

Pretreatment hematologic markers as prognostic factors in patients with nasopharyngeal carcinoma

A systematic review and meta-analysis

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Abstract

Background: Pretreatment hematologic parameters of the inflammatory response, including lymphocyte, neutrophil, and platelet counts, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio, have emerged as prognostic factors for patients with cancer. This systematic review and meta-analysis aimed to summarize the association between the hematologic markers and prognosis of nasopharyngeal carcinoma (NPC).

Methods: A systematic search of PubMed, Google Scholar, MEDLINE, EMBASE, Web of Science, and the Cochrane Library was conducted up to April 2016. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were extracted and synthesized to examine prognostic outcomes including cancer-specific survival (CSS), overall survival (OS), progression-free survival (PFS), distant metastasis-free survival, and local relapse-free survival (LRFS).

Results: Fourteen studies comprising 11,651 NPC patients were ultimately included, and all eligible studies were conducted in East Asia. The OS, CSS, PFS, distant metastasis-free survival, and LRFS risks differed among patients according to hematologic marker levels. All of the parameters were associated with prognostic outcomes in patients with NPC. NLR and lymphocyte counts were most commonly reported. A high NLR was significantly associated with poor NPC prognosis (pooled HR 1.42, 95% CI 1.21–1.67 for CSS; pooled HR 1.77, 95% CI 1.41–2.23 for OS; pooled HR 1.67, 95% CI 1.36–2.06 for PFS; pooled HR 1.64, 95% CI 1.15–2.34 for LRFS). High lymphocyte count indicated favorable NPC prognosis (pooled HR 0.72, 95% CI 0.64–0.81 for OS; pooled HR 0.71, 95% CI 0.56–0.91 for PFS).

Conclusions: Meta-analysis indicated that NLR and lymphocyte counts could be prognostic predictors in NPC for East Asian population. Patients with a high NLR or low lymphocyte count had poor prognosis. However, due to the limitation of included population, the conclusion was limited to East Asian patients only.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, DMFS = distant metastasis-free survival, HR = hazards ratio, L count = lymphocyte count, LMR = lymphocyte-to-monocyte ratio, LRFS = local relapse-free survival, Md = median, Mn = mean, Multi = multivariate analysis, N count = neutrophil count, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, OS = overall survival, P count = platelet count, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, Qua = quartile, Ran = range, SD = standard deviation, Uni = univariate analysis.

Keywords: hematologic markers, lymphocyte, nasopharyngeal carcinoma, neutrophil-to-lymphocyte ratio, prognosis

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1. Introduction

Nasopharyngeal carcinoma (NPC) is the most frequent cancer originating in the nasopharynx, which exhibits a distinct endemic distribution consisting of a particularly high incidence in Southern China and Southeast Asia.^[1] Because of inherent anatomic location and radiosensitivity, radiotherapy with or without chemotherapy is the standard treatment for NPC.^[2] Currently, the prognosis of patients with NPC is primarily evaluated using the Tumor, Node, Metastasis (TNM) staging system; however, sometimes there are discrepancies between TNM stages and the clinical outcomes in some cases.^[3] Patients within the same staging category showed various survival outcomes because of the inability of the TNM system to reflect biological heterogeneity among tumors.^[1,4] Thus, the identification of novel prognosis-related biomarkers may complement the TNM system.

Recent studies have reported a number of additional prognostic markers of NPC, which may be significantly associated with the prognosis, such as circulating Epstein-Barr virus (EBV) DNA loads,^[5] microRNA signatures,^[6,7] and abnormal expression of some functional proteins,^[8,9] but kinds of limitations, such as cost efficiency, detection difficulty, and

interlaboratory variability limited the application of these biomarkers in actual clinical use. Therefore, it is of great value to further screen for some easily applicable markers. Apart from these prognostic factors representing tumor status and molecular biology characters mentioned above, emerging evidences showed that the host inflammatory response, in particular, the systemic inflammatory response, plays an important role in the development and progression of cancer and can be implicated as a promoter of various cancers. The connection between inflammation and cancer has led to emerging interest in the prognostic value of inflammatory factors.^[10,11] Many hematologic parameters of systemic inflammatory response including leukocyte counts, neutrophil counts, monocyte counts, platelet counts, and the ratios between them such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were found to be prognostic markers in various cancers.^[12–14] Importantly, these are cheap and easily acquired markers compared with other reported markers. Hence, we aimed to conduct a systematic review and meta-analysis to reveal the predictive effect of hematologic parameters on NPC prognosis. Identifying these new biomarkers in NPC is essential to the stratification of prognosis, medical treatment, and clinical research.

2. Methods

This meta-analysis was performed in accordance to the PRISMA recommendation.

2.1. Study identification and selection

A systematic literature search of the 2 search engines PubMed and Google Scholar, and other 4 electronic databases (MEDLINE, EMBASE, Web of Science, and the Cochrane Library) was conducted to retrieve possible articles relevant to the topic of interest up to April 2016 without restriction to regions and publication types. The following MeSH terms and their combinations were searched to find potential eligible studies: “neutrophil”, “lymphocyte”, “platelet”, “monocyte”, “blood cell”, “blood routine”, “hematologic”, “nasopharyngeal neoplasms” and “head and neck neoplasms”. Two reviewers independently screened the database search for titles and abstracts. The initial selection was performed to eliminate obviously irrelevant articles and retain potentially relevant articles about prognostic role of hematologic parameters in NPC by an analysis of the title and abstract. Thereafter, the full text was reviewed according to the following eligibility criteria: studies should contain an evaluation of the prognosis value of at least 1 hematologic parameter in NPC, including lymphocyte counts, neutrophil counts, monocyte counts, platelet counts, NLR, lymphocyte-to-monocyte ratio (LMR), and PLR; and the hazard ratio (HR) of survival outcomes, along with their 95% confidence intervals (CIs) or *P* value should be available. When multiple reports describing the same population were published, the most recent or complete report was involved. Studies meeting the following criteria were excluded: duplicated literature; duplicated reported data; no available data; abstract-only laboratory studies; animal experimental studies; letters; review articles; and case reports.

2.2. Data extraction

Two reviewers (L.S. and M.W.Z.) independently extracted the following data from each study by using a standardized data-abstraction form: first author, year of publication, study period, study design, sample size, baseline characteristics of the study

cohort, cut-off value of hematologic parameters, prognostic outcomes, and statistical model. The primary outcomes were cancer-specific survival (CSS) and overall survival (OS). The secondary outcomes included progression-free survival (PFS), distant metastasis-free survival (DMFS), and local relapse-free survival (LRFS). The HR was preferred for evaluating the survival outcome since it is time-to-event data. For studies showing only survival curves, the HR values were obtained by contacting the corresponding author to obtain the original data or results, or were estimated by the methods described by Tierney et al.^[15]

2.3. Quality assessments

There are no standard quality-assessment tools for prognostic studies in systematic reviews. We chose the relatively widely used “Newcastle-Ottawa Scale (NOS)” to assess the quality of each of the involved studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This scale contains 3 domains including patient selection, comparability of the study groups, and assessment of outcome, with a total score of 0 to 9; studies achieving a score of ≥ 6 were considered to be of high quality. The quality of each eligible study was evaluated independently by 2 reviewers using a methodology assessment. The corresponding authors of the eligible studies were contacted to clarify any questions about the methodology to assess each study as accurately as possible. Any disagreement was resolved by the adjudicating the senior author.

2.4. Statistical analysis

Meta-analyses were carried out using Review Manager Version 5.3 for Windows (The Cochrane Collaboration, 2014). HR was selected as effect measure of prognostic outcomes and reported along with the corresponding 95% CI. A *P* value < 0.05 was considered statistically significant. Statistical heterogeneity across studies was explored by inspection of the forest plot, Cochran *Q* test, and Higgins *I*² statistic. Studies with a *P* < 0.1 and/or *I*² $> 50\%$ had high statistical heterogeneity. Potential publication bias was assessed by visual inspection of inverted funnel plot asymmetry.

2.5. Ethics approval

Since this is a protocol for a systematic review based on available evidences, ethics approval is not required.

3. Results

3.1. Data retrieval

The work flow chart for this study is shown in Fig. 1. Through initial searches of electronic databases and other sources, the systematic search identified 324 relevant references. A total of 128 duplicated articles were removed. After screening titles and abstracts, we excluded 106 articles, including laboratory studies, meeting abstracts, reviews, letters, and other articles irrelevant to our study. After assessment of the full text, 76 additional articles were excluded. Ultimately, 14 retrospective cohort studies^[16–29] were included in the following meta-analysis.

3.2. Study description and quality assessment

Table 1 shows the characteristics and quality assessment of the included studies. The 14 eligible studies were published between 2011 and 2015, and all were conducted in Asia. The sample sizes

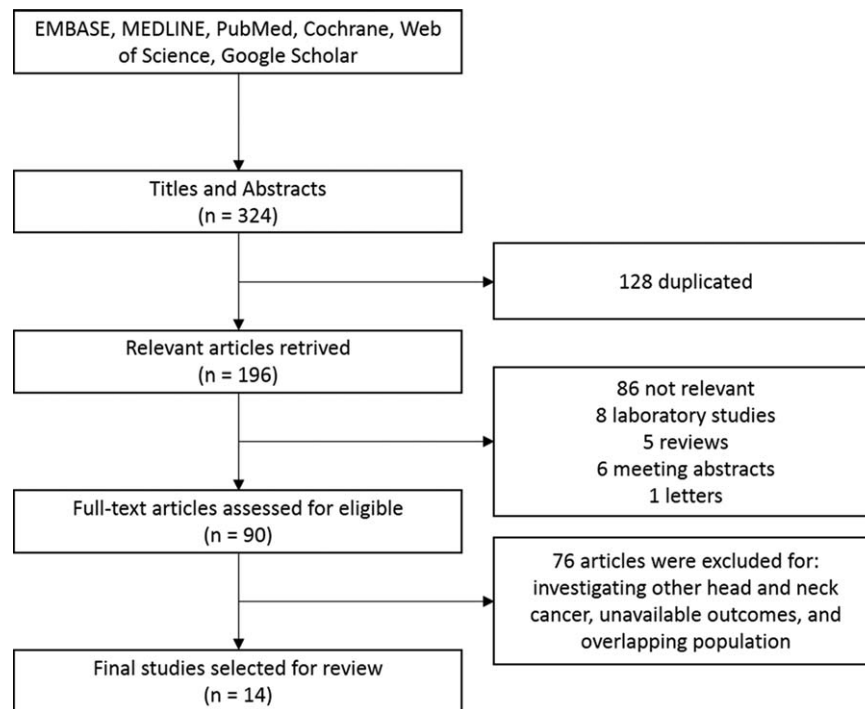


Figure 1. Literature screening flowchart.

of the included studies ranged from 62 to 1895, and a total of 11,651 cases were included. Four studies focused on metastatic NPC,^[21,22,23,27] whereas 10 studies only included patients with nonmetastatic NPC.^[16–20,24–26,28,29] The majority of studies assessed the patients' hematologic parameters before treatment. NLR and lymphocyte counts were the most reported hematologic parameters, followed by PLR and LMR. The majority of the included studies were adjusted for potential confounders using the Cox proportional-hazard model, but the adjusted factors did not conform to each study. Univariate and estimated outcomes were acquired from the article when no multivariate outcomes were reported. The NOS scores of the included studies were around 6 to 7, and the most common inadequacies in methodology were the use of a retrospective study design and incomparability between groups. The cut-off values of hematologic parameters, including NLR, PLR, LMR, lymphocyte counts, and monocyte counts, were determined by receiver-operating characteristic curves to select the most significant points in most studies;^[16,18,20,23,25,27,29] Apart from this, the study conducted by He et al^[17] and Jiang et al^[28] chose quartile values as cut-off points artificially. Because the cut-off value of hematologic parameters was artificially chosen to acquire the most significant effect and the clinicopathological features between groups in each study were incomparable, there could be both inter and intrastudy variability; thus, it was reasonable to use a random-effects model. A meta-analysis was performed using a random-effects model in the following pooled analysis.

3.3. Correlation between hematologic parameters and survival outcomes

The included studies focused on several prognostic outcomes, including CSS, OS, PFS, DMFS, and LRFS. Table 2 tabulates the

pooled results of the prognostic value of each hematologic parameter on the above outcomes.

3.4. NLR

The pooled analysis of the prognostic value of NLR is shown in Fig. 2. The effect of NLR on CSS, OS, PFS, DMFS, and LRFS was available in 3 studies,^[16,18,25] 4 studies,^[17,21,22,29] 4 studies,^[17,22,25,29] 1 study,^[16] and 2 studies,^[16,25] respectively. The synthesized HR value for each prognostic outcomes consistently favored the low NLR patients (pooled HR 1.42, 95% CI 1.21–1.67, $P < 0.001$ for CSS; pooled HR 1.77, 95% CI 1.41–2.23, $P < 0.001$ for OS; pooled HR 1.67, 95% CI 1.36–2.06, $P < 0.001$ for PFS; pooled HR 1.64, 95% CI 1.15–2.34, $P = 0.01$ for LRFS). The I^2 was 0% in each result, which meant there was no heterogeneity in the pooled estimate. The value of NLR for predicting DMFS was available in 1 study,^[16] which also favored low NLR patients (HR 2.37, 95% CI 1.37–4.10). The above findings meant that patients with a higher NLR had both higher mortality risk and recurrence risk than those with a low NLR.

3.5. PLR

Three studies reported the effect of PLR on OS, and 2 studies reported the effect of PLR on PFS.^[22,28,29] Pooled results of 3 studies including 1723 patients showed significant superiority of a low PLR on OS (pooled HR 1.68, 95% CI 1.20–2.35, $P < 0.001$). However, pooled analysis showed that PLR was not associated with PFS (pooled HR 1.46, 95% CI 0.74–2.87, $P = 0.27$). In addition, 1 study conducted by Jiang et al^[28] reported that decreased PLR values predicted better CSS and DMFS. No study reported a correlation between PLR and LRFS.

Table 1

Characteristics of the included studies.

First author/year	Duration	Country	Sample size (n)	Age	Sex (M/F)	Metastases	UICC/AJCC	Marker	Sample time	Cut-off	Outcome	Uni/multi	NOS score
Ann/2011 ^[16]	Nov 2001–Jul 2002	China	363	Med = 47 Ran = 12–76	274/89	None	I/II/III/IV 14/81/165/103	NLR	Pre	3.73	CSS, DMFS, LRFS	Multi Extracted	7
He/2012 ^[17]	Oct 2005–Oct 2007	China	1410	Mn = 46.1 Ran = 13–79	1027/383	None	(I, II/III, IV) 414/996	NLR N	Pre	2.74 5.49	OS, PFS OS, PFS	Multi Multi	7
Chang/2013 ^[18]	Jan 2001–Dec 2004	China	1895	Mn = 46.6 SD = 7.1	1455/440	None	I/II/III/IV 104/662/746/383	NLR P	Pre	2.53 2.5	OS, PFS CSS	Multi Multi	6
Gao/2013 ^[19]	2003–2004	China	1582	Mn = 50.1	1187/395	None	I/II/III/IV 77/441/693/371	P	During	300	CSS	Multi	6
Li/2013 ^[20]	2005–2008	China	1547	Med = 51	1124/423	None	(I, II/III, IV) 334/1213	LMR	Pre	5.22	OS, PFS, DMFS, LRFS	Multi	7
Jin/2013 ^[21]	Jan 2006–Dec 2011	China	229	Med = 45 Ran = 18–72	196/33	All	IVc 229	NLR N	Pre	2.145 4.76	OS, PFS, DMFS, LRFS OS	Uni Multi	6
Chen/2014 ^[22]	Oct 2005–Oct 2011	China	211	Med = 46 Ran = 14–72	181/30	All	IVc 211	NLR PLR	Pre	5 150, 300	OS, PFS OS, PFS	Multi Uni	6
Lin/2014 ^[23]	Jan 2006–Dec 2010	China	256	Mn = 53.6 Ran = 35–69	179/77	All	IVc 256	LMR M	Pre	5.07 0.35	OS OS	Multi Multi	7
Chen/2015 ^[24]	Nov 2000–Dec 2004	China	1501	<45/>45 734/767	1158/343	None	I/II/III/IV 127/583/543/248	L P	Pre	2.25 150, 300	OS OS, DMFS	Multi Multi	7
Cho/2015 ^[25]	Jul 2001–Sep 2013	Korea	62	<50/>50 26/36	43/19	None	(I, II/III, IV) 16/46	NLR L	Pre	2.9 0.245	CSS, PFS, LRFS CSS, PFS, LRFS	Uni Multi	5
Dur/2015 ^[26]	Oct 2009–Feb 2012	China	411	<50/>50 278/133	312/99	None	III/IV 314/97	mL P	During Pre	0.245 300	CSS, PFS, LRFS DMFS	Multi Multi	6
Jiang/2015 ^[27]	Jan 2003–Dec 2009	China	672	<46/>46 316/356	546/126	All	IVc 672	LMR M	Pre	2.475 0.665	OS OS	Multi Multi	7
Jiang/2015 ^[28]	Jan 2008–Dec 2010	China	1261	Med = 46 Qua = 39–55	919/342	None	I/II/III/IV 40/186/664/371	PLR	Pre	1.390 153.6	OS CSS, OS, DMFS	Multi Multi	6
Sun/2015 ^[29]	Jan 2008–Dec 2011	China	251	<50/>50 167/84	180/71	None	I/II/III/IV 6/40/119/86	NLR PLR L	Pre	2.7 167.2 1.5	OS, PFS OS, PFS PFS	Multi Multi Multi	6

CSS = cancer-specific survival, DMFS = distant metastasis-free survival, During = the hematologic markers were tested during treatment period, L count = lymphocyte count ($\times 10^9/L$), LMR = lymphocyte-to-monocyte ratio, LRFS = local relapse-free survival, M = monocyte count ($\times 10^7/L$), Mn = median, mL = the minimum absolute lymphocyte count during radiotherapy, Mn = mean, Multi = multivariate analysis, N count = neutrophil count ($\times 10^9/L$), NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle-Ottawa Scale score, OS = overall survival, P count = platelet count, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, Pre = the hematologic markers were tested before treatment, Qua = quartile, Ran = range, SD = standard deviation, Uni = univariate analysis.

Table 2**Overview of pooled results of the prognostic value of hematologic parameters.**

Biomarkers	First author, year	CSS	OS	PFS	DMFS	LRFS
NLR	An, 2011 ^[16]	1.74 (1.15–2.62)	NA	NA	2.37 (1.37–4.10)	1.51 (1.02–2.24)
	He, 2012 ^[17]	NA	1.57 (1.04–2.39)	1.68 (1.19–2.38)	NA	NA
	Chang, 2013 ^[18]	1.351 (1.128–1.618)	NA	NA	NA	NA
	Jin, 2013 ^[21]	NA	1.906 (1.310–2.771)	NA	NA	NA
	Chen, 2014 ^[22]	NA	1.800 (1.103–2.940)	1.400 (0.995–1.971)	NA	NA
	Cho, 2015 ^[25]	1.72 (0.75–3.94)	NA	2.36 (1.17–4.75)	NA	2.38 (1.05–5.40)
	Sun, 2015 ^[29]	NA	1.87 (0.89–3.95)	2.01 (1.23–3.29)	NA	NA
	Pooled results					
	No. of studies	3	4	4	1	2
	HR (95% CI), I^2 P	1.42 (1.21–1.67), 0% <0.001	1.77 (1.41–2.23), 0% <0.001	1.67 (1.36–2.06), 0% <0.001	2.37 (1.37–4.10)	1.64 (1.15–2.34), 0% 0.01
PLR	Chen, 2014 ^[22]	NA	1.311 (0.928–1.853)	1.061 (0.844–1.334)	NA	NA
	Jiang, 2015 ^[28]	1.84 (1.26–2.67)	1.83 (1.28–2.61)	NA	1.56 (1.11–2.19)	NA
	Sun, 2015 ^[29]	NA	2.64 (1.25–5.60)	2.12 (1.35–3.33)	NA	NA
	Pooled results					
	No. of studies	1	3	2	1	
	HR (95% CI), I^2 P	1.84 (1.26–2.67)	1.68 (1.20–2.35), 43% <0.001	1.46 (0.74–2.87), 86% 0.27	1.56 (1.11–2.19)	
LMR	Li, 2013 ^[20]	NA	0.558 (0.417–0.748)	0.669 (0.535–0.838)	0.543 (0.403–0.732)	0.885 (0.637–1.229)
	Lin, 2014 ^[23]	NA	0.42 (0.30–0.59)	NA	NA	NA
	Jiang, 2015 ^[27]	NA	0.5 (0.41–0.6)	NA	NA	NA
	Pooled results					
	No. of studies		3	1	1	1
HR (95% CI), I^2 P		0.50 (0.43–0.58), 0% <0.001	0.669 (0.535–0.838)	0.543 (0.403–0.732)	0.885 (0.637–1.229)	
N count	He, 2012 ^[17]	NA	1.44 (0.95–2.18)	1.30 (0.93–1.83)	NA	NA
	Jin, 2013 ^[21]	NA	1.866 (1.261–2.761)	NA	NA	NA
	Pooled results					
	No. of studies		2	1		
HR (95% CI), I^2 P		1.65 (1.24–2.20), 0% <0.001	1.30 (0.93–1.83)			
L count	He, 2012 ^[17]	NA	0.8 (0.53–1.20)	0.62 (0.44–0.87)	NA	NA
	Li, 2013 ^[20]	NA	0.647 (0.489–0.858)	0.815 (0.656–1.013)	0.733 (0.553–0.972)	0.959 (0.694–1.326)
	Jin, 2013 ^[21]	NA	0.704 (0.483–1.026)	NA	NA	NA
	Lin, 2014 ^[23]	NA	0.59 (0.43–0.81)	NA	NA	NA
	Cho, 2015 ^[25]	7.06 (1.94–25.6)	NA	2.83 (1.19–6.71)	NA	2.51 (0.91–6.93)
	Jiang, 2015 ^[27]	NA	0.77 (0.64–0.93)	NA	NA	NA
	Sun, 2015 ^[29]	NA	1.29 (0.58–2.86)	1.18 (0.74–1.90)	NA	NA
	Pooled results					
	No. of studies	1	6	4	1	2
	HR (95% CI), I^2 P	7.06 (1.94–25.6)	0.72 (0.64–0.81), 0% <0.001	0.71 (0.56–0.91), 34% 0.01	0.733 (0.553–0.972)	0.71 (0.31–1.61), 62% 0.41

CI = confidence interval, CSS = cancer-specific survival, DMFS = distant metastasis-free survival, HR = hazard ratio, L count = lymphocyte count, LMR = lymphocyte-to-monocyte ratio, LRFS = local relapse-free survival, N count = neutrophil count, NA = not available, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, P count = platelet count, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio.

3.6. LMR

Three studies provided sufficient data on OS outcome for the pooled estimate.^[20,23,27] The pooled HR favored patients with a higher LMR (pooled HR 0.50, 95% CI 0.43–0.58, $P < 0.001$). PFS, DMFS, and LRFS outcomes were available only in 1 study,^[20] which demonstrated that higher LMR predicted better PFS and DMFS, but not LRFS.

3.7. Lymphocyte counts

The pooled analysis of the prognostic value of lymphocyte counts is shown in Fig. 3. The effect of lymphocyte counts on OS, PFS, and LRFS was reported in 6 studies,^[17,20,21,23,27,29] 4 studies,^[17,20,25,29] and 2 studies,^[20,25] respectively. The pooled results showed that patients with higher lymphocyte counts had better OS (pooled HR 0.72, 95% CI 0.64–0.81, $P < 0.001$) and PFS

(pooled HR 0.71, 95% CI 0.56–0.91, $P = 0.01$). However, no significant difference in LRFS was observed (pooled HR 0.71, 95% CI 0.31–1.61, $P = 0.41$). DMFS was available in 1 study, which reported a borderline significant decreased HR in patients with higher lymphocyte counts.^[20] In addition, 1 study assessed the prognostic value of lymphocyte counts on CSS^[25] and found that both pretreatment lymphocyte counts and minimum absolute lymphocyte counts during treatment were correlated with CSS.

3.8. Neutrophil counts

In terms of prognostic value of neutrophil counts, only 2 studies^[17,21] reported OS outcome and 1 study^[17] reported PFS outcome. The pooled HR for OS favored patients with a low neutrophil counts (pooled HR 1.65, 95% CI 1.24–2.20,

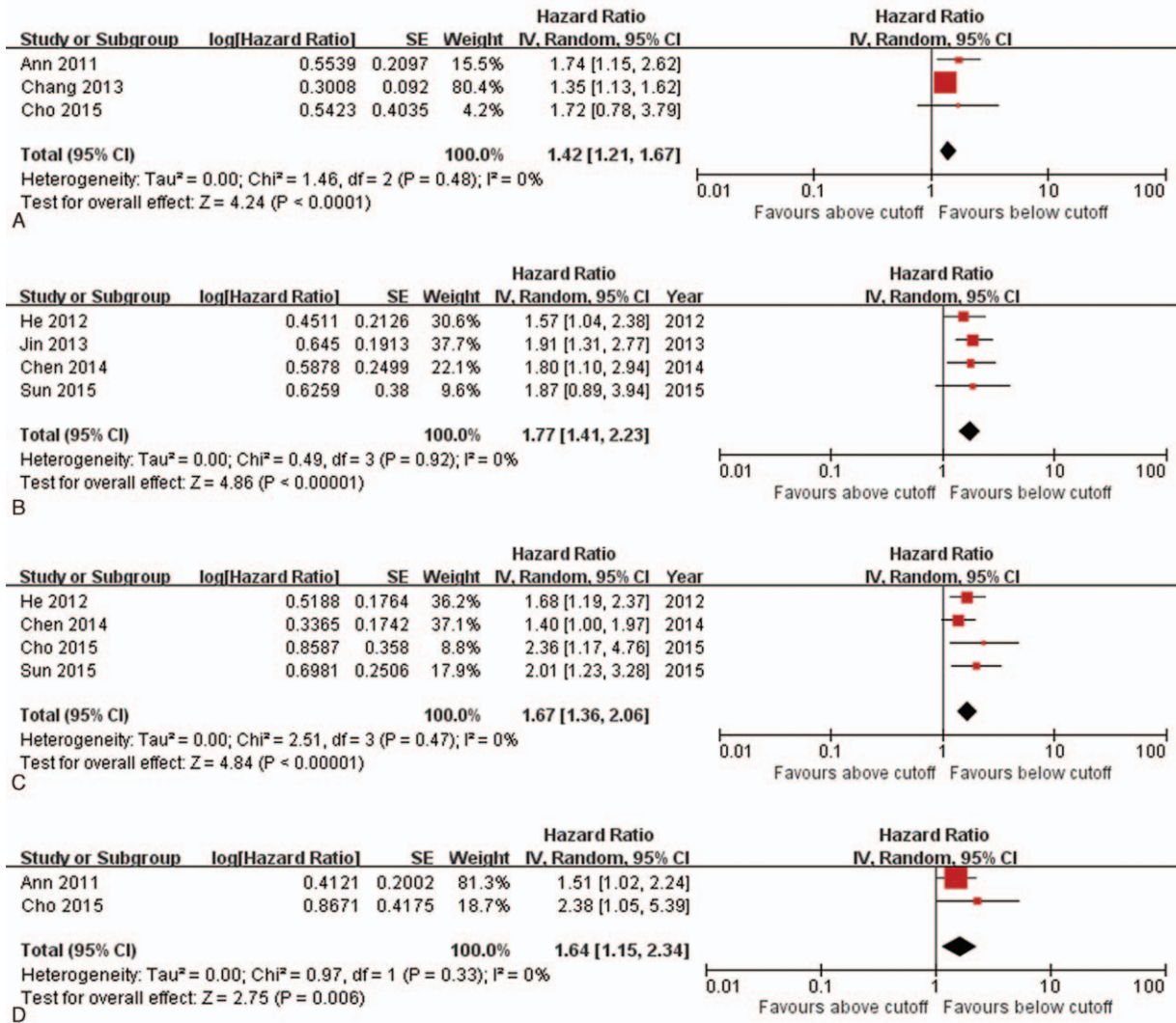


Figure 2. Forest plot and meta-analysis for relationship between pretreatment NLR and CSS, OS, PFS, and LRFS in patients with NPC. (A) Forest plot of the pooled analysis of NLR and CSS. (B) Forest plot of the pooled analysis of NLR and OS. (C) Forest plot of the pooled analysis of NLR and PFS. (D) Forest plot of the pooled analysis of NLR and LRFS. CSS=cancer-specific survival, LRFS=local relapse-free survival, NLR=neutrophil-to-lymphocyte ratio, NPC=nasopharyngeal carcinoma, OS=overall survival, PFS=progression-free survival.

$P < 0.001$). The study conducted by He et al^[17] reported that the PFS rate was not significantly different between the low and high neutrophil count groups.

3.9. Platelet counts

The prognostic value of platelet count on survival outcomes of patients with NPC is summarized in Table 3. One study^[18] evaluated the effect of platelet counts during treatment on survival, whereas 3 other studies^[19,24,26] evaluated that of the pretreatment platelet count. Most studies reported that patients with high platelet counts showed poor prognosis. However, it is worth noting that Chen et al^[24] found that patients those with lowest platelet counts ($<150 \times 10^9$) also demonstrated poor OS; additionally, the OS of patients with highest platelet counts ($>300 \times 10^9$) was not significantly lower than those with lowest platelet counts ($<150 \times 10^9$). These inconsistent results across studies suggest that patients with a very low platelet count may also have a poor prognosis.

3.10. Sensitivity analysis

The sensitivity analysis was performed of the pooled estimates that involved more than 2 studies. As shown in Table 2, in these pooled analyses, most of the I^2 values were 0%, which indicated a lack of heterogeneity. A sensitivity analysis performed by removing individual studies, and we found that both the I^2 values and statistical difference of pooled HR valued did not change significantly, indicating there was no heterogeneity caused by a single study.

3.11. Publication bias

The above analysis showed that NLR and lymphocyte counts were the 2 most commonly reported hematologic parameters. Therefore, funnel plots of the pooled analysis of these 2 parameters were created. As shown in Fig. 4, the funnel plots showed a symmetrical distribution of studies around the vertical axis. However, because the number of included studies in each pooled analysis was small, the funnel plots may not be significant.

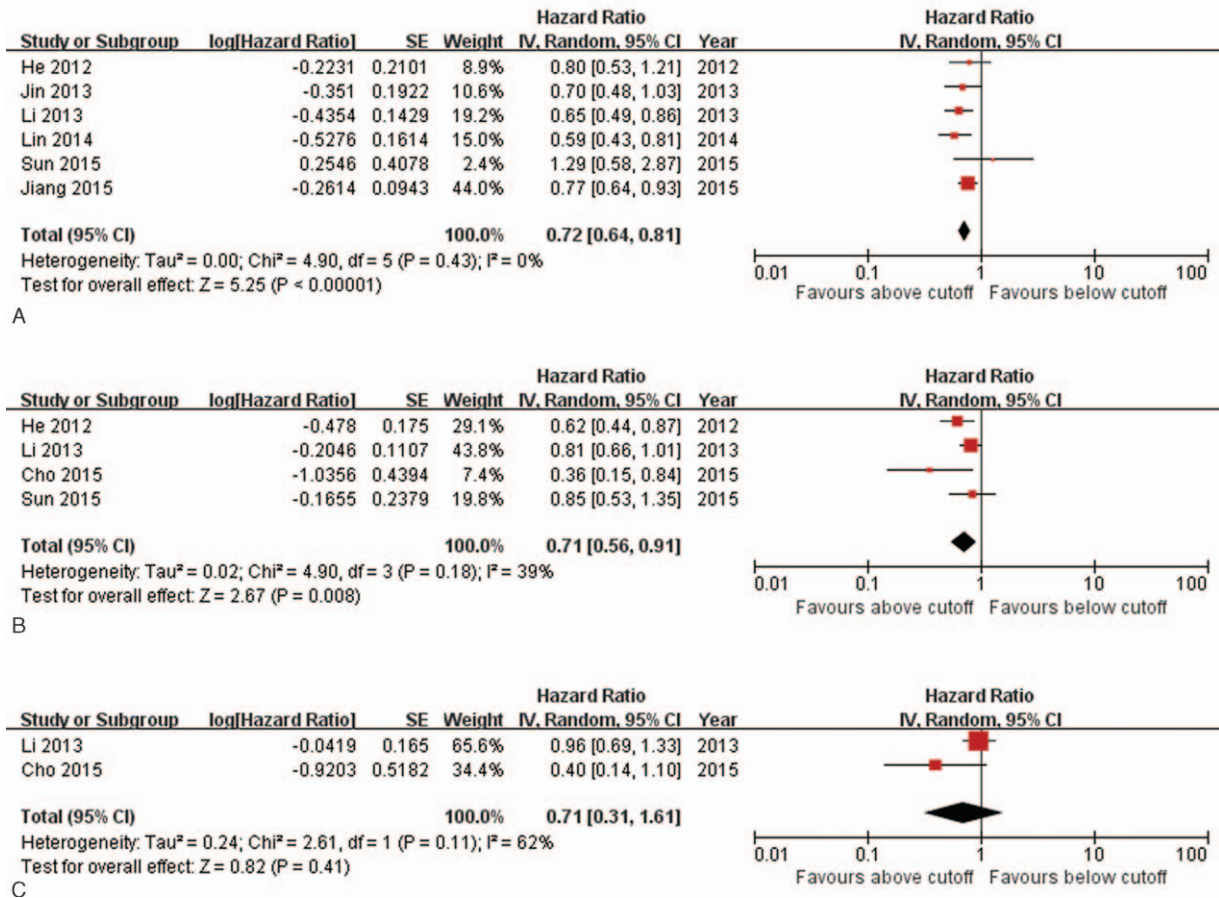


Figure 3. Forest plot and meta-analysis for relationship between pretreatment lymphocyte counts and OS, PFS, and LRFS in patients with NPC. (A) Forest plot of the pooled analysis of lymphocyte counts and OS. (B) Forest plot of the pooled analysis of lymphocyte counts and PFS. (C) Forest plot of the pooled analysis of lymphocyte counts and LRFS. LRFS=local relapse-free survival, NPC=nasopharyngeal carcinoma, OS=overall survival, PFS=progression-free survival.

4. Discussion

Several hematologic parameters of systemic inflammation, such as lymphocyte counts, neutrophil counts, monocyte counts, platelet counts, NLR, LMR, and PLR, have emerged as prognostic factors for a variety of cancer types. These markers can be measured easily and inexpensively; therefore, they may become prognostic markers with widespread actual clinical use.

Identifying these easily applicable markers related to NPC prognosis may help clinicians predict individual outcome and guide clinical treatments. In this study, we identified and summarized the published articles that reported the association between the hematologic parameters and NPC prognosis. Our pooled analysis showed that all of the above parameters, including NLR, PLR, LMR, lymphocyte counts, neutrophil counts, and platelet counts, were associated with survival

Table 3
Summary of multivariate analyses results of prognostic value of platelet counts.

First author, year	Cut-off value*	CSS	OS	DMFS
Chang, 2013 ^[18]	>300 vs ≤300	1.536 (1.162–2.028)	NA	NA
Gao, 2013 ^[19]	>300 vs ≤300	1.689 (1.269–2.259)	NA	1.652 (1.119–2.439)
Du, 2015 ^[26]	>300 vs ≤300	NA	NA	2.531 (1.288–4.977)
Chen, 2015 ^[24]	CCRT group			
	≤150 vs 150–300	NA	2.024 (1.165–3.516)	1.720 (0.670–4.412)
	>300 vs 150–300	NA	1.742 (1.090–2.786)	2.110 (1.084–4.108)
	>300 vs ≤150	NA	0.861 (0.445–1.665)	1.227 (0.429–3.512)
	RT group			
	≤150 vs 150–300	NA	1.265 (0.860–1.860)	1.148 (0.541–2.437)
>300 vs 150–300	NA	1.740 (1.283–2.362)	2.819 (1.766–4.497)	
>300 vs ≤150	NA	1.376 (0.886–2.137)	2.454 (1.121–5.372)	

CSS=cancer-specific survival, DMFS=distant metastasis-free survival, NA= not available, OS=overall survival.

* Unit of platelet is 10⁹/L.

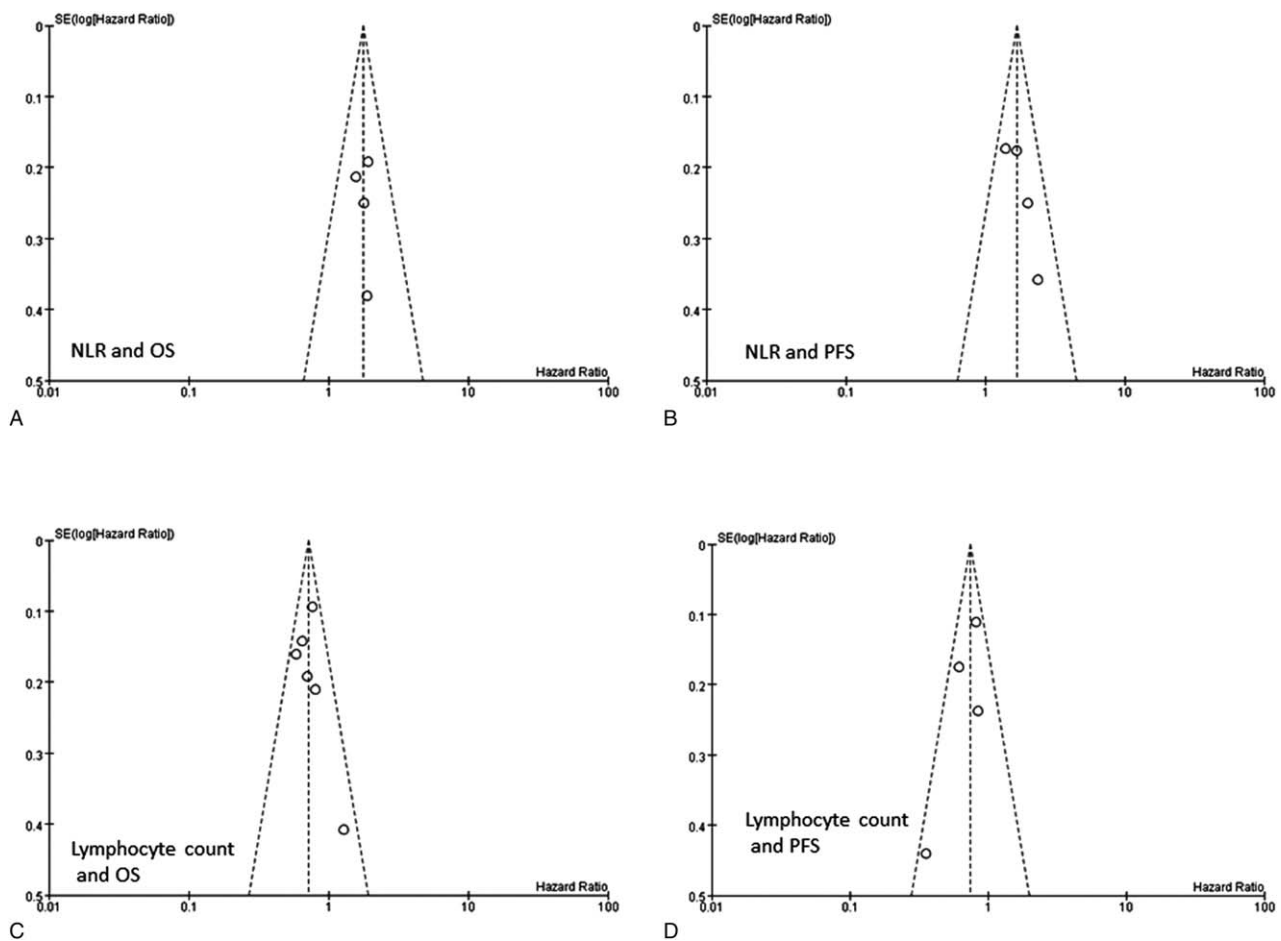


Figure 4. Funnel plots based on prognostic value of NLR and lymphocyte counts. (A) Funnel plot based on the pooled analysis of NLR and OS. (B) Funnel plot based on the pooled analysis of NLR and PFS. (C) Funnel plot based on the pooled analysis of lymphocyte counts and OS. (D) Funnel plot based on the pooled analysis of lymphocyte counts and PFS. NLR=neutrophil-to-lymphocyte ratio, OS=overall survival, PFS=progression-free survival.

outcomes of East Asian patients with NPC. NLR and lymphocyte counts were the 2 most commonly reported parameters that could be prognostic predictors for NPC. Patients with a high NLR or low lymphocyte count were deemed to have a poor prognosis.

It is now generally recognized that inflammation response plays a critical role in tumor progression and may influence survival outcomes in patients with cancer.^[30] Hanahan and Weinberg^[31] stated that an important hallmark of cancer is that tumor cells evade immunological attack from lymphocytes, macrophages, and natural killer cells. Lymphocytes are crucial components of the adaptive immune system, which eliminates cancer cells. The presence of lymphocyte infiltrate in tumors is correlated with good prognosis, and T cells have been used to target cancers.^[32,33] On the contrary, neutrophilia acts as an important component of inflammatory response and inhibits the immune system by suppressing the cytotoxicity of immune cells such as lymphocytes and activated T cells.^[34] Apart from this, neutrophils in the tumor microenvironment have been shown to produce cytokines and chemokines, such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), interleukin (IL)-6, and IL-8, which promote tumor cell growth, angiogenesis, and metastasis.^[30,35,36] A high NLR indicates systemic and local inflammation that provides a favorable microenvironment for tumor growth, migration, invasion, and metastasis.^[30] As systematic inflammatory markers, both

lymphocyte counts and neutrophil counts, and also NLR have been recognized to be associated with solid tumor prognosis.^[37–39]

We found lymphocyte counts and NLR were the 2 most reported prognostic hematologic parameters of NPC. Our pooled analysis demonstrated that a high NLR or low lymphocyte count was associated with poor prognosis in patients with NPC, which was inconsistent with these above theories. These 2 parameters, lymphocyte count and NLR, are easily reproducible and widely available markers. However, it is worth noting that all of the involved studies in this meta-analysis measured cell counts before treatment, but none evaluated the volatility of the pretreatment counts. Meanwhile, the relationship between changes in cell counts during treatment and prognosis was seldom examined. Therefore, the clinical practicability of these hematologic parameters was limited. Further data on the pretreatment volatility and continuous change during treatment of these parameters are warranted.

Platelets, another blood component, have been well-known to mediate tumor cell growth, metastasis, and angiogenesis. Activated platelets are able to interact with cancer cells through paracrine signaling or direct contact, thereby promoting tumor cell growth and survival.^[40–42] Elevated blood platelet count is a common phenomenon in kinds of malignancies and has been reported to be associated with prognosis in these cancer patients. In this meta-analysis, we found only 3 studies examined here

evaluated the prognosis value of platelet counts: Du et al,^[26] Gao et al,^[19] and Chang et al^[18] reported that thrombocytosis was associated with poor survival outcome in patients with NPC. Differently, the study conducted by Chen et al^[24] stated that low and high platelet counts may predict poor survival and distant metastasis in NPC. The contradicting conclusions among these studies revealed that the prognostic value of platelet counts in NPC requires further study and that there may be a potential “J-shape” correlation between platelet count and surviving HR.

There were some limitations that should be addressed in this study. First, all of the studies included in our meta-analysis were retrospective. Second, all of the included studies used dichotomous variables to determine the prognostic value. The cut-off values differed between the different studies, and the cut-off value for each parameter seemed to be calculated in each study to acquire the most significant effect; thus, the final significance of the outcomes seemed to be created rather than intrinsic. The other side-effect of using an artificial cut-off value was the incomparability between groups. Thus, we recommend using a continuous rather than categorical variable in future studies. Third, a number of the included studies did not report CSS, which is a critical outcome of a cancer survival analysis. Fourth, the correlation between hematologic cells and other systemic inflammatory markers should be noted, which may result in high colinearity in a multivariate analysis and affect the estimation of HR in the Cox regression model. Moreover, almost all of the studies chose a dichotomous cut-off value; therefore, the survival outcomes of patients with very low level of these hematologic parameters may be ignored. In addition, almost all of the included studies were from Chinese population, and 1 study was conducted in Korea; therefore, the conclusion might be limited to East Asian population. This might be explained by the much higher incidence of NPC and much more number of cases in China and Southeast Asia compared with other regions of the world.^[43]

5. Conclusions

To our knowledge, this is the first meta-analysis to evaluate the hematologic parameters as prognostic markers for patients with NPC. Our meta-analysis summarized the prognostic value of hematologic parameters in patients with NPC examined in the articles published to date, and the pooled results suggested that these hematologic parameters mentioned above were closely correlated with the survival outcomes of patients with NPC. NLR and lymphocyte counts were the 2 most reported parameters and could be prognostic predictors for patients with NPC. Patients with a high NLR or low lymphocyte count were deemed to have a poor prognosis. The conclusion should be limited to East Asians due to the limitation of included populations, and further well-designed, prospective studies, and also researches from other parts of the world, are needed.

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