Received: 29 August 2019 | Revised: 21 September 2019 | Accepted: 1 October 2019
DOI: 10.1002/ags3.12294

SYSTEMATIC REVIEW ARTICLE

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

Prognostic significance of systemic inflammatory markers in esophageal cancer: Systematic review and meta-analysis

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Abstract

Aim: Impact of several immune-inflammatory markers on long-term outcome has been reported in various malignancies. The aim of the present study was to evaluate through a meta-analysis the oncological outcome of immune-inflammatory markers, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and C-reactive protein to albumin ratio (CAR) in esophageal cancer.

Methods: A systematic electronic search for relevant studies was carried out in PubMed, Cochrane library, Embase, and Google scholar. Meta-analysis was done using hazard ratio (HR) and 95% confidence interval (CI) as effect measures. A systematic review and meta-analysis were undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. *P*-values <.01 were considered statistically significant.

Results: A total of 10 retrospective articles (n = 4551) were included in this study. Synthesized results showed that higher NLR and CAR were significantly associated with poor overall survival (HR 1.47, 95% CI = 1.32-1.63, P < .00001) and HR 1.88, 95% CI = 1.28-2.77, P < .001, respectively). On the contrary, PLR was not a prognostic factor in our analysis (HR 1.25, 95% CI = 1.01-1.54, P < .01). Elevated NLR, PLR, and CAR were strongly associated with a higher T stage (HR 2.28, 95% CI = 1.67-3.11; HR 1.57, 95% CI = 1.29-1.90; HR 1.76, 95% CI = 1.16-2.67, respectively). Begg's funnel plots identified significant publication bias in NLR, but not in PLR and CAR.

Conclusion: NLR and CAR represent useful guides for the management of esophageal cancer, although publication bias should be considered. Further prospective studies are needed to confirm the results of the present study.

KEYWORDS
C-reactive protein to albumin ratio, esophageal cancer, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, prognostic factor

1 | INTRODUCTION

Esophageal cancer is a highly aggressive disease with poor prognosis. According to the latest global cancer statistics, each year, an estimated 455 800 new esophageal cancer cases and 400 200 deaths occur globally. In males, it is the seventh most prevalent and sixth most highly mortal cancer, whereas in females it is the ninth most common cause of mortality.[1]

Numerous prognostic factors, including TNM stage, have been reported.[2] However, recently, inflammatory and nutritional markers such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and C-reactive protein to albumin ratio (CAR) have been recognized as useful prognostic markers for esophageal cancer patients worldwide.[3–19] Of note, the majority of these investigations were retrospective cohort studies. Only a few carried out a systematic review and meta-analysis. As a consequence, the consistency and magnitude of the prognostic impact of these markers currently remain unclear. Additionally, a systematic review and meta-analysis including CAR in esophageal cancer have not been carried out to date.

As a consequence, we carried out a systematic review and meta-analysis to assess the prognostic values of NLR, PLR, and CAR for esophageal cancer.

2 | MATERIALS AND METHODS

2.1 | Search strategy

In the present study, the search strategy was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.[20] Literature databases such as PubMed, Cochrane library, Embase, and Google scholar were searched from 2003 to 2018. The following medical subject headings were searched: "esophageal cancer (or carcinoma)" and "neutrophil to lymphocyte ratio (or NLR)," "esophageal cancer (or carcinoma)" and "platelet to lymphocyte ratio (or PLR)," and "esophageal cancer (or carcinoma)" and "C-reactive protein to albumin ratio (or CAR)." Furthermore, references in the cited articles were overlooked. A total of 341 manuscripts were identified, and 331 manuscripts were excluded according to our exclusion criteria. (Figure 1).

2.2 | Inclusion and exclusion criteria

Inclusion criteria for selecting the articles for our analysis were as follows: (i) diagnosis of esophageal cancer was made based on pathological examination; (ii) correlation of pretreatment NLR, PLR, and CAR with overall survival (OS) was reported; (iii) publications were in English language. Exclusion criteria were as follows: only stage II or III was selected (n = 1); survival outcomes were not mentioned (n = 1); other topic (n = 3); cross-over design (n = 3); only basaloid cell squamous cell carcinoma was selected (n = 1); and unable to extract data (n = 1).

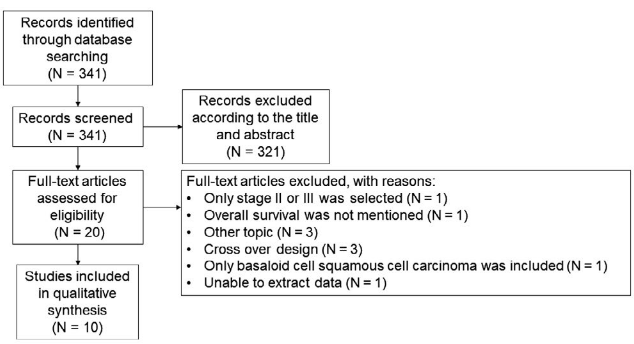

FIGURE 1 Flow diagram of the search strategy for the included studies

2.3 | Data extraction and quality evaluation

Two authors (Y.I. and H.T.) independently evaluated and extracted all candidate studies. Quality of the included studies was assessed through the Newcastle-Ottawa Quality Assessment Scale (NOS). The latter consists of three parts as follows: selection, compatibility, and outcome assessments.[21] Maximum score was 9 points and a NOS score >5 indicated acceptable quality studies.

2.4 | Statistical analysis

Hazard ratio (HR) and 95% confidence interval (CI) for OS were directly summarized from each published study. We measured heterogeneity between the included studies using Cochran's *Q* test with *P*-value and I^2 statistic.[22] *P*-value <.1 for Cochran's *Q* test and I^2 > 50% for the I^2 test suggested significant heterogeneity among the included studies. Furthermore, we used the random-effects model (DerSimonian-Laird method) for cases with significant heterogeneity (Cochran's *Q* test <0.1 or I^2 >50%).[21] Otherwise, we adopted the fixed-effects model (Mantel-Haenszel method).[23] Finally, we used Begg's funnel plots to visually assess the publication bias.[24] All analyses were carried out by Review Manager (RevMan) 5.3.5 (Cochrane Collaboration, Software Update) and JMP 12.0 (SAS Institute Inc). *P*-values <.01 were considered statistically significant.

2.5 | Risk of bias

Appropriateness of the included studies was assessed by two authors (Y.I. and H.T.) by means of the Quality in Prognostic Studies (QUIPS) tool.[25] All studies were scored as low, moderate, or high risk. Each included the following six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

3 | RESULTS

Flow diagram of the search strategy for the included studies is shown in Figure 1. A total of 341 articles were identified in the databases. Subsequently, in line with the inclusion and exclusion criteria, 10 retrospective cohort studies (n = 4551 patients with esophageal cancer) were included in the present meta-analysis (Table 1).

3.1 | Neutrophil to lymphocyte ratio

As shown in Figure 2, a total of nine studies (n = 4042 patients) reported the prognostic value of NLR. The cut-off value of the included studies ranged from 1.7 to 3.5 (median, 2.57). Patients treated for

TABLE 1 Detailed data of the included studies reporting the relationship of NLR, PLR, or CAR and prognosis after an esophageal cancer resection

Authors	Year	Study period	Histology	NLR cut-off	PLR cut-off	CAR cut-off	Outcome	Measures	Number	Age	Gender	Stage	Included patients were all performed curative resection	Adjuvant therapy	Median follow up month (range)	NOS
Ishibashi et al[17]	2018	2009-2014	All types	3	135	0.085	OS and CSS	NLR, PLR, CAR	143	<65 = 29 ≥65 = 114	Female = 22 Male= 121	I = 33 II = 33 III = 60 IV = 17	Yes	No = 71 Yes = 72	22.8 mo (0.6-87.2 mo)	7
Hirahara et al[3]	2018	2006-2014	SCC	1.6	147	NA	OS	NLR, PLR	147	<70 = 56 ≥70 = 91	Female = 15 Male= 132	I = 59 II = 33 III = 55	Yes	None	NR	6
Wang et al[5]	2017	2012-2013	SCC	2	159	NA	OS and DFS	NLR, PLR	280	64.1 ±7.4	Female = 47 Male = 233	0/I / II = 179 III / IV = 101	Yes	No = 166 Yes = 114	NR	6
Gao et al[6]	2017	2005-2015	SCC	2.86	NA	NA	OS	NLR	1281	NLR <2.86 = 58.1 ± 9.1 NLR ≥ 2.86 = 60.4 ± 31.17	Female = 276 Male = 1005	0 = 27 I = 125 II = 586 III = 520 IV = 23	No	NR	NR	6
Miyazaki et a.[7]	2016	2004-2014	All types	3.49	NA	NA	OS	NLR	192	65.8 (42-86)	Female = 19 Male = 173	I = 58 II = 50 III = 60 IV = 24	Yes	None	26.5 mo (1-108 mo)	7
Geng et al[11]	2016	2002-2012	SCC	1.7	120	NA	OS	NLR, PLR	916	<60 = 455 ≥60 = 461	Female = 220 Male = 696	0-I = 168 II = 395 III = 353	Yes	None	39 mo (3-146 mo)	6
Wei et al[13]	2015	2006-2010	SCC	1.835	163.8	0.095	OS	NLR, PLR, CAR	423	<54 = 146 ≥54 = 277	Female = 82 Male = 341	I = 54 II = 168 III = 142 IV = 59	No	NR	35.7 mo (0.6-95.6 mo)	7
Xu et al[14]	2015	2000-2010	SCC	2.4	147	0.5	OS	CAR, NLR, PLR	468	<58 = 227 ≥58 = 241	Female = 52 Male = 416	I = 24 II = 181 III = 142	Yes	No=272 Yes=196	49.9 mo (10.9-88 mo)	6
Han et al[16]	2015	2007-2008	SCC	2.6	244	NA	OS and DFS	NLR, PLR	218	<60 = 109 ≥60 = 109	Female = 41 Male = 177	I+II =133 III = 85	Yes	No=136 Yes=82	38.6 mo (3-71 months)	6
Feng et al[15]	2014	2005-2008	SCC	3.5	150	NA	OS	NLR and PLR	483	<60 = 273 ≥60 = 210	Female = 72 Male = 411	NR	Yes	NR	NR	6

Abbreviations: CAR, C-reactive protein to albumin ratio; CSS, cancer-specific survival; DFS, disease-free survival; NA, not applicable; NLR, neutrophil to lymphocyte ratio; NOS, Newcastle-Ottawa Quality Assessment Scale; OS, overall survival; PLR, platelet to lymphocyte ratio; SCC, squamous cell carcinoma.

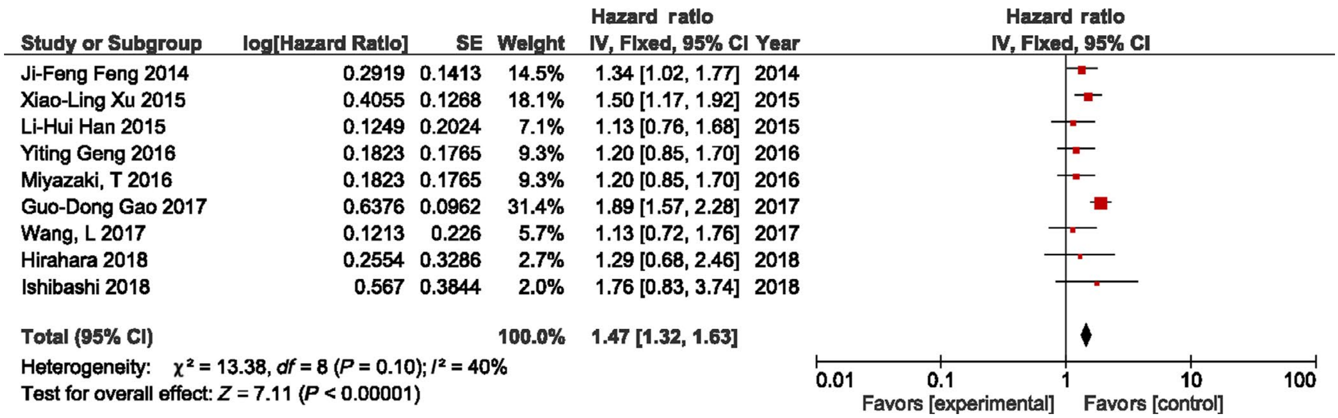

FIGURE 2 Forest plot for the association between neutrophil to lymphocyte ratio (NLR) and overall survival of patients treated by surgery for esophageal cancer

esophageal cancer with higher pretreatment NLR had a significant association with poorer prognosis in (HR 1.47, 95% CI = 1.32-1.63, $P < .00001$). As heterogeneity was not significant, the analysis was estimated using a fixed-effects model ($P = .1$, $I^2 = 40\%$; Figure 2). We observed that a higher NLR was significantly associated with male gender (OR 1.6, 95% CI = 1.13-2.27, $P = .008$) and T3 or T4 of tumor depth (OR 2.28, 95% CI = 1.67-3.11, $P < .00001$; Table 2). In contrast, age, tumor location, tumor differentiation, and lymph node metastasis were not associated with higher NLR. OS subgroup analysis was carried out using histology, curative resection, cut-off value, sample size, and HR from multivariate analysis (Table S1). All subgroups with the exception of small sample size, strengthened the prognostic value of NLR for OS.

3.2 | Platelet to lymphocyte ratio

Platelet to lymphocyte ratio was reported in seven studies (n = 2655 patients), and the cut-off value of the included studies ranged from 135 to 244 (median, 157.4). Results of the meta-analysis show an absence of association between PLR and OS (Figure 3). Due to significant heterogeneity, the analysis was carried out with a random-effects model ($P = .03$, $I^2 = 58\%$). We observed that a higher PLR was strongly associated with deeper tumor depth (OR 1.57, 95% CI = 1.29-1.90, $P < .00001$). In contrast, PLR was not associated with gender, age, lymph node metastasis, tumor differentiation, and main tumor location (Table 3). OS subgroup analysis was done using histology, cut-off value, sample size, and HR from multivariate analysis (Table S2). PLR could not indicate a prognostic value for OS in any of the subgroups.

3.3 | C-reactive protein to albumin ratio

Only three studies (n = 1033 patients) evaluated the prognostic value of CAR. The cut-off value of the included studies ranged from 0.085 to 0.5 (median, 0.22). Higher CAR was strongly associated with poorer survival versus lower CAR groups (HR 1.88, 95%

TABLE 2 Link between clinicopathological features and elevated NLR

Clinical features	No. of studies	No. of patients	Pooled results OR	95%CI	*P*-value	Analytical effects model
Male (vs Female)	7	3294	1.60	1.13-2.27	.008	Random
Age (y) ≥60 vs <60	3	1617	0.92	0.75-1.13	.40	Fixed
Tumor depth						
T3, T4 (vs T1, T2)	6	2097	2.28	1.67-3.11	<.00001	Random
Lymph node metastasis						
N0, N1 (vs N2, N3)	4	1398	1.35	1.01-1.81	.04	Fixed
Differentiation						
Poor (vs well, moderate)	5	2951	1.24	1.01-1.53	.04	Fixed
Location						
Upper (vs middle, lower)	7	3294	0.96	0.75-1.24	.77	Random

Abbreviations: Fixed, fixed-effects model; NLR, neutrophil to lymphocyte ratio; Random, random-effects model.

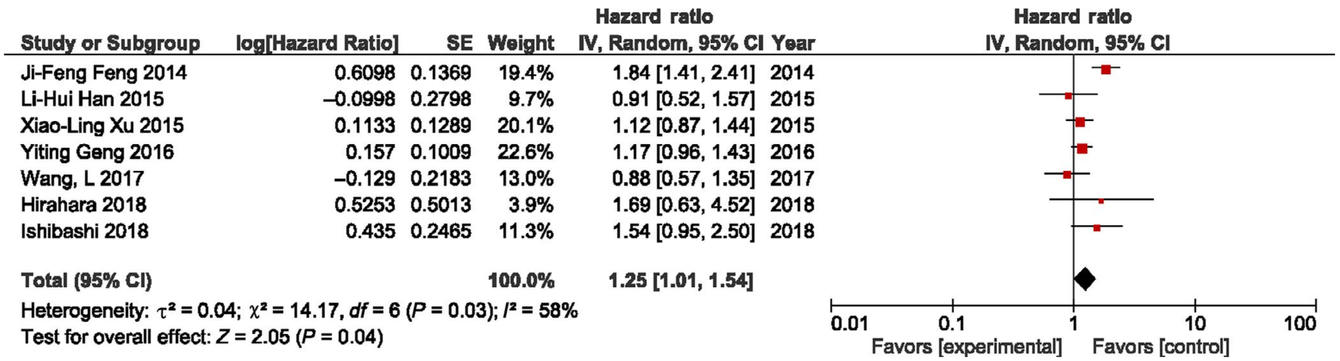

FIGURE 3 Forest plot for the association between platelet to lymphocyte ratio (PLR) and overall survival of patients treated by surgery for esophageal cancer

TABLE 3 Link between clinicopathological features and elevated PLR

Clinical features	No. of studies	No. of patients	Pooled results			Analytical effects model
			OR	95%CI	*P*-value	
Male (vs Female)	5	1675	0.79	0.41-1.51	.47	Random
Age (y) ≥60 vs <60	3	1617	0.94	0.77-1.15	.56	Fixed
Tumor depth						
T3, T4 (vs T1, T2)	5	1907	1.57	1.29-1.90	<.00001	Fixed
Lymph node metastasis						
N0, N1 (vs N2, N3)	3	1206	1.37	1.03-1.83	.03	Fixed
Differentiation						
Poor (vs well, moderate)	4	1760	1.22	0.99-1.52	.07	Fixed
Location						
Upper (vs middle, lower)	5	1907	1.08	0.76-1.55	.66	Fixed

Abbreviations: Fixed, fixed-effects model, PLR, platelet to lymphocyte ratio; Random, random-effects model.

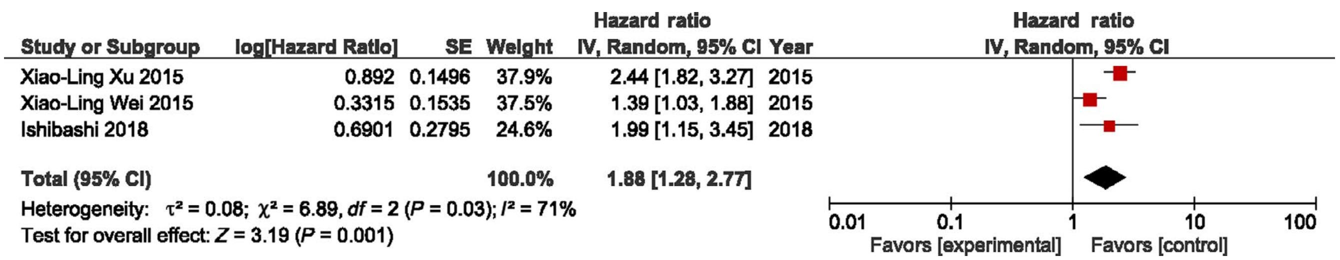

FIGURE 4 Forest plot for the association between C-reactive protein to albumin ratio (CAR) and overall survival of patients treated by surgery for esophageal cancer

CI = 1.28-2.77, P = .001). (Figure 4) A random-effects model for significant heterogeneity was used to carry out the analysis (P = .03, I^2 = 71%). Our results show that CAR had significant association with gender (OR 1.76, 95% CI = 1.16-2.67, P = .008), tumor depth (OR 2.44, 95% CI = 1.25-4.77, P = .009), and tumor differentiation (OR 1.7, 95% CI = 1.24-2.32, P = .0009; Table 4). Due to an insufficient number of studies for CAR in esophageal cancer, subgroup analysis could not be carried out.

3.4 | Publication bias

Begg's funnel plots were used to visually assess the publication bias in the present study. (Figure S1) A significant publication bias was found in NLR for OS, as the funnel plots of NLR were asymmetrical. No obvious publication bias was found in PLR and CAR for OS, although there were a relatively small number of included studies.

TABLE 4 Link between clinicopathological features and elevated CAR

Clinical features	No. of studies	No. of patients	Pooled results OR	95%CI	*P*-value	Analytical effects model
Male (vs Female)	3	1033	1.76	1.16-2.67	.008	Fixed
Tumor depth						
T3, T4 (vs T1, T2)	3	1033	2.44	1.25-4.77	.009	Random
Lymph node metastasis						
N0, N1 (vs N2, N3)	3	1033	1.96	1.05-3.67	.03	Random
Differentiation						
Poor (vs well, moderate)	3	1033	1.7	1.24-2.32	.0009	Fixed

Abbreviations: CAR, C-reactive protein to albumin ratio; Fixed, fixed-effects model; Random, random-effects model.

3.5 | Risk of bias

Risk of bias summary and graph using the QUIPS tool are described (Figure S2A,B). A lower risk of bias was present in study participation, study attrition, prognostic factor measurement, outcome measurement, and statistical analysis and reporting. However, in the study-confounding section, 40% of the high-risk studies were included.[6,13,16,17]

4 | DISCUSSION

Predicting prognosis using preoperative factors should be pivotal in determining perioperative treatment strategy. TNM tumor staging has been recognized to have the most predictive power for prognosis; however, it is well known that preoperative staging is not always consistent with postoperative staging.[26]

In recent years, the influence of systemic inflammatory responses on the short- and long-term outcomes of various malignancies has been widely recognized.[27] Immune-inflammatory measures (eg, NLR, PLR, and CAR) are easily obtained from peripheral blood tests and have been widely recognized as significant prognostic markers in solid tumors such as gastric,[28–31] colorectal,[32–34] liver,[35] and lung[36,37] cancers.

In esophageal cancer, there are currently a few systematic reviews and meta-analyses of immune-inflammatory measures as prognostic factors.[38] In the present study, we investigated and summarized the prognostic powers of NLR, PLR, and CAR for esophageal cancer using meta-analysis. Results of the meta-analysis showed a strong association between poor prognosis and high pretreatment NLR and CAR. However, PLR was not a significant prognostic marker for OS, which was not consistent with the result of a meta-analysis by Yodying et al[38] We speculated the reasons for these conflicting results as follows. Unlike NLR and CAR, many studies showed less impact of PLR on the prognosis than the other immune-inflammatory markers in various malignancies, including esophageal cancer.[39–44] We previously reported that NLR and CAR were significant prognostic measures in esophageal cancer. On the contrary, similar to the current meta-analysis, PLR did not play the same role in esophageal cancer.[17] Interestingly, we previously reported that patients who did not undergo antiplatelet or anticoagulant therapy and who had a higher PLR value had a significantly poorer OS versus those with a lower PLR. However, such differences were not observed in patients who received antiplatelet and/or anticoagulant therapies. Of the studies included in the present meta-analysis, none has described the use of antiplatelet or anticoagulant therapy. Antiplatelet or anticoagulant therapy may affect the function of the platelet and coagulation systems. Further studies investigating in more detail antiplatelet or anticoagulant therapy may help clarify the actual prognostic value of PLR for survival.

Interestingly, this meta-analysis showed that NLR, PLR, and CAR were significantly associated with T stages. Tumor invasion is a neoplastic process, closely related to inflammatory cells. The latter orchestrate the tumor microenvironment, namely cancer-related inflammation. It has been reported that cancer-related inflammation suppresses effective antitumor immunity by increasing regulatory T cells and activating cytokines in various malignancies.[27] Additionally, inflammatory mediators or immunocompetent cells are involved in migration and invasion. As a consequence, local cancer-related inflammation and/or mediators spill out of the systemic circulation potentially linking immune-inflammatory measures and tumor progression.[45]

Various limitations can be identified in the present systematic review and meta-analysis. First, in esophageal cancer, a smaller number of studies on immune-inflammatory measures for prognosis have been reported compared to other gastroenterological malignancies. Second, all studies were retrospective investigations, and clinicopathologically detailed covariates were not adequately adjusted. A high risk of bias regarding study confounding affected nearly half of the included studies. As a consequence, higher quality studies focusing on these confounding factors or prospectively carried out studies are needed. Third, the optimal cut-off values for each immune-inflammatory measure are still under debate. Seven studies used time-dependent receiver operating characteristics curve, two studies used online cut-off finding software, and one study used median value to determine the cut-off value. According to the reports, there were also differences in cut-off values. In order to apply these markers in the clinical setting, in future, it will be necessary to determine the ideal cut-off values.

In conclusion, NLR and CAR, but not PLR, are useful prognostic markers for esophageal cancer. Further prospective studies are required in order to confirm the results of this systematic review and meta-analysis.

ACKNOWLEDGEMENTS

The authors thank Shinsuke Nomura, Keita Kouzu, Yujiro Itazaki, Satoshi Tsuchiya, Mayu Tashiro, Takao Sugihara, Nozomi Ito, Hiroyuki Horiguchi, and Shuichi Hiraki for their critical review of this manuscript.

DISCLOSURE

Conflicts of Interest: Authors have no conflicts of interest to disclose and received no financial support for this study. All authors certify that they have no commercial associations that might pose a conflict of interest with respect to the submitted article.

The protocol of the present study was registered in PROSPERO and conforms to provisions of the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Ishibashi Y, Tsujimoto H, Yaguchi Y, Kishi Y, Ueno H. Prognostic significance of systemic inflammatory markers in esophageal cancer: Systematic review and meta-analysis. *Ann Gastroenterol Surg*. 2020;4:56–63. https://doi.org/10.1002/ags3.12294