Original Article

Prognostic and clinicopathological significance of platelet to lymphocyte ratio in esophageal cancer: a meta-analysis

Juhong Deng[1], Peng Zhang[2], Yue Sun[2], Ping Peng[2], Yu Huang[2]

[1]Department of Endocrinology, Liyuan Hospital, [2]Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Contributions: (I) Conception and design: Y Huang; (II) Administrative support: Y Sun, P Peng; (III) Provision of study materials or patients: Y Huang, J Deng; (IV) Collection and assembly of data: Y Sun, J Deng, P Zhang; (V) Data analysis and interpretation: Y Huang, J Deng, P Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yu Huang. Department of Oncology, Tongji Hospital, Tongji Medical School, Huazhong University of Science and Technology, No.1095 Jie Fang Avenue, Hankou, Wuhan 430030, China. Email: huangyu03tj@163.com.

Background: The prognostic and clinicopathological significance of the platelet to lymphocyte ratio (PLR) has been studied in various cancers. However, studies examining the role of PLR in esophageal cancer have not yielded consistent results. The purpose of this meta-analysis was to study the prognostic and clinicopathological significance of PLR in esophageal cancer patients.

Methods: We performed a literature search in three major databases: PubMed, Web of Science and Embase (up until May 1, 2017). The clinicopathologic significance of PLR and its prognostic significance were analyzed.

Results: Our meta-analysis consisted of 13 studies with 4,621 patients. The pooled hazard ratios (HRs) showed that a high PLR was associated with poor survival of esophageal cancer [HR =1.283; 95% confidence interval (CI): 1.173–1.404; P<0.001]. Subgroup analysis revealed that elevated PLR was associated with poor survival in esophageal squamous cell carcinoma (HR =1.281; 95% CI: 1.098–1.493; P=0.002). The pooled odds ratio (OR) indicated that high PLR was also associated with the depth of tumor invasion (OR =1.543, 95% CI: 1.269–1.876, P<0.001), lymph node metastasis (OR =1.427, 95% CI: 1.195–1.705, P<0.001), tumor length (OR =1.81, 95% CI: 1.331–2.461, P<0.001), and Tumor stage (OR =1.459, 95% CI: 1.235–1.724, P<0.001).

Conclusions: Our results demonstrate that elevated PLR was significantly associated with poor prognosis of esophageal cancer. Furthermore, the high PLR might predict worse clinicopathological features of esophageal cancer patients.

Keywords: Meta-analysis; esophageal neoplasms; platelet to lymphocyte ratio (PLR); prognosis

Submitted Sep 09, 2017. Accepted for publication Jan 26, 2018.
doi: 10.21037/jtd.2018.02.58
View this article at: http://dx.doi.org/10.21037/jtd.2018.02.58

Introduction

Esophageal cancer is one of the most common cancer types worldwide with a poor prognosis. Although multimodal therapeutic strategies have been used to treat esophageal cancer, including radical operation, chemotherapy, and radiotherapy, the 5-year survival rate remains low (1-3). The identification of prognostic factors in esophageal cancer is thus urgently required to better treat this disease.

Previous studies have established a close relationship between inflammation and cancer (4). Chronic inflammation can induce the development of various types of cancers, and the microenvironment caused by inflammation or by the oncogenic changes during tumorigenesis may promote cancer angiogenesis and metastasis (4,5). Some inflammatory factors in the blood, such as lymphocytes, neutrophils,

monocytes and platelets, show alterations in cancer (6-8). Many inflammatory factors have been associated with prognosis in various cancers. The combination of inflammatory factors, such as platelet-to-lymphocyte ratio (PLR), was also reported to be a prognostic factor in many cancers such as breast, lung and gastric cancers (9-12).

Recent studies have shown that a high PLR might be associated with poor prognosis of esophageal cancer (13,14). However, this result was not confirmed in other studies (15,16). In addition, several inflammatory factors may affect tumor characteristics, such as tumor length and depth of tumor invasion. We performed this meta-analysis to examine the potential role of PLR in the prognosis of esophageal cancer and its relationship with tumor pathological characteristics.

Methods

Search strategy

We performed a literature search in the PubMed, Embase, and Web of Science databases (up until May 1, 2017). We used the following search terms: prognosis (e.g., "prognoses", "prognostic", "survival"), PLR (e.g., "platelet lymphocyte ratio", "platelet to lymphocyte ratio", "platelet-to-lymphocyte ratio"), and esophageal cancer (e.g., "esophageal neoplasm", "esophageal cancer", "esophageal carcinoma") (details seen in Supplementary).

Selection criteria

We used the following criteria for inclusion: the diagnosis for esophageal cancer was proven by pathology, and the correlation between pretreatment PLR and overall survival (OS) was studied. The exclusion criteria were as follows: article types of reviews, letters, abstracts, and case reports; studies written in a language other than English; absence of hazard ratio (HR) and 95% confidence interval (CI) values; and studies without a cutoff value of PLR.

Data extraction and quality assessment

Two researchers (Deng JH and Sun Y) independently extracted data from relevant studies. In cases of disagreements, another researcher (Zhang P) was consulted. The following information was collected: authors' names, year of publication (we included the final published year), study country, study design, gender, age, stage of disease, pathological type, cutoff values for PLR, HR with 95% CI of PLR for OS, type of study, treatment intent, treatment strategy and survival data. We used the Newcastle-Ottawa Scale (NOS) for quality assessment of the included research (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). If the NOS score was ≥6 points, we considered the article was high quality

Statistical analysis

Meta-analysis was performed using Stata 12.0 software (STATA, College Station, TX, USA). HRs for the association of PLR and esophageal cancer were obtained from the research. When HRs was reported in both univariate and multivariate analyses, we used the multivariate-adjusted HRs. The pooled HRs was finally summarized from each study of HRs and their 95% CI. The I-squared (I^2) statistic was used to evaluate the heterogeneity of the studies. If I^2 >50%, meta-analysis was chosen to evaluate with a random effects model; otherwise, the fixed effect model was chosen. Odds ratios (ORs) were used to estimate the association between PLR and clinicopathological characteristics. We estimated publication bias by Begg's funnel plot test and Egger's linear regression test. We also used country, cutoff, patient's number (simple size), treatment strategy and pathologic type for subgroup analysis.

Results

Study Characteristics

A total of 59 studies were initially identified after searching the databases. After browsing the title and abstracts, 34 studies were excluded. We then reviewed the remaining 25 studies and excluded 12 studies for the following reasons: two studies used data with a continuous PLR level for survival analysis, without a clear cutoff value; one study performed the analysis in the samples with a repeated population; four studies did not use OS as an endpoint; two studies did not describe the relationship between PLR and OS; and three studies did not report the HR value. A final 13 studies were included in the meta-analysis, with 4,621 patients (*Figure 1*) (13-25). These studies were published from 2013 to 2017. The most common type of pathology involved in these studies was esophageal squamous carcinoma (ESCC). The PLR cutoff point ranged from 117.07 to 244. The detailed information of these studies is shown in *Table 1*. NOS scores of all the studies were at least 6 or more.

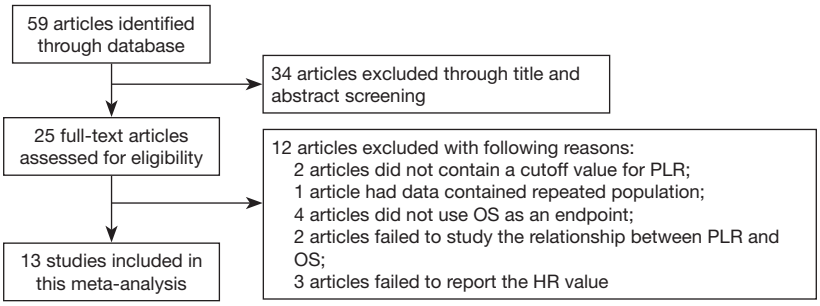

Figure 1 The flow diagram for selection of studies. PLR, platelet to lymphocyte ratio; OS, overall survival; HR, hazard ratio.

The role of PLR in the prognosis of esophageal cancer

All 13 studies retrospectively reported the relationship between PLR and OS. We found that a high PLR was positively related to poor OS (pooled HR =1.283, 95% CI: 1.173–1.404; P<0.001, *Figure 2*). We used the fixed-effect model, for no obvious heterogeneity existed (I^2 =49.4%, P_h=0.022). First we performed subgroup analysis with the pathologic type. We found that 10 studies reported the association between PLR and OS in ESCC and demonstrated that a high PLR was related to poor OS (HR =1.281, 95% CI: 1.098–1.493, P=0.002) of ESCC (*Figure 3*); here we used random effect model for I^2 >50%. We also performed subgroup analysis by cutoff value, sample size and countries. Subgroup analysis by cutoff values showed an HR for cutoff value ≥150 of 1.413 (95% CI: 1.136–1.758, P=0.002, I^2 =56.1%, P_h=0.026) and for cutoff value <150 of 1.187 (95% CI: 1.05–1.341; P=0.006; I^2 =7.4%, P_h=0.365). In patients treated with surgery alone, the combined HR was 1.407 (95% CI: 1.018–1.945; P=0.039; I^2 =73.2%, P_h=0.024); for research with multimodal treatment, the HR was 1.255 (95% CI: 1.102–1.43; P=0.001; I^2 =48.6%, P_h=0.049) (*Table 2*). Subgroup analyses by sample size and countries are shown in *Table 2*.

PLR and clinicopathological features

The association between PLR and clinicopathological characteristic features was studied in several articles (13-15,18,21-25). Six studies reported the association of PLR with depth of tumor invasion in esophageal cancer. The combined OR revealed that a high PLR was related to a deeper tumor invasion (OR =1.543, 95% CI: 1.269–1.876, P<0.001). Seven studies reported that a high PLR was positively associated with lymph node metastasis of esophageal cancer (OR =1.427, 95% CI: 1.195–1.705, P<0.001). Furthermore, a high PLR was positively associated a longer tumor length (OR =1.810; 95% CI: 1.331–2.461, P<0.001) and a higher TNM stage (OR =1.459, 95% CI: 1.235–1.724, P<0.001). The level of PLR was not related to other clinicopathological factors (tumor differentiation OR =1.196, 95% CI: 0.978–1.462; P=0.081; vascular invasion OR =1.104, 95% CI: 0.709–1.717, P=0.663) (*Table 3*).

Publication bias

Egger's and Begg's test was used evaluate publication bias. No publication bias was detected (P=0.126 and P=0.127 for Egger's and Begg's tests, respectively; *Figure 4*).

Discussion

Inflammation plays an important role in the development of cancer. The cells and mediators of inflammation create a specific microenvironment, which influences tumor growth, progression, angiogenesis and metastasis (26). Systematic inflammatory response is a highlight in various research studies, and current interest is focused on the prevention and treatment of cancer by addressing abnormal inflammation (27).

Platelets play an important role in immune and inflammation responses and participate in cancer invasion and metastasis (28). Many platelet-associated chemokines can modulate inflammation within the tumor environment and tumor angiogenesis, such as platelet factor 4 (PF-4/CXCL4) and connective tissue activating peptide III (CTAP-III) (29). Lymphocytes have been shown to exert an important role in the cancer immunosurveillance process. Shankaran *et al.* reported that lymphocytes and IFN-gamma collaborate to protect against the development of

Table 1 Characteristics of all eligible studies

Study	Year	Country	No. (male/female)	Age (mean or median)	Treatment	Intent	Stage	Cutoff value	Median OS (m) (low/high PLR)	HR (M/U)	Result	Histology	Study type
Feng *et al.*	2013	China	43 (30/13)	58.7±7.8	Mix	Cur	I–III	150	NR	M	Positive	Small cell	Uni/Re
Feng *et al.*	2014	China	483 (411/72)	59.1±8.0	S	Cur	I–III	150	NR	M/U	Positive	SCC	Uni/Re
Han *et al.*	2015	China	218 (177/41)	60.5	Mix	Cur	I–III	244	40/29.9	M/U	Negative	SCC	Uni/Re
Xu *et al.*	2015	China	468 (416/52)	58	Mix	Cur	I–III	147	NR	U	Negative	SCC	Uni/Re
He *et al.*	2015	China	820 (526/294)	60.0±9.3	S or NR	NR	I–IV	194	NR	M	Negative	SCC + others	Uni/Re
Messager *et al.*	2015	UK	153 (128/25)	64.9	Mix	Cur	I–III	192	NR	M/U	Positive	ADC	Uni/Re
Geng *et al.*	2016	China	916 (696/220)	60	S	Cur	I–III	120	53/36	M/U	Negative	SCC	Uni/Re
Ji *et al.*	2016	China	41 (38/3)	56.6±7.2	Mix	Cur	I–III	130	NR	U	Positive	SCC	Uni/Re
Sun *et al.*	2016	China	362 (268/94)	58	Mix	Cur	I–III	150	NR	U	Negative	SCC	Uni/Re
Toyokawa *et al.*	2016	Japan	185 (152/33)	64	Mix	Cur	I–IV	193	NR	M	Negative	SCC	Uni/Re
Zhang *et al.*	2016	China	468 (376/92)	59.5±9	Mix	Cur	I–III	117.07	NR	M/U	Negative	SCC	Uni/Re
He *et al.*	2017	China	317 (268/49)	60	Mix	Cur	I–IV	150	44/22.1	M	Positive	SCC	Uni/Re
Hirahara *et al.*	2017	Japan	147 (132/15)	NR	S	Cur	I–III	147	NR	U	Negative	SCC	Uni/Re

No., patient number; M, hazard ratio from multivariate analysis; U, HR from univariate analysis; Mix, mixed treatment, combing different treatment methods (such as surgery, radiotherapy, chemoradiotherapy or chemotherapy); S, surgery; NR, not reported; HR, hazard ratio; Intent, treatment intent; Cur, curative intent; OS, overall survival; SCC, squamous cell carcinoma; ADC, adenocarcinoma; Uni, Uni-centric; Re, retrospective.

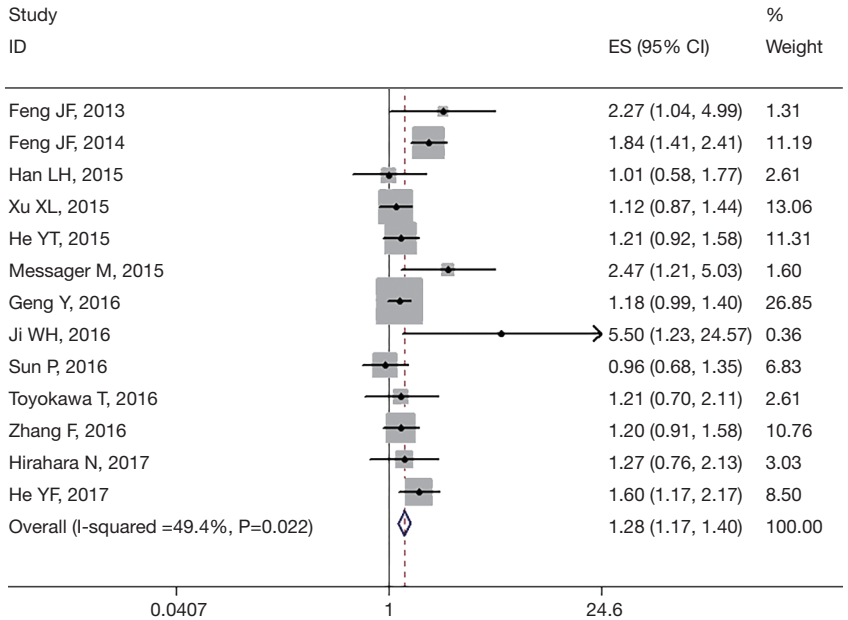

Figure 2 Forest plot of meta-analysis between PLR and OS in esophageal cancer. PLR, platelet to lymphocyte ratio; OS, overall survival; HR, hazard ratio; CI, confidence interval; ES, effect size.

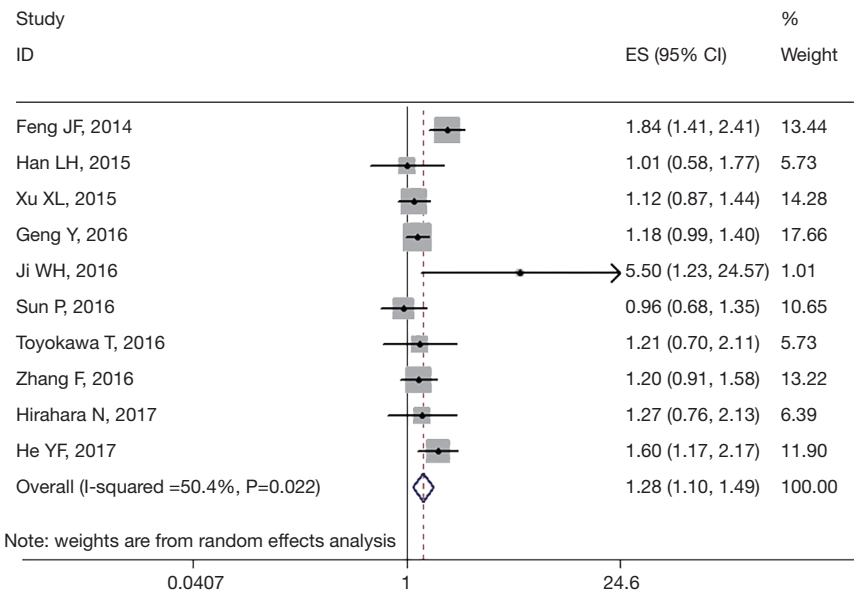

Figure 3 Forest plot of meta-analysis between PLR and OS in ESCC. PLR, platelet to lymphocyte ratio; OS, overall survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; ES, effect size.

chemically-induced sarcomas and spontaneous epithelia carcinomas (30). Inflammation plays an important role in the development of esophageal cancer. Chronic inflammation triggered by environmental exposures may activate the proinflammatory signaling pathway, which promotes the proliferation and survival of cancer cells (31).

The levels of platelets and lymphocytes are altered in the blood of cancer patients (7,8,32,33). Furthermore, the prognostic role of a combination of blood platelets and lymphocytes has been reported in various solid tumors

Table 2 Meta-analysis results of PLR in esophageal cancer prognosis

Factor	No. of study	No. of patients	Effect model	HR (95% CI)	P value	Heterogeneity	
						I^2 (%)	P_h
OS							
Overall	13	4,621	Fix	1.283 (1.173, 1.404)	0.000	49.4	0.022
			Random	1.321 (1.146, 1.523)	0.000		
Country							
China	10	4,136	Fix	1.271 (1.158, 1.396)	0.000	55.8	0.016
			Random	1.300 (1.113, 1.520)	0.001		
Japan	2	332	Fix	1.243 (0.852, 1.814)	0.260	0.0	0.907
			Random	1.243 (0.852, 1.814)	0.260		
Treatment							
Surgery	3	1,546	Fix	1.339 (1.164, 1.540)	0.000	73.2	0.024
			Random	1.407 (1.018, 1.945)	0.039		
Mix	9	2,255	Fix	1.255 (1.102, 1.430)	0.001	48.6	0.049
			Random	1.317 (1.073, 1.615)	0.008		
Cutoff value							
≥150	8	2,581	Fix	1.407 (1.233, 1.606)	0.000	56.1	0.026
			Random	1.413 (1.136, 1.758)	0.002		
<150	5	2,040	Fix	1.187 (1.050, 1.341)	0.006	7.4	0.365
			Random	1.189 (1.042, 1.356)	0.010		
Sample size							
≥300	7	3,834	Fix	1.261 (1.147, 1.388)	0.000	56.9	0.031
			Random	1.273 (1.095, 1.479)	0.002		
<300	6	787	Fix	1.461 (1.124, 1.908)	0.005	42.5	0.122
			Random	1.564 (1.085, 2.254)	0.016		
Pathologic type							
ESCC	10	3,605	Fix	1.267 (1.150, 1.396)	0.000	50.4	0.034
			Random	1.281 (1.098, 1.493)	0.002		
Other types*	3	1,016		1.386 (1.093, 1.759)	0.007	60.7	0.078
				1.717 (1.014, 2.906)	0.044		

*, the article included other pathologic types except squamous cell carcinoma or with a mixed type. OS, overall survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; Mix, mixed treatment, combing different treatment methods, including surgery, radiotherapy, chemoradiotherapy or chemotherapy.

(10,11). Evaluation of the PLR is easy to perform in most patients. Some studies have shown that a high PLR might be associated with the poor prognosis of esophageal cancer, but this association has not been completely confirmed. Therefore, we performed this meta-analysis to confirm the role of PLR in esophageal cancer.

In this meta-analysis, we found that a high PLR predicts poor prognosis in esophageal cancer. We then

Table 3 Relationship between PLR and the clinicopathologic features

Variable	No. of studies	No. of patients	Effect of model	OR (95% CI)	P value	Heterogeneity		Egger's P value
						I^2 (%)	P_h	
Tumor invasion (T3/4 *vs*. T1/2)	6	1,848	Fixed	1.543 (1.269, 1.876)	0.000	0.0	0.629	0.022
			Random	1.543 (1.269, 1.876)	0.000			
Lymph node metastasis (yes *vs*. no)	7	2,165	Fixed	1.427 (1.195, 1.705)	0.000	17.9	0.294	0.341
			Random	1.461 (1.175, 1.816)	0.001			
Differentiation (poor *vs*. well/moderate)	6	2,128	Fixed	1.196 (0.978, 1.462)	0.081	0.0	0.477	0.677
			Random	1.196 (0.978, 1.462)	0.081			
Vascular invasion (yes *vs.* no)	3	567	Fixed	1.104 (0.709, 1.717)	0.663	0.0	0.961	0.749
			Random	1.104 (0.709, 1.717)	0.663			
TNM stage (stage III/IV *vs.* I/II))	7	2,612	Fixed	1.459 (1.235, 1.724)	0.000	29.6	0.202	0.345
			Random	1.504 (1.198, 1.889)				
Tumor length (>3 *vs*. ≤3 cm)	4	1,061	Fixed	1.810 (1.331, 2.461)	0.000	12.3	0.331	0.607
			Random	1.774 (1.255, 2.507)	0.001			

P_h, P value for heterogeneity; No., number; OR, odds ratio; CI, confidence interval; TNM, tumor node metastasis; T, depth of tumor invasion.

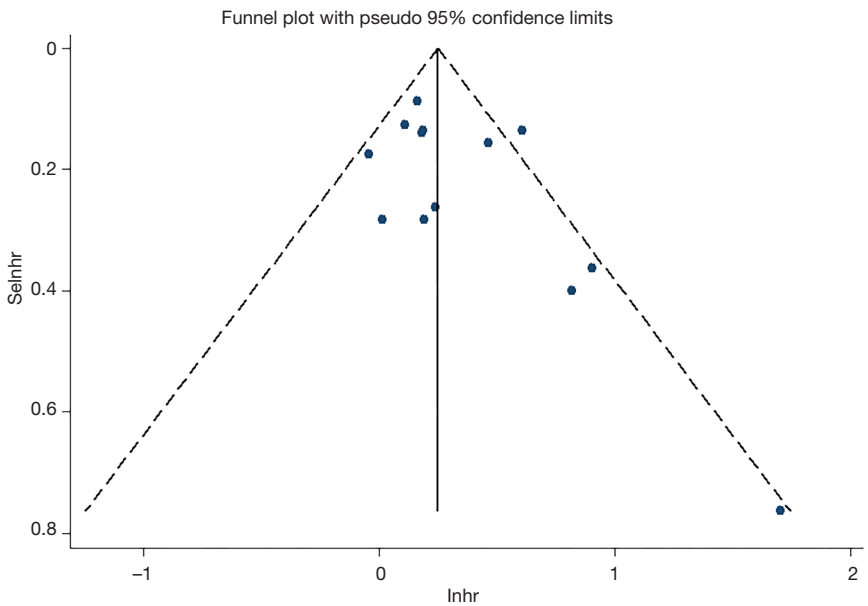

Figure 4 Funnel plot for the publication bias of HR for OS. LNHR, natural logarithm hazard ratio; SELNHR, standard error of natural logarithm hazard ratio; HR, hazard ratio; OS, overall survival.

performed a subgroup analysis and also determined a prognostic role of PLR in ESCC, the major histological type. We also analyzed the relationship between PLR and clinicopathologic features. The result indicated that the elevated PLR level was associated with deeper tumor invasion, lymph node metastasis, longer tumor length and higher tumor stage. Taken together, these data suggest that the level of PLR is important for predicting the prognosis and the status of clinicopathologic features. As well known, the PLR is easily measured in the clinical setting because

each patient undergoes a blood test before treatment and the cost is low. Thus, PLR might be a useful and convenient tool for clinicians when performing clinical treatment and evaluating the outcomes.

One previous study performed a meta-analysis to investigate the prognostic significance of PLR in esophageal cancer (34). In this previous study, the authors found that high PLR was significantly predictive of poorer OS, deeper tumor invasion, and lymph node metastasis. However, they only included four studies. They did not perform a subgroup analysis according to the pathological types. In the present study, we evaluated a much larger group, including 4,621 patients from 13 studies. We demonstrated for the first time the prognostic role of PLR in ESCC. Furthermore, we concluded that more clinical features might be associated with PLR, such as tumor length and tumor stage.

Our study had several limitations. First, most of the studies were performed in Asian countries (China and Japan), and only one study was performed in a Western country. We did find some studies published in Western countries (35,36), but they did not meet the study criteria. Therefore, our preliminary findings need to be confirmed in other regions. Second, the most prevalent histological type was ESCC. However, different subtypes of esophageal cancer show different biological behaviors and prognoses. Our study did not include enough data on esophageal adenocarcinoma and small cell carcinoma. Only one article in our meta-analysis definitely studied the relationship between esophageal adenocarcinoma and PLR. The researchers found that high PLR is associated with poor OS and disease-free survival (DFS) for esophageal and junction adenocarcinoma (13). This is a positive result but needs further study to prove the result. We should also take this result in caution. Most tumors in their study were located in the esophagus, but a small part of the carcinoma was located in the gastro-esophageal junction, close to the esophagus, often studied, and treated with esophageal tumor (2). In another article, 80% of the patients were diagnosed as having adenocarcinoma (37). In their study, they found that elevated PLR might be predictive of worse OS in esophageal cancer. However, it was excluded in our meta-analysis for using data without a clear cutoff value for analysis. Therefore, more studies are needed to confirm the role of PLR in other pathological subtypes.

Conclusions

Our meta-analysis confirmed that a high PLR was associated with poor prognosis of esophageal cancer, especially in ESCC. Furthermore, the PLR level is related to clinicopathologic features of esophageal cancer. More studies are required in other histologic types and geographic regions. More effort is required to predict prognosis of esophageal cancer patients more accurately and develop novel treatment strategies, including anti-inflammatory therapy.

Acknowledgements

We thank Dr. Xiang Wang for statistic assistance.
Funding: This work was supported by a grant from a research fund of Wuhan Tongji Hospital [2015].

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Deng J, Zhang P, Sun Y, Peng P, Huang Y. Prognostic and clinicopathological significance of platelet to lymphocyte ratio in esophageal cancer: a meta-analysis. J Thorac Dis 2018;10(3):1522-1531. doi: 10.21037/jtd.2018.02.58

Supplementary

PubMed search strategy

(((((((((Prognosis) OR Prognoses) OR prognostic) OR outcome) OR survival) OR mortality)) AND ((((((Esophageal Neoplasm) OR Esophagus Neoplasm) OR Esophagus Cancer) OR Esophageal Cancer) OR esophageal carcinoma) OR Esophagus carcinoma)) AND ((((platelet lymphocyte ratio) OR platelet to lymphocyte ratio) OR platelet-to-lymphocyte ratio) OR PLR)

Embase strategy

Search date	Combine	Results
May 2017	#20. #17 AND #18 AND #19	37
	#19. #13 OR #14 OR #15 OR #16	3,004
	#19. #13 OR #14 OR #15 OR #16	64,034
	#17. #1 OR #2 OR #3 OR #4 OR #5 OR #6	3,512,600
	#16. 'plr'	2,678
	#15. 'platelet-to-lymphocyte ratio'	766
	#14. 'platelet to lymphocyte ratio'	766
	#13. 'platelet lymphocyte ratio'/exp	1,245
	#12. 'esophagus carcinoma'	15,242
	#11. 'esophageal carcinoma'	7,771
	#10. 'esophageal cancer'	24,793
	#9. 'esophagus neoplasm'	17
	#8. 'esophageal neoplasm'	421
	#7. 'esophagus cancer'/exp	57,252
	#6. 'mortality'	1,073,552
	#5. 'survival'	1,391,365
	#4. 'outcome'	2,054,741
	#3. 'prognostic'	359,252
	#2. 'prognoses'	9,581
	#1. 'prognosis'/exp	605,644

Web of science

Search format	Results	Combine
#4	50	#3 AND #2 AND #1
		Index=SCI-EXPANDED, SSCI time span=1992-2017
#3	2,777	Term: (platelet lymphocyte ratio) OR term: (platelet to lymphocyte ratio) OR term: (platelet-to-lymphocyte ratio) OR term: (PLR)
		Index=SCI-EXPANDED, SSCI time span=all years
#2	42,988	Term: (Esophageal Neoplasm) OR term: (Esophagus Neoplasm) OR term: (Esophagus Cancer) OR term: (Esophageal Cancer) OR term: (esophageal carcinoma) OR term: (Esophagus carcinoma)
		Index=SCI-EXPANDED, SSCI time span=all years
#1	2,864,518	Term: (Prognosis) OR term: (Prognoses) OR term: (prognostic) OR term: (outcome) OR term: (survival) OR term: (mortality)
		Index=SCI-EXPANDED, SSCI time span=all years