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Meta-analysis of multiple hematological biomarkers as prognostic predictors of survival in bladder cancer

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Abstract

Background: Accumulating emerging studies have demonstrated that systemic inflammation can obviously affect tumor occurrence and progression. Nevertheless, the prognostic value of hematological inflammation biomarkers in bladder cancer is controversial. Thus, we conducted a meta-analysis to evaluate the key hematological biomarkers with various clinical outcomes in bladder cancer.

Methods: We used online databases PUBMED and EMBASE to search relevant studies published prior to August 2019. After collecting the basic characteristics and prognostic data from the studies included, overall survival (OS), cancer-specific survival (CSS) and progression-free survival (PFS) were used as primary results. Subgroup analyses were performed according to ethnicity, the number of samples, survival outcomes, the value of cut-off, follow-up time and metastasis stage.

Results: Thirty-three independent studies with 17,087 bladder cancer patients were added in the present analysis. The collected results showed that the increased neutrophil-to-lymphocyte ratio was associated with a poor OS (hazard ratio [HR] = 1.48, 95% confidence interval [CI]: 1.32–1.67, $P < .00001$), CSS (HR = 1.71, 95%CI: 1.35–2.18, $P < .0001$) and PFS (HR = 1.59, 95%CI: 1.38–1.83, $P < .00001$). Additionally, the elevated platelet-to-lymphocyte ratio was related to a poor OS (HR = 1.29, 95% CI: 1.07–1.54, $P = .007$), CSS (HR = 1.14, 95%CI = 0.98–1.34, $P = .02$) and PFS (HR = 1.2, 95%CI: 1.08–1.34, $P = .0008$). Moreover, a decreased lymphocyte-to-monocyte ratio was associated with a poor OS (HR = 0.77, 95% CI: 0.70–0.84, $P = .001$), CSS (HR = 0.76, 95%CI: 0.70–0.84). An elevated modified Glasgow prognostic score was also associated with a poor OS (HR = 2.71, 95%CI: 1.08–2.82, $P = .003$), CSS (HR = 1.50, 95%CI: 0.56–4.05) and PFS (HR = 1.52, 95%CI: 1.23–1.88, $P = .001$).

Conclusions: Our study indicated that the pretreatment hematological biomarkers (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and modified Glasgow prognostic score) were predicative biomarkers of prognosis in bladder cancer patients. Further research is needed to conduct further prospective and multicenter studies to confirm our findings.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, mGPS = modified Glasgow prognostic score, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, TURBT = transurethral resection of bladder tumor.

Keywords: bladder cancer, hematological markers, meta

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1. Introduction

Bladder cancer has become one of the most commonly seen malignancies of the urinary system in the United States of America. An American research estimates that 80470 new bladder cancer patients and 1767 deaths in 2019.[1] In China, the mortality and morbidity rate associated with bladder cancer ranked second compared to all other malignancies of urinary system.[2] Bladder cancer is generally divided into 2 types, muscle-invasive bladder cancer (20%–30%) and non-muscle invasive bladder cancer (70%–80%).[3] For muscle-invasive bladder cancer, OS after radical cystectomy is poor and about 50% of patients have distant metastasis and death after radical cystectomy.[4,5] The transurethral resection of bladder tumor (TURBT) marks the foremost step for patients with non-muscle invasive bladder cancer and recurrent tumors are also usually treated by repeat TURBT surgery. However, it is very difficult to sort out the eligible patients because of the weak prognostic value of the traditional TNM staging system. Therefore, finding novel and effective prognostic biomarkers is significant for improving survival rate for patients with bladder cancer.

Accumulating emerging studies have demonstrated that systemic inflammation could obviously affect tumor occurrence and progression,[6,7] like albumin-to-globulin ratio,[8] C-reactive protein/albumin ratio,[9] inflammation-based index,[10] neutrophil-to-lymphocyte ratio (NLR),[11] platelet-to-lymphocyte ratio (PLR),[12] lymphocyte-to-monocyte ratio (LMR)[13] and modified Glasgow prognostic score (mGPS).[14] These novel biomarkers are more easily accessible and inexpensive compared with traditional biomarkers. However, the prognostic function of these aforementioned hematological biomarkers in bladder cancer have not been completely expounded. Thus, we conducted a meta-analysis to evaluate the key hematological biomarkers (NLR, PLR, MLR and mGPS) with various survival outcomes in bladder cancer.

2. Methods

2.1. Search strategy

This meta-analysis was done with regards to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] In August 2019, a systematic literature search was conducted with the help of PubMed and EMBASE. The search terms were as follows: "hematologic biomarkers", "NLR", "LMR", "PLR", "mGPS", "prognosis" and "bladder cancer".

2.2. Studies inclusion and exclusion criteria

We added some studies that met the inclusion criteria given below:

(1) the patients with bladder cancer;
(2) studies with a clear presentation of the main outcomes including at least 1 hematologic biomarker, such as NLR, PLR, LMR, and mGPS;
(3) must contain risk estimates, such as hazard ratio (HR), with 95% confidence intervals (95%CIs).

The exclusion criteria:

(1) reviews, letters, laboratory studies, case reports and meta-analysis;
(2) studies without survival data, such as overall survival (OS), cancer-specific survival (CSS), disease-specific survival, progression-free survival (PFS), recurrence-free survival, disease-free survival and modified Glasgow prognostic score (mGPS);
(3) article not published in English.

2.3. Data extraction and quality assessment

Data extraction and quality evaluation were independently performed by 2 investigators (Longqing Li, Junxiao Liu). Any disagreements were decided by another author (Lianghao Zhang). The following information was recorded: ethnicity, sample size, survival outcomes, cut-off value, follow-up time, disease stage, HRs and 95%CIs. The quality of the included articles was assessed by the Newcastle-Ottawa Quality Scale (NOS).[16] The NOS includes the following 3 parts:

(1) selection (0–4 points);
(2) comparability (0–2 points); and
(3) outcome (0–3 points).

The maximum score is 9 points and NOS scores ≥ 6 were considered as high-quality studies.

2.4. Statistical analyses

Considering the similar survival outcomes, we combined disease-specific survival and CSS and regarded them as CSS. In addition, recurrence-free survival and PFS were combined as PFS. Meanwhile, pooled HRs and corresponding 95%CIs were used to analyze the association between hematological biomarkers and OS, CSS and PFS for patients with bladder cancer. We measured the heterogeneity among studies was measured by Cochrane Q test and the I^2 statistic. A random-effects model (DerSimonian-Laird method) was selected if there was significant heterogeneity ($I^2 > 50\%$, $P < .05$).[17] Otherwise, the fixed-effect model (Mantel-Haenszel method) was adopted. In addition, we performed[18] subgroup analyses to examine the heterogeneity by treatment method, ethnicity, sample size, cut-off and tumor stage of NLR, PLR, and LMR. Publication bias was evaluated by Begg funnel plots and Egger tests.[19] The statistical analyses were conducted using RevMan5.3 (Cochrane Collaboration) and $P < .05$ was considered statistically significant.

3. Results

The flowchart of the literature selection process was shown in Figure 1. We initially identified 485 potentially relevant articles, after removing 124 duplicates, 361 studies remained. After title and/or abstract examination, 193 papers were excluded and 168 records were evaluated by full-text reading. Among these 168 studies, 43 full text studies were eliminated because of various reasons. Thirty-three studies enrolling 17087 participants met the eligible criteria strictly and were included in the final analysis (Table 1).

3.1. The prognostic significance of NLR in bladder cancer

Twenty studies[20–39] comprising 11013 patients provided data for estimating the association between NLR and OS in bladder cancer patients. In these studies, high NLR was significantly correlated with poor OS, HR was 1.48 (95%CI: 1.32–1.67, $P < .00001$), and had significant heterogeneity ($I^2 = 81\%$, $P < .00001$; Fig. 2).

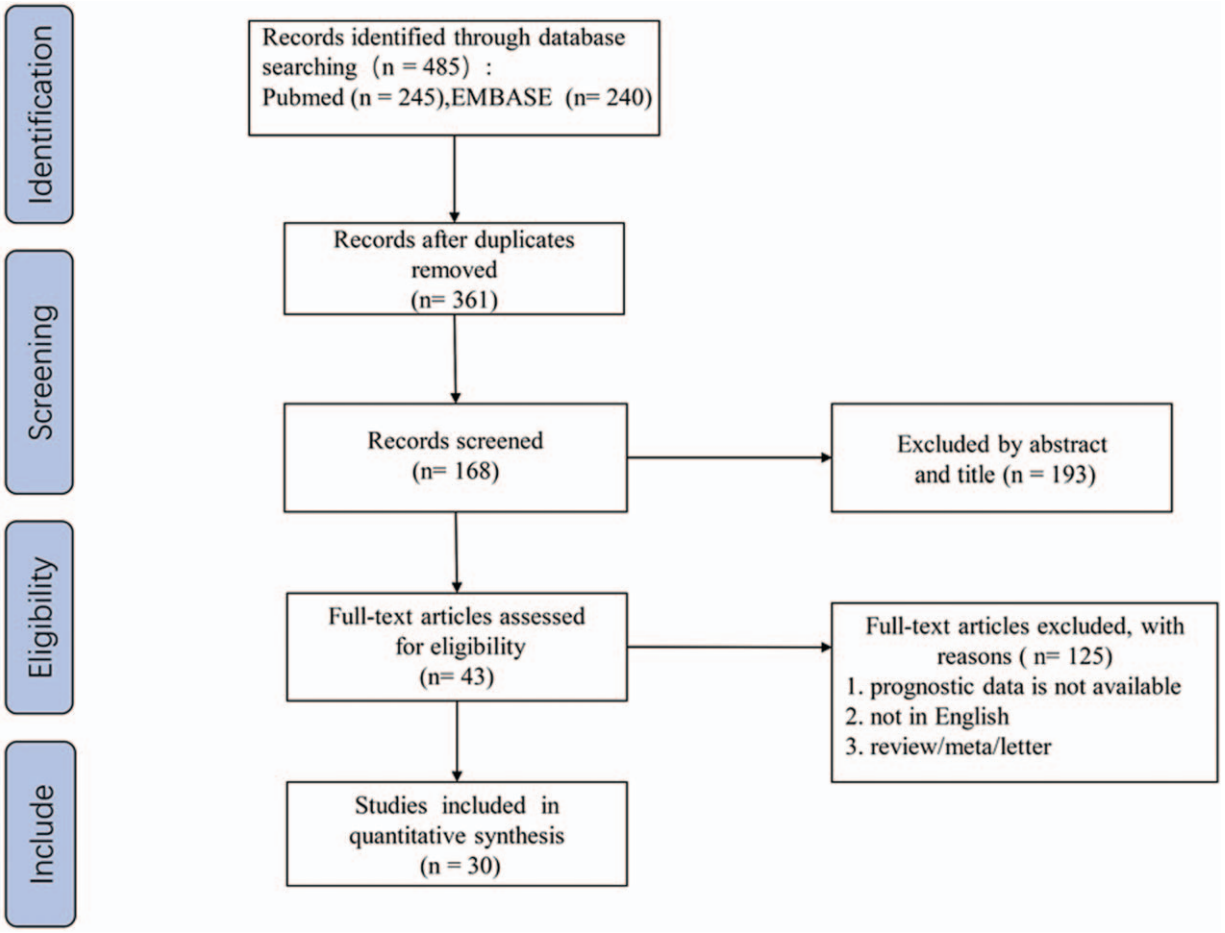

Figure 1. Flow diagram for study selection process.

In total, 14 studies,[20,21,23,25,26,28,30,33,34,36,38–41] including 9602 patient, studied in the NLR analysis of CSS. As demonstrated in Figure 2, the higher NLR was correlated with poor CSS and the pooled HR was 1.71 (95%CI: 1.35–2.18, $P < .0001$) but with moderate heterogeneity ($I^2 = 65\%$, $P = .003$; Fig. 2).

Finally, the association between NLR and PFS was investigated in 13 studies[20,21,23–25,28,29,31,34,38,42–44] involving 9539 bladder cancer patients. NLR had a significant prognostic effect on PFS and the pooled HR was 1.59 (95%CI: 1.38–1.83, $P < .00001$) and with significant heterogeneity ($I^2 = 71\%$, $P < .0001$; Fig. 2).

The subgroup analysis (Table 2) shown that the significant prognostic value for NLR on OS, CSS and PFS in most subgroups but the CSS TURBT group had no significant prognostic value.

3.2. The prognostic significance of PLR in bladder cancer

There were ten researches,[23,24,26,29,30,36,37,45–47] including 4281 patients, providing data for estimating the prognostic effect of PLR on OS in patients with bladder cancer. The pooled analysis illustrated that a high PLR was associated with poor OS, with the pooled HR being 1.29 (95%CI: 1.07–1.54, $P = .007$) with significant heterogeneity ($I^2 = 80.0\%$, $P < .00001$; Fig. 3).

The correlation between PLR and CSS was reported in 6 studies[23,26,30,36,46,47] involving 3284 bladder cancer patients. Combined data of these 6 cohorts suggested non-significant prognostic effect of PLR on CSS and HR was 1.14 (95% CI: 0.98–1.34, $P = .10$; $I^2 = 63\%$, $P = .02$; Fig. 3).

In terms of effect of PLR on PFS, there were 3 studies[23,24,47] presenting it including 1214 bladder cancer patients. The pooled data showed that a high PLR was related to a poor PFS, HR was 1.2 (95%CI: 1.08–1.34, $P = .0008$), without heterogeneity ($I^2 = 0\%$, $P = .60$; Fig. 3).

The subgroup analysis (Table 3) shown that the OS TURBT group, OS Asian group, OS Sample size ≥200 group had no significant prognostic value.

3.3. The prognostic significance of LMR in bladder cancer

Six studies[21,30,37,46,48,49] including 4969 patients investigated the association between LMR and OS. The pooled HR was 0.77 (95%CI: 0.70–0.84, $P = .0002$), which reveal that a high LMR was great connection with favorable OS ($I^2 = 63\%$, $P = .001$; Fig. 4).

We also investigated the impact of LMR on CSS 21,30,46. The summary HR was 0.76 and the result indicated that a high LMR was related to favorable CSS (95%CI: 0.70–0.84, $P < .00001$) in a random-effects model for bladder cancer patients. There was no heterogeneity among these studies ($I^2 = 0\%$, $P = .88$; Fig. 4).

Table 1

Baseline characteristics of studies included in the meta-analysis.

References	Ethnicity	Sample size	Treatment	Metastasis	Cut-off value	Makers	Outcome	Follow-up (mo)
Andrea 2016[21]	Caucasian	4335	RC	non	2.7/3.5	NLR; LMR	OS; CSS; RFS	42.4
Andrea 2017[42]	Caucasian	918	TURBT	non	3	NLR	PFS; RFS	NA
Bambury 2015[22]	Caucasian	129	NAC	metastasis	2.5/3.0	NLR	OS	NA
Bhindi 2015l[23]	Caucasian	418	RC	non	2.5/150	NLR; PLR	OS; CSS; RFS	NA
Buisan 2016[20]	Caucasian	75	NAC	non	2.5	NLR	OS; CSS; PFS	31
Buisan 2017[38]	Caucasian	50	MIX	non	5	NLR	OS; CSS; PFS	29
Ferro 2015[51]	Caucasian	1037	TURBT	non	1	mGPS	OS; CSS; RFS	22
Gondo 2012[40]	Asia	189	RC	non	2.5	NLR	DSS	25.1
Hwang 2012[50]	Asia	67	NAC	non	1	mGPS	OS	NA
Guo 2018[24]	Asia	131	RC	non	3.8/210.9	NLR; PLR	OS; PFS	39.72
Hermanns 2014[25]	Caucasian	424	RC	non	3	NLR	OS; CSS; RFS	58.1
Kang 2015[27]	Asia	385	RC	non	2.1	NLR	OS; CSS	NA
Kang 2016l[39]	Asia	1555	TURBT	non	2.1/24	NLR; PLR	OS; CSS	52
Kimura 2018[52]	Caucasian	1096	TURBT	non	1	mGPS	PFS; RFS	64.8
Krane 2012l[27]	Caucasian	68	RC	non	2.5	NLR	OS	NA
Lee 2015[45]	Caucasian	226	TURBT	non	218	PLR	OS	NA
Mano 2015[44]	Caucasian	107	TURBT	non	2.41/2.43	NLR	PFS; RFS	40
Mbeutcha 2016[43]	Caucasian	1117	TURBT	non	2.5	NLR	PFS; RFS	64
Miyake 2017[46]	Asia	117	RC	non	150/3.3/1	PLR; LMR; mGPS	DSS; OS	22
Morizawa 2015[28]	Asia	110	RC	non	2.6	NLR	OS; CSS; PFS	37.5
Ozcan 2015[41]	Asia	286	RC	non	2.5	NLR	DSS	28
Peng 2017[29]	Asia	516	RC	non	2.3/136/4	NLR; PLR	OS	37
RAJWA 2018[30]	Caucasian	144	RC	non	3/160.59/2.44	NLR; PLR; LMR	OS; CSS	14
Rossi 2014 1]	Caucasian	292	NAC	metastasis	3	NLR	OS; PFS	NA
Schulz 2017[47]	Caucasian	665	RC	non	28	PLR	OS; CSS; PFS	27
Su 2017[32]	Asia	303	NAC	metastasis	3	NLR	OS	61.1
Taguchi 2014[33]	Asia	200	NAC	metastasis	3	NLR	OS; CSS	NA
Temraz 2014[48]	Asia	68	RC	non	2.87	LMR	OS	24
Vartolomei 2018[34]	Caucasian	1046	TURBT	non	3	NLR	OS;CSS;PFS;RFS	43
Yoshida 2015[49]	Asia	181	RC	non	3.51	LMR	OS	72
Yoshida 2016[35]	Asia	323	RC	non	2.7	NLR	OS	63.5
Yuk 2019[36]	Asia	385	TURBT	non	1.5/171	NLR; PLR	OS; CSS	80
Zhang 2015[37]	Asia	124	RC	non	2.1/4/140	NLR; LMR; PLR	OS	50.8

CSS = cancer-specific survival, DSS = disease-specific survival, LMR = lymphocyte-to-monocyte ratio, mGPS = modified glasgow prognostic score, NA = not available, NAC = neoadjuvant chemotherapy, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, RC = radical cystectomy, RFS = recurrence-free survival, TURBT = transurethral resection of bladder tumor.

The subgroup analysis (Table 4) shown that the significant prognostic value for LMR on OS in most subgroups but the OS cut-off < 3.0 group had no significant prognostic value.

3.4. The prognostic significance of mGPS in bladder cancer

Three studies[46,50,51] presenting data dealing with the effect of GPS on OS among 1221 different patients were observed. The gathered analysis showed that an elevated high GPS was closely associated with a poor OS, HR was 2.71 (95%CI: 1.08–2.82, $P = .003$), with significant heterogeneity ($I^2 = 80.0\%$, $P = .007$; Fig. 5).

Then we also found 2 studies,[46,51] containing 1154 bladder cancer patients, reported the effect of GPS on CSS. The summary HR was 1.50 (95%CI: 0.56–4.05, $P = .42$; Fig. 5) in a random-effects model for bladder cancer patients and both 2 cohorts suggested non-significant prognostic effect of mGPS on CSS.

At last, only 2 studies[51,52] including 2133 patients investigated had the association between mGPS and PFS, and the combined HR was 1.52(95%CI: 1.23–1.88, $P = .0001$) without heterogeneity ($I^2 = 0\%$, $P = .73$; Fig. 5).

3.5. The Association of hematological biomarkers and clinicopathological factors

We analyzed eleven studies which reported the relationship between hematological biomarkers (NLR, PLR, LMR and mGPS) and clinicopathological factors including sex, tumor grade, tumor stage, age and tumor size. As shown in Table 5 and Fig. S1, http://links.lww.com/MD/E590, high PLR was found to be significantly associated with tumor grade G3 (OR = 2.58, 95% CI:1.67–3.99, $P < .001$).

4. Discussion

Among all the cancers in U.S, bladder carcinoma stands the 4th most commonly diagnosed among men and 10th most commonly diagnosed among women.[1] In previous studies, the role of several promising molecular prognostic biomarkers, like Ki-67 overexpression or fibroblast growth factor receptor 3 mutations, were not convincing. In addition, when combined with standard clinical and pathological parameters, some emerging biomarkers, such as tumor protein 53 mutations or p53 overexpression, have failed to show the clinical value.[53]

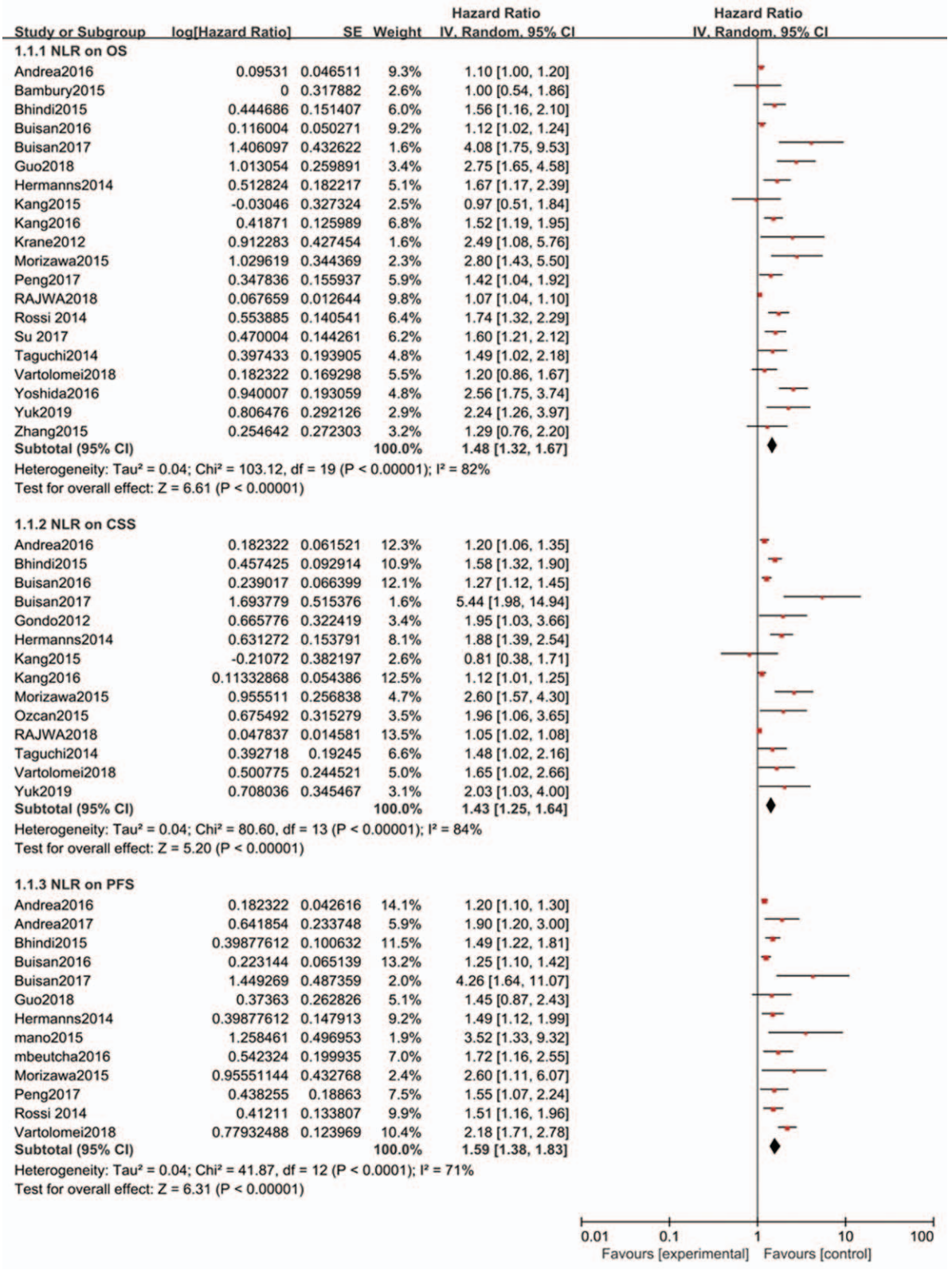

Figure 2. Forest plots of NLR for OS, CSS and PFS.

Table 2

Subgroup analysis of the combination between NLR and OS, CSS, PFS.

Subgroup title	No. of studies	I^2 (%)	HR (95%CI)	P
OS				
Total	20	83	1.50 (1.33, 1.69)	P < .0001
Treatment				
RC	11	83	1.50 (1.27, 1.77)	P < .00001
NAC	5	72	1.38 (1.10, 1.75)	P = .006
TURBT	3	44		P = .004
Mix	1	NA	4.08 (1.75, 9.53)	P = .001
Ethnicity				
Asian	10	49	1.72 (1.43, 2.06)	P < .00001
Caucasian	10	79	1.36 (1.16, 1.58)	P = .0001
Sample size				
< 200	8	80	1.47 (1.19, 1.81)	P = .0005
≥200	12	74	1.52 (1.29, 1.79)	P < .00001
Cut-off				
< 3.0	11	76	1.49 (1.25, 1.76)	P < .00001
≥3.0	8	84	1.56 (1.22, 1.99)	P = .0004
Metastatic				
Non	16	82	1.09 (1.07, 1.12)	P < .00001
Metastasis	4	0	1.57 (1.33, 1.86)	P < .00001
CSS				
Total	14	65	1.71 (1.35, 2.18)	P < .0001
Treatment				
RC	8	87	1.47 (1.20, 1.81)	P = .0003
NAC	2	0	1.29 (1.14, 1.46)	P < .0001
TURBT	3	61	1.40 (0.97, 2.03)	P = .07
Mix	1	NA	5.44 (1.98,14.94)	P = .001
Ethnicity				
Asian	7	70	1.57 (1.16, 2.13)	P = .004
Caucasian	7	89	1.40 (1.17, 1.68)	P = .0002
Sample size				
< 200	5	88	1.55 (1.17, 2.05)	P = .002
≥200	9	68	1.42 (1.21, 1.66)	P < .0001
Cut-off				
< 3.0	5	70	1.39 (1.20, 1.61)	P < .0001
≥3.0	4	87	1.65 (1.12, 2.45)	P = .01
PFS				
Total	13	71	1.59 (1.38, 1.83)	P < .00001
Treatment				
RC	6	48	1.40 (1.21, 1.63)	P < .0001
NAC	2	38	1.33 (1.12, 1.57)	P = .001
TURBT	4	0	2.06 (1.71, 2.48)	P < .00001
Mix	1	NA	4.26 (1.64,11.07)	P = .003
Ethnicity				
Asian	3	0	1.61 (1.21, 2.14)	P = .001
Caucasian	10	77	1.58 (1.35, 1.86)	P < .00001
Sample size				
< 200	4	69	1.99 (1.25, 3.19)	P = .004
≥200	7	76	1.57 (1.32, 1.87)	P < .00001
Cut-off				
< 3.0	5	59	1.40 (1.22, 1.61)	P < .00001
≥3.0	6	47	1.77 (1.44, 2.18)	P < .00001

CSS = cancer-specific survival, NA = not available, NAC = neoadjuvant chemotherapy, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PFS = progression-free survival, RC = radical cystectomy, TURBT = transurethral resection of bladder tumor.

Nowadays, serum biomarkers are commonly used in the diagnosis of tumors, of which inflammation biomarkers are the most important. As early as 19th century, Rudolf Virchow observed leucocytes in neoplastic tissues and established the hypothesis about the relationship between inflammation and tumor.[54] Due to the limitations of the times and technology, this speculation has been silent for many years. In recent years, more and more evidence suggest that inflammation of the tumor microenvironment promotes tumorigenesis, progression and metastasis and there is a link between inflammation and tumor.[55–57]

NLR is the most meaningful hematological inflammation biomarker. Studies have shown that tumor infiltrating lymphocytes may limit the metastatic cascade of cancer cells while

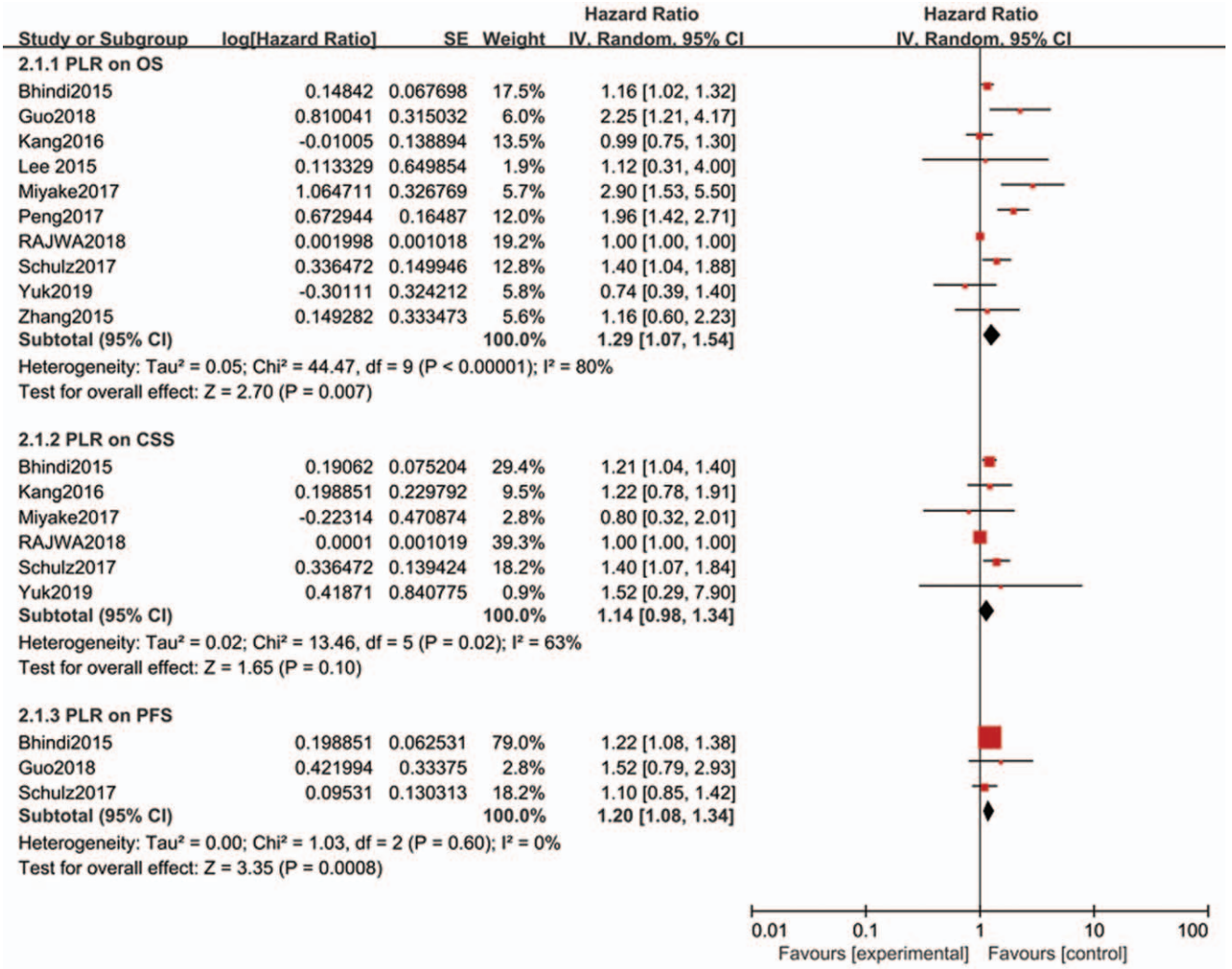

Figure 3. Forest plots of PLR for OS, CSS and PFS.

neutrophils may contribute to tumor cell migration and metastasis by remodeling the extracellular matrix and promotion of angiogenesis.[58–60] Wu et al[61] has conducted a meta-analysis on the clinical use of NLR in bladder cancer patients, and their results are similar to ours. However, we added more latest qualified studies compared to theirs. What's more, we have also used more detailed and in-depth methods, such as sensitivity analysis, "trim and fill" analysis to discover the potential heterogeneity and validate our conclusions.

Platelets can mediate tumor cell growth, angiogenesis, and proliferation by secreting vascular endothelial growth factor, basic fibroblast growth factor, platelet-derived growth factor and other angiogenesis and tumor growth factors, and also protect tumor cells from immune elimination and support tumor metastasis.[62–64] Previous researches have shown the prognostic function of PLR in different cancers, but these studies still have limitations, such as Xingmu Wang et al[65] only reported association between PLR and tumor metastasis for OS. In our study, we included more indicators that are prognostic and rationally combined them. Furthermore, we discovered that the prognostic function of high PLR for poorer OS, PFS and non-significant prognostic effect of PLR for CSS. The prognostic value of PLR could be insignificant as the follow-ups of CSS is comparatively short. Notably, in the research of the correlation between PLR and clinicopathological factors, we found that PLR was significantly associated with tumor grade G3 ($P < .001$). Tumor differentiation may be related to tumor microenvironment lymphocyte infiltration, however, research on this aspect is still insufficient. Research on tumor lymphocyte infiltration will become a hot spot in the future.

Recently, LMR, as an integrated inflammatory-based prognostic system, it has shown spectacular prognostic value in numerous cancers. Macrophages derived from circulating monocytes might accelerate tumor progression and angiogenesis.[66] In this meta-analysis, we explored the prognostic value of LMR in bladder cancer and focused on more outcome's indicator contain OS and CSS than previous studies.

Moreover, our study included more valuable significant biomarkers. None of these meta-analyses about prognostic significance of hematological biomarkers for bladder cancer concentrated on the value of mGPS until now. Furthermore, we investigated the prognostic value of NLR, PLR, LMR and mGPS in same 1 study for the first time and these biomarkers could show more reliable prognostic value in bladder cancer.

Table 3

Subgroup analysis of the combination between PLR and OS, CSS.

Subgroup title	No. of studies	I^2 (%)	HR (95%CI)	P
OS				
Total	10	80	1.29 (1.07, 1.54)	P=.007
Treatment				
RC	7	86	1.43 (1.14, 1.79)	P=.002
TURBT	3	0	0.95 (0.74, 1.22)	P=.70
Ethnicity				
Asian	6	77	1.47 (0.99, 2.21)	P=.06
Caucasian	4	69	1.12 (0.96, 1.30)	P=.15
Sample size				
<200	4	83	1.59 (0.91, 2.77)	P=.11
≥200	6	65	1.23 (0.98, 1.55)	P=.07
Cut-off				
<150	4	71	1.35 (0.97, 1.86)	P=.02
≥150	6	78	1.22 (0.98, 1.53)	P=.0004
CSS				
Total	6	63	1.14 (0.98, 1.34)	P=.10
Treatment				
RC	4	76	1.14 (0.95, 1.36)	P=.17
TURBT	2	0	1.24 (0.80, 1.91)	P=.33
Ethnicity				
Asian	3	0	1.14 (0.77, 1.70)	P=.50
Caucasian	3	84	1.15 (0.95, 1.40)	P=.15
Sample size				
<200	2	0	1.00 (1.00, 1.00)	P=.92
≥200	4	0	1.25 (1.10, 1.41)	P=.0004
Cut-off				
<150	2	0	1.35 (1.07, 1.70)	P=.01
≥150	4	56	1.07 (0.92, 1.25)	P=.89

CSS = cancer-specific survival, NA = not available, OS = overall survival, PLR = platelet-to-lymphocyte ratio, RC = radical cystectomy, TURBT = transurethral resection of bladder tumor.

Table 4

Subgroup analysis of the combination between LMR and OS.

Subgroup title	No. of studies	I^2 (%)	HR (95%CI)	P
OS				
Total	6	75	0.77 (0.70, 0.84)	P=.0002
Ethnicity				
Asian	4	62	0.48 (0.36, 0.64)	P=.001
Caucasian	5	0	0.81 (0.74, 0.89)	P<.0001
Sample size				
<200	5	77	0.52 (0.34, 0.80)	P=.003
≥200	1	NA	0.83 (0.73, 0.95)	P=.006
Cut-off				
<3.0	2	71	0.60 (0.30, 1.21)	P=.15
≥3.0	4	82	0.56 (0.35, 0.90)	P=.02

CI = confidence interval, LMR = lymphocyte-to-monocyte ratio, NA = not available, OS = overall survival.

Nevertheless, our study also has following several limitations.

(1) Despite we conducted a lot of subgroup analysis; we still cannot eliminate the significant heterogeneity between several studies. After discussion, we finally believe that the heterogeneity attributes to the grade of bladder cancer, histological type and individual patient difference.
(2) In the studies we included, some did not have multivariate analysis data, so we just included a part of the univariate analysis data.
(3) Most hematological biomarkers have different cut-off value.
(4) Included studies were all retrospective studies.
(5) Several biomarkers, such as C-reactive protein/albumin ratio and plasma fibrinogen have been studied too little to conduct meta-analysis. In the future, large-scale studies about these biomarkers are needed to validate the results.

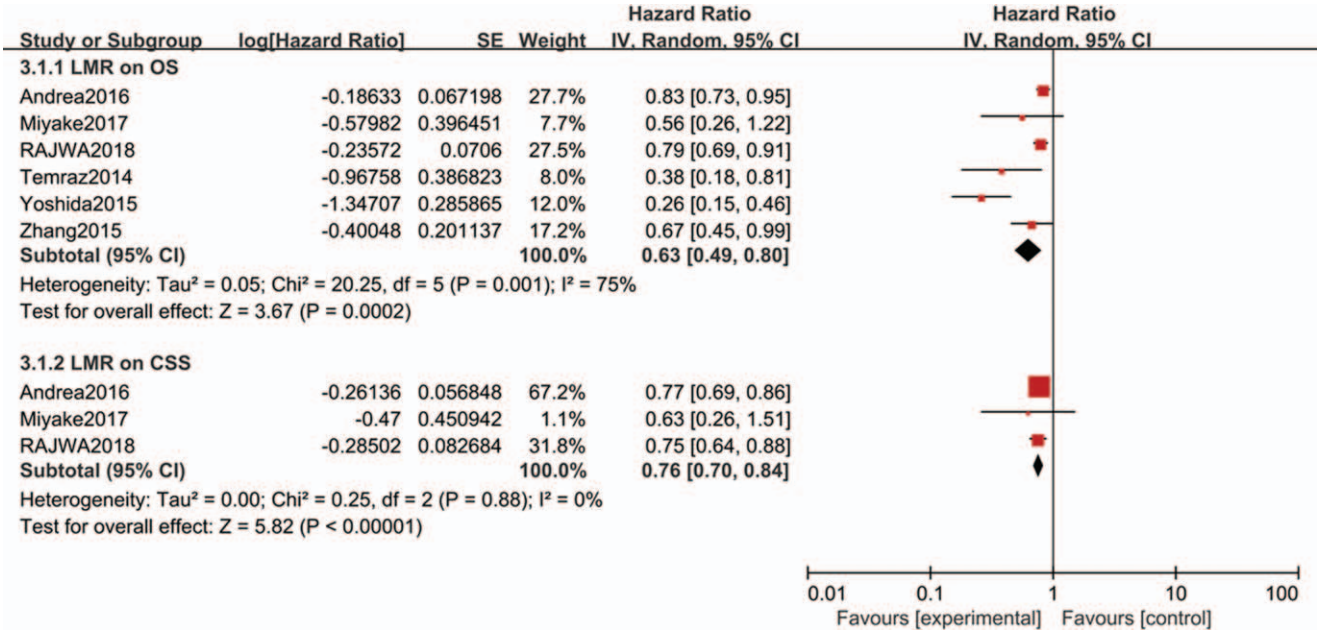

Figure 4. Forest plots of LMR for OS and CSS.

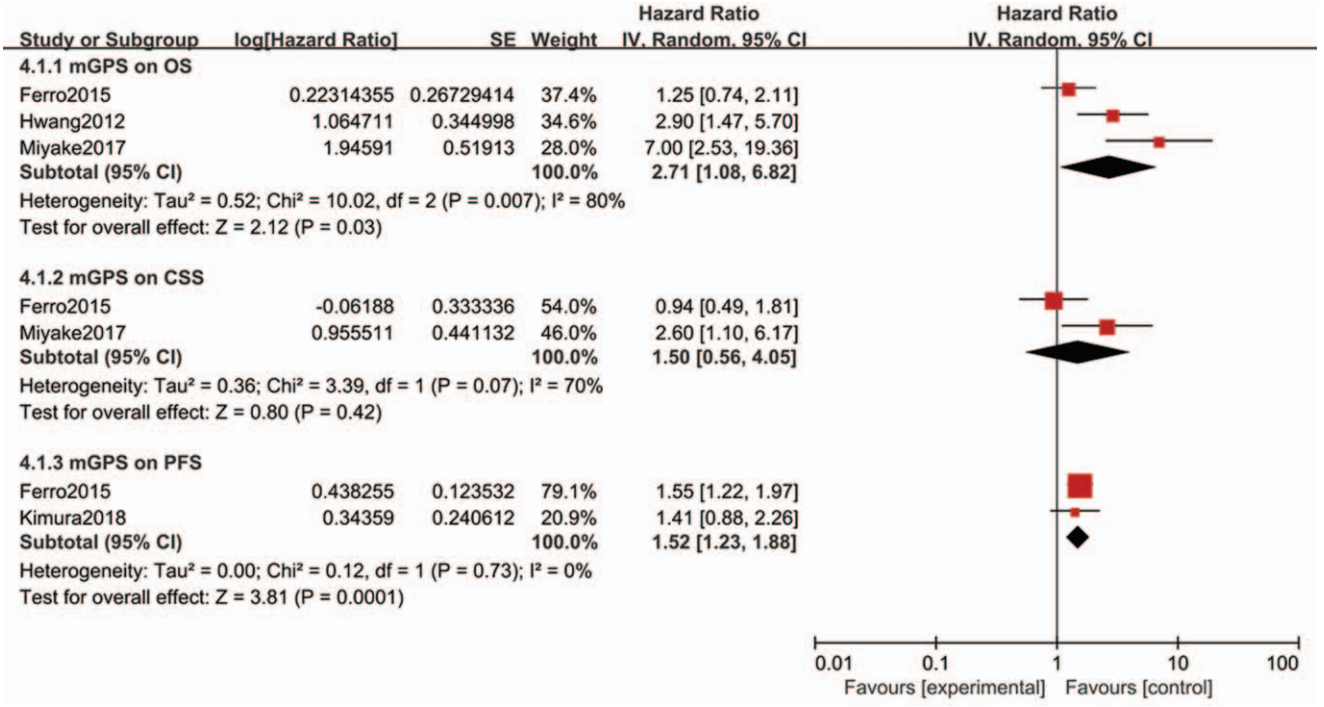

Figure 5. Forest plots of mGPS for OS, CSS and PFS.

4.1. Publication bias

Publication bias was insignificant with respect to the prognostic value of NLR on OS ($P = .456$, Fig. 6A), NLR on CSS ($P = .381$, Fig. 6B) and PLR on OS ($P = .754$, Fig. 6C) according to the plots of publication given in Fig. 6. Begg's funnel plots showed notable asymmetry regarding the NLR with PFS ($P = .033$, Fig. 6D) in bladder cancer patients. Moreover, we performed "trim and fill" analysis and the results suggested that there were 3 unpublished studies assessing NLR on PFS (Fig. 6E). The results of "trim and fill" showed no significant difference in the previous and new HRs (HR = 1.513, 95% CI: 1.310–1.747; $P < .001$).

5. Conclusions

Our study indicated that the pretreatment hematological inflammation biomarkers could be regarded as 1 of predicative biomarkers in bladder cancer patients. Therefore, hematologic biomarkers are promising and inexpensive biomarkers that can be used in clinical management and foresee survival outcome in

Table 5

Meta-analysis results of multiple hematological biomarkers and clinicopathological parameters in patients with bladder cancer.

Clinicopathological factors	No. of studies	OR (95% CI)	*P*	I^2 (%)	*P*-value for heterogeneity	Analysis model
NLR						
Sex (M vs F)	11	0.96 (0.78,1.18)	.70	50	.03	Random
Tumor grade (G3 vs G1/G2)	5	1.46 (0.89,2.39)	.14	90	<.001	Random
Tumor stage (T2-T4 vs Ta-T1)	7	1.40 (0.93,2.11)	.11	71	.002	Random
Age (yr) (≥65 vs <65)	2	1.13 (0.74,1.74)	.56	29	.23	Fixed
Tumor size (cm) (≥3 vs < 3)	4	1.09 (0.93,1.27)	.30	0	.89	Fixed
PLR						
Sex (M vs F)	3	1.06 (0.67,1.66)	.81	13	.32	Random
Tumor grade (G3 vs G1/G2)	3	2.58 (1.67,3.99)	<.001	0	.86	Fixed
Tumor stage (T2-T4 vs Ta-T1)	2	2.34 (0.68,8.05)	.18	73	.06	Random
Age (y) (≥65 vs <65)	2	0.93 (0.55,1.55)	.77	62	.11	Random
LMR						
Sex (M vs F)	3	0.90 (0.51,1.59)	.71	65	.06	Random
Tumor grade (G3 vs G1/G2)	4	1.43 (0.60,3.39)	.42	84	<.001	Random
Tumor stage (T2-T4 vs Ta-T1)	3	0.96 (0.80,1.14)	.63	0	.73	Fixed
mGPS						
Sex (M vs F)	2	0.53 (0.25,1.10)	.09	93	<.001	Random
Tumor grade (G3 vs G1/G2)	2	0.95 (0.63,1.42)	.79	65	.09	Random

CI = confidence interval, LMR = lymphocyte-to-monocyte ratio, mGPS = modified glasgow prognostic score, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

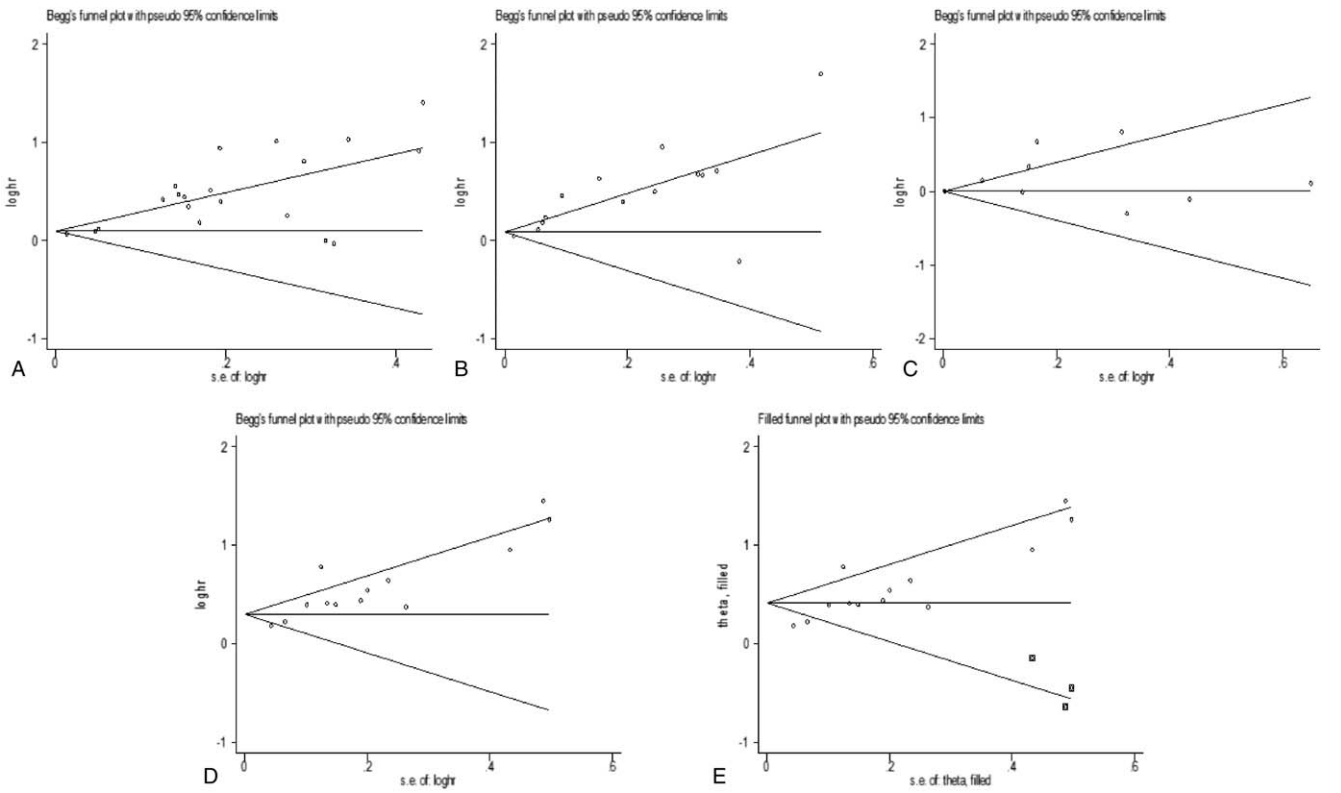

Figure 6. Begg's funnel plots of (A) NLR for OS, (B) NLR for CSS, (C) PLR for PFS and (D) NLR for PFS. Filled funnel plots of (E) NLR for PFS.

bladder carcinoma. However, further prospective and innovative studies are required to validate our conclusions.

Author contributions

Lianghao Zhang collected and analyzed the data and wrote the paper. Longqing Li, Junxiao Liu assisted in collecting the data and participated in the writing. Jiange Wang, Yafeng Fan, Biao Dong assisted in the design of this study. Zhaowei Zhu and Xuepei Zhang are responsible for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript.

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