis aimed to summarize the association between the hematologic markers and prognosis of gastroenteropancreatic neuroendocrine tumors (GEP–NETs).

Methods: A computerized systematic search of PubMed, Embase, and Web of Science was conducted up to August 2016. Studies evaluating prognosis value of hematologic parameters in patients with GEP–NETs were retrieved. For meta-analysis, hazard ratios (HRs) with 95% confidence intervals (95% CIs) were extracted and synthesized using Review Manager software.

Results: We identified eight retrospective cohort studies comprising a total of 724 cases. The majority of included studies focused on pancreatic neuroendocrine tumors (PNETs). The prognostic values of NLR, PLR, and platelet count were reported in six studies, two studies, and one study, respectively. All the parameters were associated with prognostic outcomes in patients with GEP–NETs. A high NLR was significantly associated with poor prognosis in GEP–NETs (pooled HR 3.05, 95% CI 1.96–4.76, $I^2 = 0\%$, $P < 0.00001$ for overall survival (OS); pooled HR 3.30, 95% CI 2.04–5.32, $I^2 = 0\%$, $P < 0.00001$ for recurrence-free survival [RFS]). In PNETs, pooled-analyses also showed significant superiority of a low NLR on OS (pooled HR 4.21, 95% CI 1.95–9.13, $I^2 = 0\%$, $P = 0.0003$) and RFS (pooled HR 5.37, 95% CI 2.14–13.47, $I^2 = 0\%$, $P = 0.003$).

Conclusions: These findings suggest that the elevated NLR could be an adverse prognosis factor for GEP–NETs. The conclusion should be mainly limited to PNETs as the majority of included cases were PNET patients. The prognostic value of other hematologic parameters deserves further investigation. We recommend that further studies should use a continuous NLR variable and adopt a prospective and matched study design.

Keywords: neuroendocrine tumor, blood cell, lymphocyte, neutrophil, platelet, prognosis

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP–NETs) are biologically diverse neoplasms that arise from the diffuse endocrine system in the gastrointestinal tract and/or pancreas.[1] In recent decades, GEP–NETs have exhibited a significantly increased incidence,[2] and today comprise approximately 2% of all malignant gastrointestinal tumors.[3] Due to the highly heterogeneous features and unpredictable biological behaviors of GEP–NETs, discovery of markers with efficient diagnosis and/or prognosis

effect could help determine optimal clinical managements and follow-up strategies.[4–7]

The link between chronic inflammation and cancer has been established for a long time.[8,9] Numerous epidemiologic studies support a clear connection between chronic inflammation and the development of many cancers. In turn, the tumor itself can initiate and maintain inflammatory processes that foster tumor growth and development. Many inflammation-related cytokines and chemokines have been extensively documented in cancers of the stomach, liver, lung, esophagus, breast, and prostate. In addition, an important hallmark of cancer is that cancer cells evade immunological attack, and recent studies have identified that chronic inflammation is associated with immunosuppression, mediated primarily by immature myeloid-derived suppressor cells.[10–12]

Studies in the past decades have identified a close connection between GEP–NETs and chronic inflammation. It was shown that chronic inflammation can lead to hyperplasia and neoplastic transformation of enteroendocrine cells.[13–15] Additionally, single nucleotide polymorphisms of some inflammatory cytokines, such as TNF-α −1031T/C, IL-6 −174 C/G, and IL-2 −330T/G allele, have been identified to be associated with the overall susceptibility to develop GEP–NETs.[16–18] Nowadays, many typical factors of systematic inflammation, such as C-reactive protein, interleukin, some growth factors and chemokines have been validated as predictive in various types of cancer.[19–21] Recently, emerging studies have focused upon the prognosis value of hematologic parameters of systemic inflammation, including leukocyte counts, neutrophil counts, platelet counts, and the ratios between them such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) because they are cheap and easily acquired markers during clinical practice.[22–26] Hence, we aimed to conduct a systematic review and meta-analysis to evaluate the prognostic value of hematologic parameters in patients with GEP–NETs.

Methods
Study identification and selection
A systematic literature search of PubMed, Embase, and the Institute for Scientific Information (ISI) Web of Knowledge was conducted in August, 2017, by two independent reviewers (Yu Zhou & Dezhi Li) to retrieve potential relevant studies with restriction to English language. We used Mesh terms and text words to retrieve potential eligible studies with the following retrieval logic: ("neutrophil" or "lymphocyte" or "leukomonocyte" or "monocyte" or "platelet" or "thrombocyte" or "blood cell" or "blood routine" or

"hematologic" or "hematological") and ("neuroendocrine tumor" or "neuroendocrine tumour" or "neuroendocrine neoplasm" or "neoplasm cancer" or "neoplasm malignancy" or "carcinoid" or "insulinoma" or "vipoma" or "gastrinoma" or "paraganglioma"). We did not limit the search based on tumor site of gasteoenteropancreatic organs in case of missing articles. Reference lists of the retrieved articles were also searched for relevant studies. The initial selection was performed to eliminate obviously irrelevant articles, reviews, meeting abstracts, comments, letters, and basic research. We retained potentially relevant articles about hematologic parameters or GEP–NET prognostic risk factors by reviewing the titles and abstracts. Thereafter, the full-text was reviewed. Studies of patients with GEP–NETs that evaluated the effect of at least one of the hematologic parameters on prognosis were included.

Data extraction and quality assessment
The investigators (Yu Zhou & Dezhi Li) extracted information independently using a standardized data extraction table. The information about the basic characteristics of included studies and population, details of methodological characteristics, and relevant outcomes were recorded, including first author, year of publication, study period, study design, sample size, clinicopathologic characters of the study cohort, cut-off value of hematologic parameters, method of statistical analysis, and clinical outcomes. The hazard ratio (HR) was preferred for evaluating the survival outcome since it is time-to-event data. The values of HRs, 95% CIs, and *P*-values were extracted. For studies that did not provide sufficient data, the HR values were obtained by contacting the corresponding authors or were estimated by the methods described by Tierney et al.[44] The primary outcomes were cancer-specific survival (CSS) and overall survival (OS). The secondary outcomes included recurrence-free survival (RFS), distal metastasis-free survival (DMFS), local relapse-free survival (LRFS), and progression-free survival (PFS). There are no standard quality-assessment tools for prognostic studies in systematic reviews. The Newcastle-Ottawa Quality Assessment Scale (NOS) was adopted to assess the quality of each included study independently by our two investigators. NOS scores more than 6 were considered as high-quality studies. The two investigators had discussions to reach a consensus when there was any disagreement.

Statistical analysis
All the synthesis analyses were carried out using the Review Manager software (Version 5.3, The Cochrane Collaboration,

Copenhagen, Denmark). A two-tailed *P*-value < 0.05 was considered statistically significant. HRs with 95% CIs were used to evaluate the prognosis value of hematological parameters (high level vs low level). When the study reported both univariate and multivariate results, we chose multivariate analysis for final calculation. Cochran's Q test and Higgins I^2 statistic were performed for evaluating heterogeneity among studies. Studies with a $P \geq 0.1$ or $I^2 < 50\%$ were considered to have low heterogeneity and the fixed-effects model was used. Otherwise, the random-effects model was applied. A funnel plot was performed to assess publication bias.

Ethics approval

Since this was a protocol for a systematic review based upon available evidence, ethics approval was not required.

Results

Data retrieval

Figure 1 shows the flow chart for study search and selection. After searching the database of PubMed, Embase, and ISI Web of Knowledge, we finally identified 716 relevant

references, of which 226 were duplicated. After removing duplicate articles, and further screening titles and abstracts, 389 articles were excluded, including laboratory investigations, case reports, meeting abstracts, comments, letters, reviews, and other articles irrelevant to our topic. After the full-text review, a total of eight studies were ultimately included.

Characteristics of studies and data quality

Tables 1 and 2 show the characteristics of included studies. The eight eligible studies were published between 2009 and 2017, and all were retrospective analysis.[27–34] A total of 724 cases were involved, and the sample sizes of included studies ranged from 34 to 165. Five studies only enrolled PNETs patients,[27–30,34] one study only enrolled patients with gastric neuroendocrine tumors (G–NETs),[31] one study enrolled patients with gastro-entero-pancreatic neuroendocrine tumors (GEP–NETs),[32] and another study enrolled patients with neuroendocrine tumors regardless of the primary site.[33] The prognosis values of NLR were reported in six articles,[27–29,31–33] the prognosis values of PLR were reported
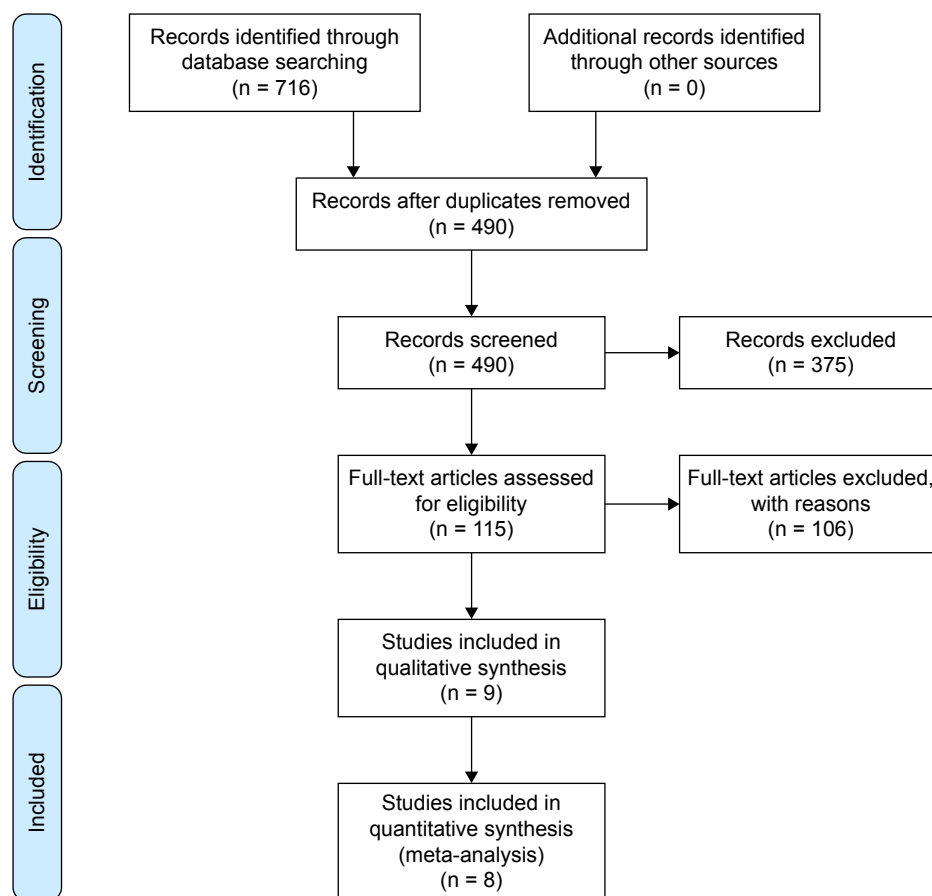

Figure 1 Literature screening flowchart.

Table 1 Basic characteristics of included studies

Author/year	Disease composition	Index	Cut-off value	Sample size	Age (years)	Gender (M/F)	Tumor size (cm)	Functioning (non/functional)	Tumor histology[§]	Treatment
Arima et al, 2017[27]	100% PNET	NLR	2.4	58	58 (17–81)[¶]	27/31	1.5 (0.5–9.0)[¶]	31/27	46/9/3 (G1/G2/G3)	100% SR
Luo et al, 2017[28]	100% PNET	NLR	2.4	165	≤ 50, 69 cases > 50, 96 cases	76/89	≤ 3.0, 50 cases > 3.0, 97 cases	147/18	63/58/15 (G1/G2/G3)	53% SR
Tong et al, 2017[29]	100% PNET	NLR	1.4	95	54.4 ± 12.1[*]	39/56	NA	74/21	52/32/11 (G1/G2/G3)	100% SR
Kaltenborn et al, 2016[30]	100% PNET	P count	228	41	55 (20–77)[¶]	22/19	NA	NA	NA	100% SR
Cao et al, 2016[31]	100% G–NET	NLR	2.2	147	≤ 70, 114 cases > 70, 33 cases	106/41	≤ 3.5, 50 > 3.5, 97	NA	20/21/36 (NET/NEC/MANEC)	100% SR
Salman et al, 2016[32]	37.9% PNET and 62.1% GE-NET	NLR PLR	2.17 181.5	132	56.7 ± 12.8[*]	72/60		NA	44/41/47 (G1/G2/G3)	100% CR
Yucel et al, 2014[33]	55.8% GEP-NET and 44.2% NET of other sites	NLR	5	52	58 (26–88)[¶] < 65, 32 cases ≥ 60, 20 cases	22/30		NA	33/19 (G1–G2/G3)	52% SR
Sakka et al, 2009[34]	100% PNET	PLR	300	34	54 (44–71)[¶] median IQR	12/22	20 (14–38) median IQR	24/10	33/1 (well/poor-differentiated)	100% SR

Notes: [§]Histologic grades of the tumors were assessed according to the World Health Organization (WHO) 2010 classification; [¶]median (range); [*]mean ± standard deviation. Functioning refers to whether the tumor is functional or not. Non refers to a non-functional neuroendocrine tumor, and functional denotes a functional neuroendocrine tumor.
Abbreviations: M/F, male/female; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; P count, platelet count; NA, not available; PNET, pancreatic neuroendocrine tumor; GEP-NET, gastroenteropancreatic neuroendocrine tumor; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; SR, surgical resection; CR, chemotherapy; IQR, interquartile range; G-NET, gastric neuroendocrine tumors; GE-NET, gastrointestinal neuroendocrine tumors.

in two articles,[34] and only one study reported the prognosis value of platelet count.[30] Most studies determined the cut-off values of the hematologic markers by using receiver operating characteristic (ROC) curves to select the most significant points. The HRs for survival outcomes were provided in seven studies.[27–31,33,34] and all of them were adjusted for potential confounders using the Cox proportion hazard model. The NOS scores of the included studies ranged from 6 to 7. The major inadequacies among the included studies were incomparability between groups.

Correlation between hematologic parameters and survival outcomes
NLR

Table 3 summarizes the results of the prognostic value of each hematologic parameter. Most studies focused on the prognosis value of NLR. The effect of NLR on OS, RFS, and LMFS was available in four studies,[27,28,31,33] four studies,[27,29,31,32] and one study,[27] respectively. All of these studies suggested that NLR was a marker for poor prognosis. Using the Cox proportional-hazard model, four studies showed patients with high NLR had poor OS,[27,28,31,33] and three studies reported that high NLR correlated with poor RFS.[27,29,31] Arima et al also specifically reported NLR was an independent predictor of postoperative liver metastasis.[27] In addition, Salman et al found that a median NLR of 2.17 accurately predicted a PFS of 11.5 months (area under the curve [AUC] 0.94, $P < 0.001$) with 98.5% sensitivity and 53.7% specificity on the ROC curve.[32] Pooled-analyses of the HRs revealed that patients with elevated NLR had both higher mortality risk and recurrence risk than those with a low NLR (pooled HR 3.05, 95% CI 1.96–4.76, $I^2 = 0\%$, $P < 0.00001$ for OS; pooled HR 3.30, 95% CI 2.04–5.32, $I^2 = 0\%$, $P < 0.00001$ for RFS).

PLR

Two studies reported the effect of PLR on prognosis.[32,34] The study conducted by Sakka et al found that decreased PLR values predicted better OS thorough the Kaplan–Meier method and survival curves.[34] Salman et al showed patients with lower PLR values had decreased median PFS time in comparison with patients with higher PLR values, and additionally they also revealed that a median PLR of 181.5 accurately predicted a PFS of 12.5 months by using the ROC analysis.[32] Because the study by Sakka et al only reported HR value, pooled-analysis was not performed.[34] The results of these two studies suggested lower PLR predicted better prognosis, but more evidence is needed.

Table 2 Methodology characters of included studies

Author/year	Index	Cut-off value	Method to determine the cut-off value	Reported survival outcomes	Methods for survival analysis	Adjusted factors	NOS score
Arima et al, 2017[27]	NLR	2.4	ROC curve	OS, RFS, LMFS	KMC, MR	Age, gender, tumor size, functioning	6
Luo et al, 2017[28]	NLR	2.4	ROC curve	OS	KMC, MR	TNM stage, histologic grade, symptom	7
Tong et al, 2017[29]	NLR	1.4	ROC curve	RFS	KMC, MR	Histologic grade, TNM stage, lymph node metastasis, tumor thrombus	7
Kaltenborn et al, 2016[30]	P count	228	ROC curve	OS	KMC, MR	Differentiation, Ki-67 index, lymph node metastasis, liver metastasis, and other distal metastasis	7
Cao et al, 2016[31]	NLR	2.2	ROC curve	OS, RFS	MR	Tumor size, depth of invasion, lymph node ratio, Ki-67	7
Salman et al, 2015[32]	NLR	2.17	Median value	PFS	ROC	–	6
	PLR	181.5	Median value	PFS	ROC		
Sakka et al, 2009[34]	PLR	300	The normal reference range of laboratory examination	OS	KMC, MR	Age, albumin, alkaline phosphatase, alanine aminotransferase	7
Yucel et al, 2013[33]	NLR	5	NA	OS	MR	Age, sex, performance status, histologic grade, primary site, surgical treatment	6

Note: Functioning refers to whether the tumor is functional or not.
Abbreviations: ROC, receiver operator characteristic; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; LMFS, liver-metastasis-free survival; KMC, Kaplan–Meier curve; MR, multivariate Cox regression analysis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; P count, platelet count; NOS, Newcastle-Ottawa Scale.

P count

Only one study reported the prognosis value of platelet count. The study by Kaltenborn et al found the OS was significantly different between patients with low platelet counts and those with high platelet counts and showed that patients with higher platelet counts had better OS.[30]

NLR in PNET

Five studies enrolled only PNET patients. Among them, two studies[27,28] provided sufficient data on OS,[27–30,34] and two studies provided sufficient data on RFS outcome for the pooled estimate.[27,29] As shown in Figure 2, the result of meta-analysis showed significant superiority of a low NLR on OS

Table 3 Reported outcomes in each study

Biomarkers	Study	OS	RFS	LMFS
NLR	Reported HRs			
	Arima, 2017[27]	5.35 (1.57–18.23)[¶]	6.01 (1.84–21.2)[¶]	7.57 (2.17–30.2)[¶]
	Cao, 2016[31]	2.334 (1.286–4.237)[¶]	2.751 (1.572–4.813)[¶]	NR
	Luo, 2017[28]	3.60 (1.33–9.71)[¶]	NR	NR
	Tong, 2017[29]	NR	4.516 (1.048–19.468)[¶]	NR
	Yucel, 2013[33]	4.4 (1.2–15.7)[¶]	NR	NR
	Reported ROC curves			
	Salman, 2015[32]	NR	A median NLR of 2.17 accurately predicted a PFS of 11.5 months (AUC 0.94, $P < 0.001$) with 98.5% sensitivity and 53.7% specificity	NR
	Pooled result of HRs			
	No of studies	4	3	1
	HR (95% CI), I^2	3.05 (1.96–4.76), 0%	3.30 (2.04–5.32), 0%	7.57 (2.17–30.2)
	P-value	$P < 0.00001$	$P < 0.00001$	$P = 0.0016$
PLR	Reported HRs			
	Sakka, 2009[34]	1.004 (1.000–1.008)	NR	NR
	Reported ROC curves			
	Salman, 2015[32]	NR	A median PLR of 181.5 accurately predicted a PFS of 12.5 months (AUC 0.94, $P < 0.001$) with 98.5% sensitivity and 63.6% specificity	NR
P count	Reported HRs			
	Kaltenborn, 2016[30]	0.985 (0.972–0.998)	NR	NR

Note: [¶]Data presented as HR (95% CI).
Abbreviations: HR, hazard ratio; ROC, receiver operator characteristic; AUC, area under the curve; OS, overall survival; RFS, recurrence-free survival; LMFS, liver-metastasis-free survival; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; P count, platelet count; NR, no report; HR, hazard ratio; CI, confidence interval.
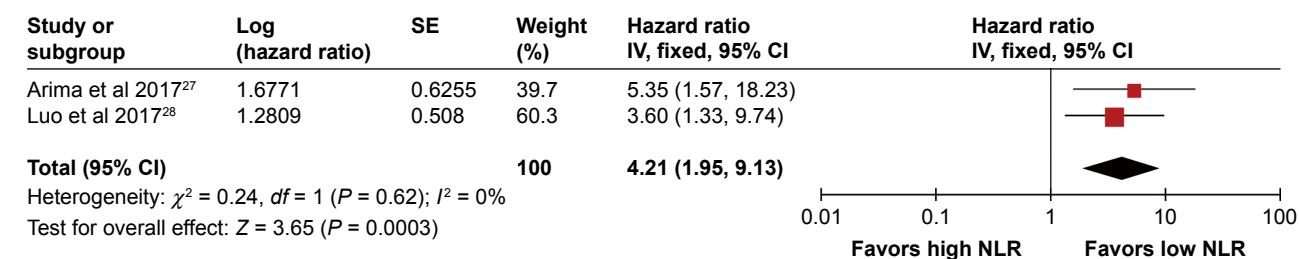
Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI	Hazard ratio IV, fixed, 95% CI
Arima et al 2017[27]	1.6771	0.6255	39.7	5.35 (1.57, 18.23)	
Luo et al 2017[28]	1.2809	0.508	60.3	3.60 (1.33, 9.74)	
Total (95% CI)			**100**	**4.21 (1.95, 9.13)**	
Heterogeneity: $\chi^2 = 0.24$, $df = 1$ ($P = 0.62$); $I^2 = 0\%$					
Test for overall effect: $Z = 3.65$ ($P = 0.0003$)					

0.01   0.1   1   10   100
Favors high NLR   Favors low NLR

Figure 2 Forest plot of HR and 95% CI for predictive effect of NLR on overall survival in patients with PNETs.
Abbreviations: HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PNETs, pancreatic neuroendocrine tumors.

(pooled HR 4.21, 95% CI 1.95–9.13, $I^2 = 0\%$, $P = 0.0003$). Meanwhile, the pooled HR for RFS also favored patients with a low NLR (pooled HR 5.37, 95% CI 2.14–13.47, $I^2 = 0\%$, $P = 0.003$) (Figure 3).

Publication bias
The funnel plot showed an unsymmetrical distribution around the vertical axis (Figure 4). However, because the number of included studies was small, the funnel plots may make little sense.

Discussion
Several hematologic parameters of systemic inflammation, such as lymphocyte counts, neutrophil counts, platelet counts, NLR, LMR, and PLR, have emerged as prognostic factors for a variety of cancer types.[35–38] Because these markers can be easily acquired from blood routine test, they are cheap and easily acquired prognostic markers with a potential for widespread clinical use, many studies have focused on the association between these markers and prognosis in kinds of cancers. GEP–NETs are a type of relatively rare tumor, and the prognostic factors and surveillance strategy for GEP–NETs patients have not been well established due to the complexity and rarity of this disease. Therefore, a clear demonstration of the prognosis values of these easily applicable markers in GEP–NETs patients may help predict individual outcome and guide clinical decisions. In this study, we have summarized

the published evidence on the association between the hematologic parameters and GEP–NETs outcomes. We found, in the field of this rare tumor, NLR, PLR, and platelet counts were all correlated with prognosis. Our pooled-analysis identified that NLR is an effective prognosis factor in GEP–NETs patients. The prognosis value of other hematologic parameters warrants interest and further study.

Most patients involved in the present study were PNET patients. The management of PNETs remains a big challenge because of their heterogeneous pathologic features and unpredictable clinical behaviors. Several markers have been identified as diagnosis markers or prognosis factors in PNETs. Chromogranin A (CgA) is the most commonly used biomarker and has been reported to be elevated in 50%–80% of PNET patients.[39] However, its prognosis value has been questioned due to some studies which showed there was no association between CgA and survival in PNETs.[40] Other potential markers include neurokinin A, pancreatic polypeptide, serotonin, neuron-specific enolase, etc., but their role is still unclear. Future research is needed to discover new markers and to determine which markers provide better prognostic information.[6,41–43] Although the number of studies investigating the predictive value of NLR in PNETs is much less than studies for other tumors, they all revealed that NLR was a remarkable prognosis marker for predicting both survival and recurrence in PNETs. Therefore, NLR has the potential to serve as a supplemental prognostic marker.
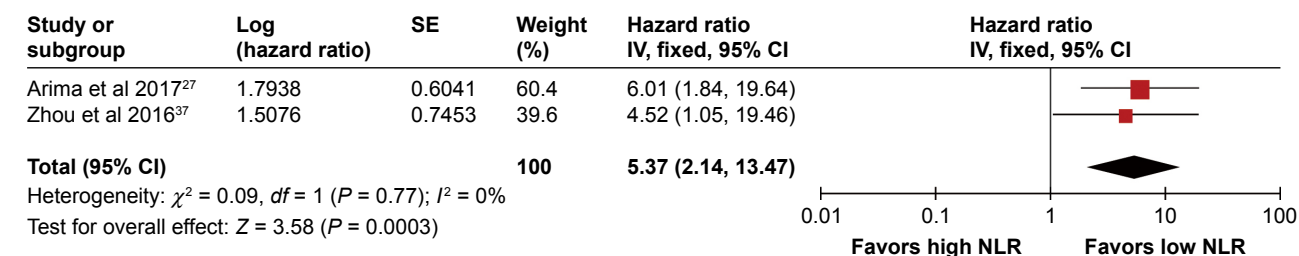
Study or subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, fixed, 95% CI	Hazard ratio IV, fixed, 95% CI
Arima et al 2017[27]	1.7938	0.6041	60.4	6.01 (1.84, 19.64)	
Zhou et al 2016[37]	1.5076	0.7453	39.6	4.52 (1.05, 19.46)	
Total (95% CI)			**100**	**5.37 (2.14, 13.47)**	
Heterogeneity: $\chi^2 = 0.09$, $df = 1$ ($P = 0.77$); $I^2 = 0\%$					
Test for overall effect: $Z = 3.58$ ($P = 0.0003$)					

0.01   0.1   1   10   100
Favors high NLR   Favors low NLR

Figure 3 Forest plot of HR and 95% CI for predictive effect of NLR on recurrence-free survival in patients with PNETs.
Abbreviations: HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PNETs, pancreatic neuroendocrine tumors.
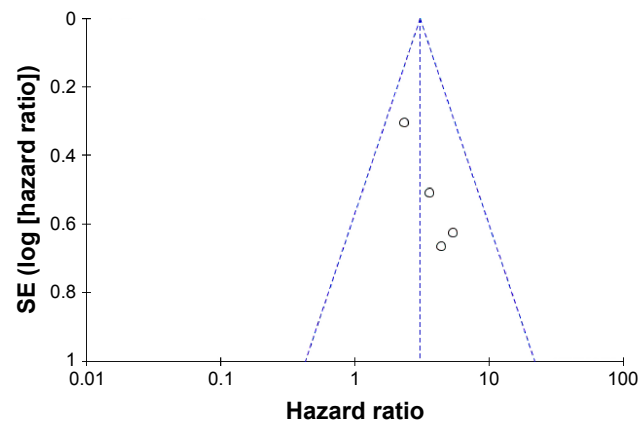
Figure 4 Funnel plot based on the studies reporting the effect of NLR in predicting overall survival outcome.
Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

Besides, NLR is an easily available marker obtained from routine blood tests, which enhances the practicality.

There are some limitations in the present study. Most of the included studies used ROC curve to determine a cut-off value for hematologic parameters.[27–31] Therefore, the NLR and PLR were used as dichotomous variables. Additionally, since the cut-off values were artificially chosen, the clinicopathological characters between groups in each study were incomparable. Moreover, the hematologic parameters could be affected by different conditions and diseases, and the survival time of NETs is usually longer than other cancers because most NETs are biologically less aggressive, but all studies only used one result before treatment and did not monitor hematologic parameters during follow-up. Besides, because G3 tumors are invariably lethal, and the malignant potentials of G1 and G2 tumors were relative indolent, it is better for further studies to give additional information regarding the association between hematologic markers and prognosis in G1/G2 patients and G3 patients separately. We also noted that no study reported cancer-specific survival, which is a better outcome indicator than OS because of the relatively long survival time of patients with GEP–NETs. Last but importantly, due to the retrospective nature of the current study, patients may be prone to potential selection bias. Prospective and larger studies with a longer follow-up are required to confirm these findings.

In conclusion, this present systematic review and meta-analysis summarized the current evidence on the prognosis values of hematologic parameters in GEP–NETs. Our results showed that NLR was an effective prognostic predictor. The prognostic value of other hematologic parameters deserves further investigation. The conclusion should be limited mainly to PNETs due to the majority of included cases

being PNETs. We recommend that future studies should use a continuous NLR variable and adopt a prospective and matched study design.

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Disclosure

The authors report no conflicts of interest in this work.

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