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*Review Article*

# Prognostic value of neutrophil to lymphocyte ratio in patients with bladder cancer: a meta-analysis

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**Abstract:** Many studies reported the prognostic value of neutrophil to lymphocyte ratio (NLR) for bladder cancer, however, these studies presented conflicting results. In the present study, we intended to comprehensively investigate the associations between pretreatment NLR and overall survival (OS), cancer-specific survival (CSS)/disease-specific survival (DSS), and recurrence-free survival (RFS) through meta-analysis. The values of hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) from 9 studies with 2,300 patients were extracted and combined. The results suggested that increased NLR was correlated with shorten OS (HR=1.48, 95% CI=1.05-2.09, P=0.027) and CSS/DSS (HR=1.58, 95% CI=1.01-2.46, P=0.044), but had no correlation with RFS (HR=1.41, 95% CI=0.92-2.17, P=0.112). Furthermore, subgroup analyses stratified by different clinicopathological factors demonstrated that elevated NLR still predicted poor OS in large sample size studies and held prognostic value for RFS when NLR≤2.5. In conclusion, the current study identifies NLR as a prognostic factor for poor OS and CSS/DSS, but not for RFS in bladder cancer.

**Keywords:** Bladder cancer, neutrophil to lymphocyte ratio, meta-analysis, prognosis

## Introduction

Bladder cancer is the most common form of urinary tract malignancy and represents the sixth most prevalent malignancy in men around the world [1, 2]. In USA alone, bladder cancer is estimated to account for 58,950 new cases and 11,820 deaths in men in 2012 [3]. Radical cystectomy (RC) is first-line treatment approach for muscle-invasive bladder cancer (MIBC) and high-risk non-muscle invasive bladder cancer (NMIBC) [4]. Unfortunately, about one half of these patients will develop distant metastases and disease progression, and in patients with locally advanced disease, the 5-year survival rates are 40-60% [5, 6]. Insufficiency of useful biomarkers for risk stratification in bladder cancer is partially responsible for the disappointing prognosis; therefore, novel and promising markers are needed to improve the current ability for prognostication.

Inflammation plays a pivotal role in cancer initiation, progression and distant metastasis and is considered as one of the hallmarkers of cancer [7, 8]. Systemic inflammatory responses and inflammatory tumor microenvironment are heavily involved in tumorigenesis and inflammatory-related factors have attracted extensive attention in recent years [9, 10]. The serum based index, neutrophil-lymphocyte ratio (NLR), is one of the recently found and novel prognostic markers for many cancers, included, but not limited to lung cancer [11], colorectal cancer [12], breast cancer [13], prostate cancer [14] and bladder cancer [15]. However, data concerning the prognostic role of NLR in bladder cancer remains controversial [16-19]. Therefore, it is necessary for us to comprehensively reveal the predictive efficiency of NLR on bladder cancer prognosis.

In the present study, we evaluated the relationships between pretreatment NLR and OS, CSS/DSS and RFS in patients with bladder cancer by the approach of meta-analysis, to derive a more reliable assessment.

## Materials and methods

### *Search strategy*

A comprehensive literature search was performed through electronic platforms of PubMed,

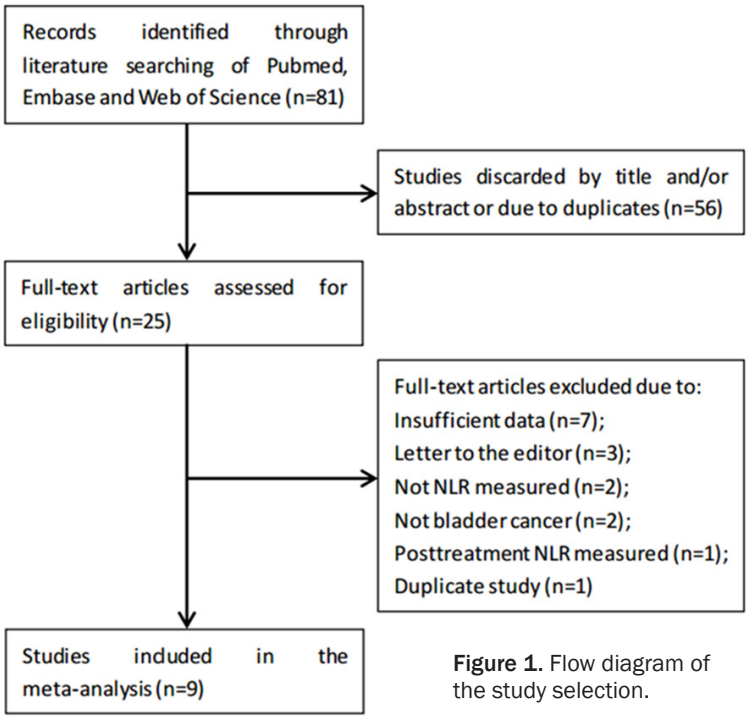


**Figure 1.** Flow diagram of the study selection.

Embase and Web of Science. The search strategy was based on MeSH terms as well as a combination of free words as follows: "NLR", "neutrophil-lymphocyte ratio", "neutrophil to lymphocyte ratio", "bladder cancer", "bladder carcinoma", "bladder tumor", "urinary bladder cancer" and "urinary bladder neoplasms". The last search was updated on March 2016. The reference lists were also manually retrieved to find potentially relevant articles. Articles publication language was limited to English.

*Article selection criteria*

The inclusion criteria were as follows: (1) the diagnosis of bladder cancer was histopathologically confirmed; (2) pretreatment NLR was measured by serum-based method; (3) hazard ratios (HRs) and 95% confidence intervals (CIs) for NLR in the analysis of OS, CSS/DSS and/or RFS were reported in the text or sufficient data was provided to allow to calculate these data; (4) the cut-off value of NLR was reported; (5) the publication language was English. Exclusion criteria were applied as follows: (1) letters to the editor, review papers, comments or meeting abstracts; (2) animal studies; (3) articles not written in English. When duplicate articles were encountered, the more informative one was selected. Overall survival was calculated from the date of initial treatment to date of death of any cause. CSS/DSS were identified as the time from the treatment to death of bladder cancer. RFS was calculated as the time from treatment to tumor recurrence.

*Data extraction*

Two investigators (XB Gu and XS Gao) independently extracted data from the included studies. The following characteristics from eligible studies were recorded: surname of first author, publication year, country where the study was performed, study duration period , follow-up information, sample size, treatment methods, the cut-off values to define elevated NLR and HRs along with 95% CIs for survival analysis. Any discrepancies between the two investigators were settled by discussion.

*Statistical analysis*

Hazard ratios (HRs) and 95% confidence intervals (CIs) for OS, CSS/DSS and/or RFS were directly extracted from the text, if provided, or were calculated according to the methods described by Tierney [20]. Cochran's Q test and Higgins $I^2$ statistic were used to assess heterogeneity. $P>0.1$ and $I^2<50\%$ was defined as no significant heterogeneity, and subsequently, a fixed-effects model was carried out. Otherwise, a random-effects model was adopted to calculate pooled HRs. Potential publication bias was tested by using Begg's funnel plot. All statistical analyses were conducted with STATA version 12.0 (STATA Corporation, College Station, TX) and $P<0.05$ was considered as statistically significant.

## Results

*Study characteristics*

A total of 9 studies [16-19, 21-25] published from 2012 to 2016 were included in the final meta-analysis. Detailed literature screening and selection process was shown in **Figure 1** and the basic information of included studies

**Table 1.** Characteristics of included studies

| Study | Year | Country | Ethnicity | Duration | Follow-up (month) | Sample size (M/F) | Age (year) mean (range) | Treatment | Cut-off | Survival analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| Gondo | 2012 | Japan | Asian | 2000-2009 | 25.1 (2.1-127.9) | 189 (158/31) | 68.4 (38-85) | RC | 2.5 | DSS |
| Krane | 2013 | USA | Caucasian | 2005-2011 | To Apr 2012 | 68 (55/13) | 67.4 | RC | 2.5 | OS |
| Hermanns | 2014 | Canada | Caucasian | 1992-2012 | 58.4 | 424 (325/99) | 70.1 (60.6-76.3) | RC | 3 | OS, RFS, CSS |
| Viers | 2014 | USA | Caucasian | 1994-2005 | 130.8 | 899 (723/176) | 69 | RC | 2.7 | OS, RFS, CSS |
| Bamburg | 2015 | USA | Caucasian | 2008-2013 | NA | 129 (97/32) | 66 (45-85) | Chemotherapy | 3 | OS |
| Mano | 2015 | Isreal | Caucasian | 2003-1010 | 40 | 107 (91/16) | 68 | TURBT | 2.41 | RFS |
| Ozcan | 2015 | Turkey | Caucasian | 1990-2013 | 28 (0-144) | 286 (256/30) | 60.7 (29-83) | RC | 2.5 | DSS |
| Zhang | 2015 | China | Asian | Jan 2009-Dec 2009 | To Jun 2014 | 124 (100/24) | 65 (30-78) | RC | 2.1 | OS |
| Kawahara | 2016 | Japan | Asian | 1999-2014 | 24.2 | 74 (58/16) | 64.1 | RC | 2.38 | OS |

RC: radical cystectomy; TURBT: transurethral resection of bladder tumor; DSS: disease-specific survival; OS: overall survival; RFS: recurrence-free survival; CSS: cancer-specific survival; NA: not availbale.

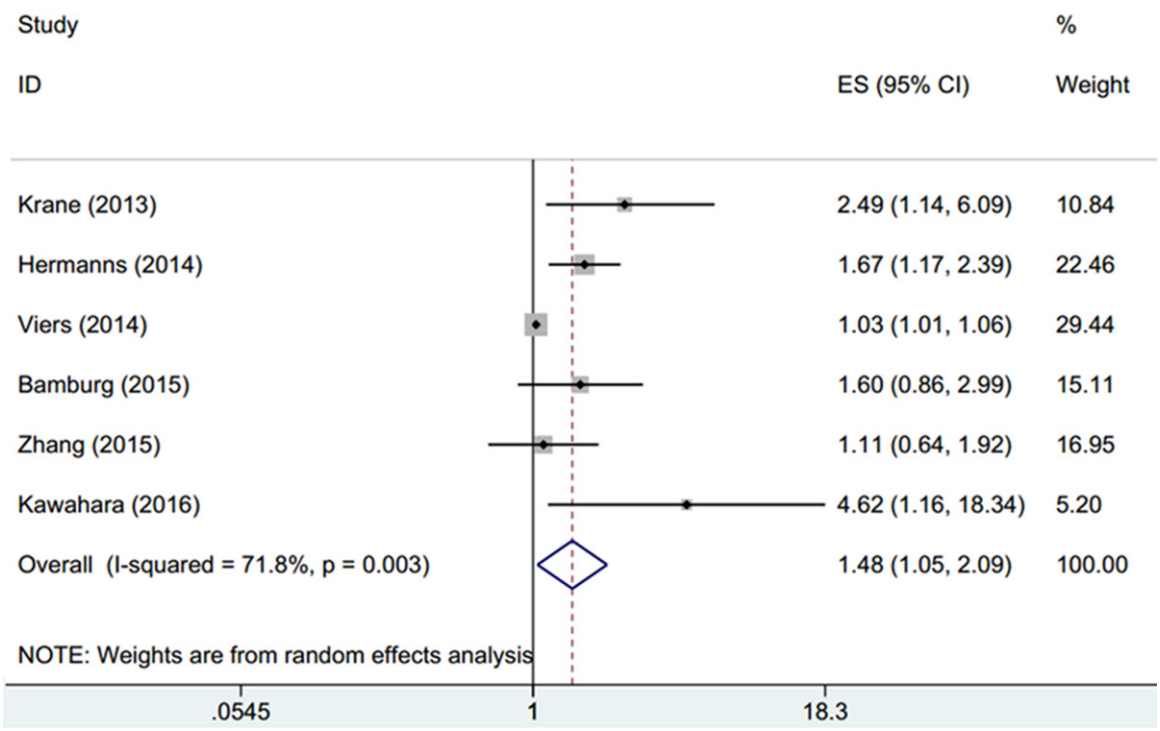


**Figure 2.** Forest plot of the studies assessing NLR in bladder cancer for OS.

**Table 2.** Main results of the meta-analysis

| | Factor | No. of studies | No. of patients | Effects model | HR (95% CI) | *P*-value | Heterogeneity $I^2$ (%) | Ph |
|---|---|---|---|---|---|---|---|---|
| OS | Overall | 6 | 1,718 | Random | 1.48 (1.05-2.09) | 0.027 | 71.8 | 0.003 |
| | Ethnicity | | | | | | | |
| | Caucasian | 4 | 1,520 | Random | 1.46 (0.98-2.19) | 0.063 | 77.2 | 0.004 |
| | Asian | 2 | 198 | Random | 1.96 (0.5-7.68) | 0.336 | 71.7 | 0.06 |
| | Sample size | | | | | | | |
| | Large (n>400) | 2 | 1,323 | Fixed | 1.59 (1.12-2.28) | 0.01 | 40.5 | 0.169 |
| | Small (n<400) | 4 | 395 | Random | 1.27 (0.79-2.03) | 0.322 | 85.7 | 0.008 |
| | Treatment | | | | | | | |
| | RC | 5 | 1,589 | Random | 1.47 (1-2.18) | 0.053 | 74.7 | 0.003 |
| | Chemotherapy | 1 | 129 | - | 1.48 (1.05-2.09) | 0.139 | - | - |
| | Cut-off | | | | | | | |
| | NLR≤2.5 | 3 | 266 | Random | 1.98 (0.89-4.37) | 0.092 | 60.3 | 0.08 |
| | NLR>2.5 | 3 | 1,452 | Random | 1.33 (0.9-1.96) | 0.156 | 77.5 | 0.012 |
| CSS/DSS | Overall | 4 | 1,798 | Random | 1.58 (1.01-2.46) | 0.044 | 86.5 | <0.001 |
| | Ethnicity | | | | | | | |
| | Caucasian | 3 | 1,609 | Random | 1.5 (0.91-2.47) | 0.111 | 89.3 | <0.001 |
| | Asian | 1 | 189 | - | 1.95 (1.03-3.66) | 0.039 | - | - |
| | Cut-off | | | | | | | |
| | NLR≤2.5 | 2 | 475 | Fixed | 1.96 (1.26-3.04) | 0.003 | 0 | 0.983 |
| | NLR>2.5 | 2 | 1,323 | Random | 1.37 (0.77-2.45) | 0.285 | 86.5 | <0.001 |
| RFS | Overall | 3 | 1,430 | Random | 1.41 (0.92-2.17) | 0.112 | 83 | <0.001 |

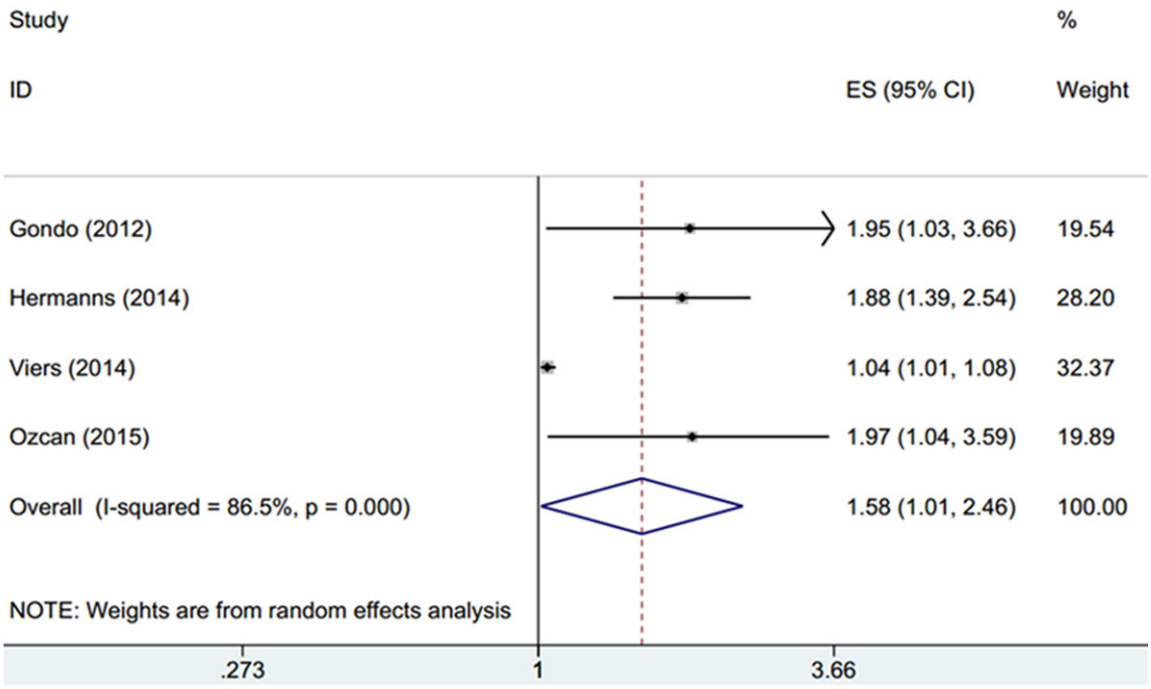


**Figure 3.** Forest plot of the studies assessing NLR in bladder cancer for CSS/DSS.

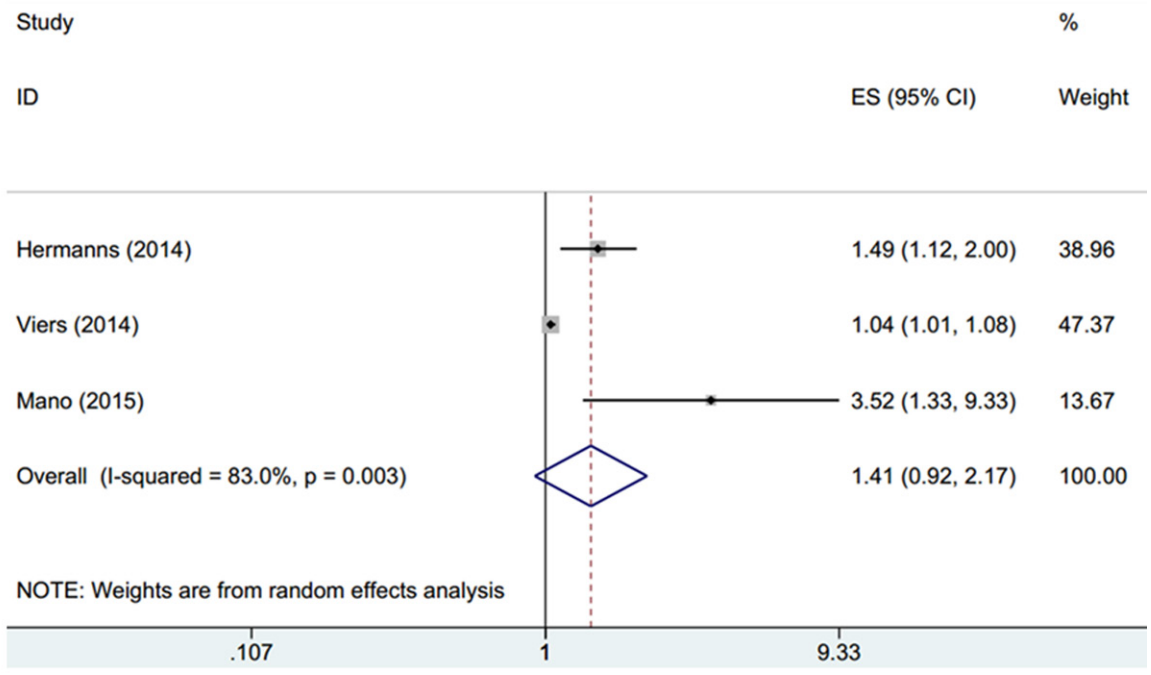


**Figure 4.** Forest plot of the studies assessing NLR in bladder cancer for RFS.

was depicted in **Table 1**. Finally, as shown in **Table 1**, a total of 2,300 patients ranging from 68 to 899 subjects in single work were analyzed. Three studies were performed in USA [16, 18, 22], two studies were conducted in Japan [21, 25], one study was carried out in Canada [17], one in Israel [23], one in Turkey [24] and one in China [19], respectively. All the

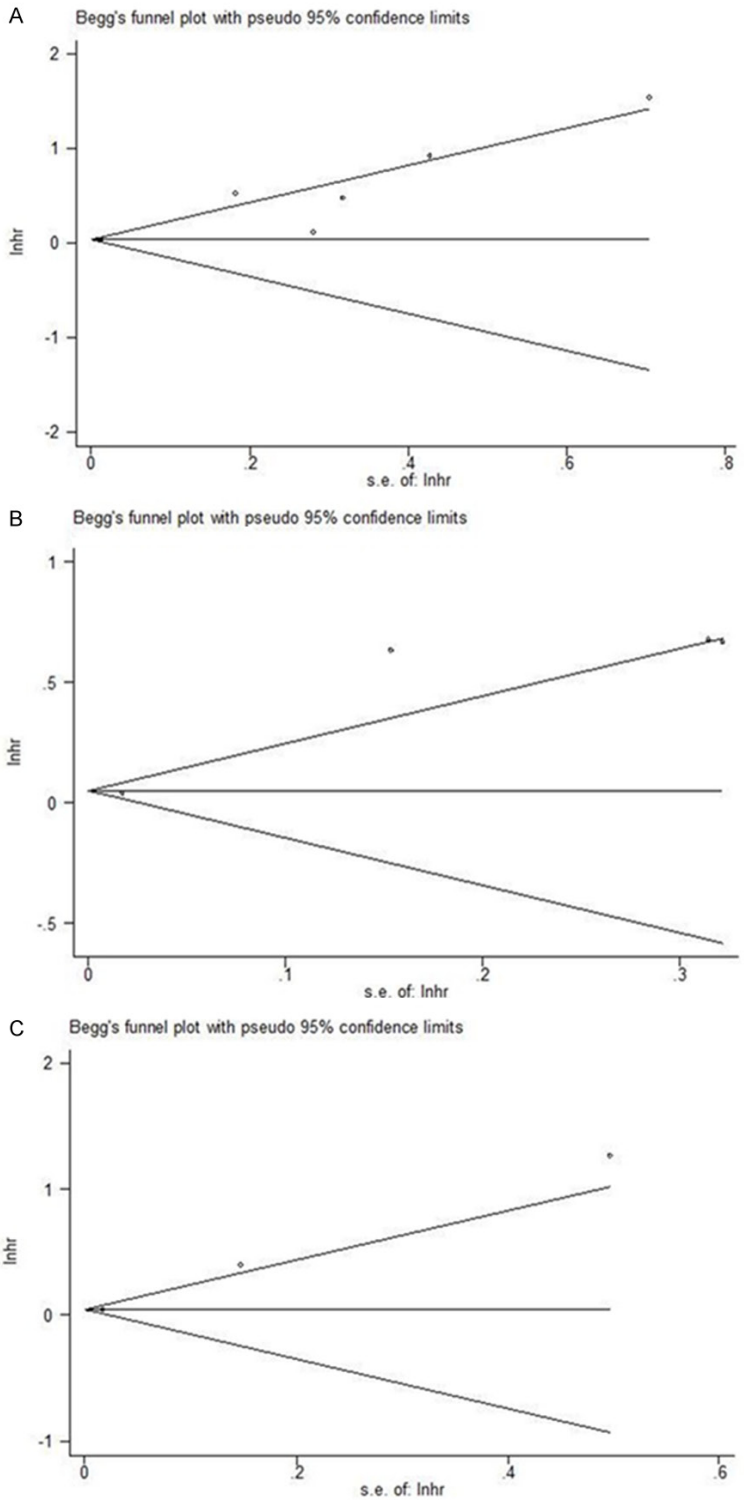


**Figure 5.** Begg's funnel plot of publication bias test for (A) OS, (B) CSS/DSS and (C) RFS in bladder cancer.

nine studies were retrospective study design. Six studies [16-19, 22, 25] reported the association between NLR and OS, four studies [17, 21, 22, 24] reported information concerning CSS/DSS and three studies [17, 22, 23] presented RFS analysis. NLR cut-off values ranged from 2.38 to 3.

*Correlation of NLR with OS, CSS/DSS and RFS*

Six studies [16-19, 22, 25] with 1,718 subjects presented data on NLR and OS. The combined HR and 95% CI suggested that increased NLR had an association with shorter OS (HR=1.48, 95% CI=1.05-2.09, P=0.027; $I^2$=71.8%, Ph=0.003; **Figure 2**; **Table 2**). Four studies [17, 21, 22, 24] with 1,798 subjects investigated the relationship between NLR and CSS/DSS and our combined results showed that elevated NLR predicted poor CSS/DSS (HR=1.58, 95% CI=1.01-2.46, P=0.044; $I^2$=86.5%, Ph<0.001; **Figure 3**; **Table 2**). However, data from three studies [17, 22, 23] comprising 1,430 patients showed that high NLR had no association with poor RFS (HR=1.41, 95% CI=0.92-2.17, P=0.112; $I^2$=83%, Ph<0.001; **Figure 4**; **Table 2**). Subgroup analyses were conducted for further investigations. As shown in **Table 2**, when stratified by ethnicity, sample size, treatment methods and NLR cut-off value, NLR was not correlated with poor OS, except for patients included in large sample studies (HR=1.59, 95% CI=1.12-2.28, P=0.01; $I^2$=40.5%, Ph=0.169; **Table 2**). Intriguingly, subgroup analyses for CSS/DSS demonstrated that NLR≤2.5 remained a significantly unfavorable indicator (HR=1.96, 95% CI=1.26-3.04, P=0.003; $I^2$=0, Ph=0.983; **Table 2**). Subgroup analysis was not conducted for RFS due to limited amount of studies.

*Publication bias*

To evaluate publication bias of included literature, we carried out Begger's funnel plot. As shown in **Figure 5**, there was no evidence for significant publication bias for OS, CSS/DSS and RFS (Begg' P=0.26, 1 and 0.296, respectively).

## Discussion

In the current study, by combining data from 9 studies with 2,300 patients, we evaluated the potential prognostic value of NLR in bladder cancer for different end-point events including OS, CSS/DSS and RFS prediction using meta-analysis. The pooled results showed that high NLR was generally associated with poor OS and CSS/DSS, but did not suggest poor RFS in bladder cancer. Subgroup analyses demonstrated that NLR still predicted shorter OS in large sample size studies and NLR≤2.5 held prognostic value for RFS. To the best of our knowledge, the current study is the first meta-analysis to date evaluating the prognostic significance of NLR for bladder cancer.

Increasing evidence has shown that host inflammatory responses are linked with carcinogenesis, with inflammatory cells being involved in tumor progression [26, 27]. Inflammatory responses can reflect non-specific responses necrosis, tissue damage and tumor hypoxia in tumor microenvironment [28]. The complicated changes in inflammatory status are considered to promote tumor proliferation and facilitate metastasis [29]. Serum tumor markers which could reflect the balance and imbalance between host immune system and tumor are proposed and validated in recent years, including C-reactive protein (CRP) [30, 31], Glasgow Prognostic Score (GPS) [32] and NLR [19, 24, 25]. Among these parameters, NLR is most attractive because it is derived from the results of blood tests, which is easily available and inexpensive.

Our study showed that NLR was associated with poor OS and CSS/DSS in bladder cancer, which was in line with the results acquired from other forms of cancer [13, 14, 33, 34]. We have noticed that, recent studies [35, 36] reported the prognostic value of NLR in urologic tumors, including bladder cancer, through meta-analysis. However, in Wei's study [35], only two primary publication [16, 21] concerning bladder cancer were included. The credibility of their study may be underpowered due to small sample size in bladder cancer, although they also concluded that NLR was correlated with poor RFS/CSS in bladder cancer, which was in accordance with our results. Another meta-analysis [36] containing 5 studies of bladder cancer only conducted subgroup analyses based on the dichotomous NLR, whereas bladder cancer was not separately analyzed. Therefore, to date, our study was the most comprehensive meta-analysis concerning NLR in bladder cancer. The results suggest that NLR has clinical utility for risk stratification in patients with bladder cancer.

There are several limitations to our study. First, the general sample size of this meta-analysis was relatively small. That may explain the negative results in subgroup analyses for OS and CSS/DSS, because fewer subjects were included in subgroup analyses. Second, the cut-off values of NLR were various in primary studies, which could introduce heterogeneity when the results were combined. Therefore, our results need to be further confirmed by a large scale study using uniform cut-off value to provide a better conclusion.

In summary, our meta-analysis showed that elevated NLR predicted poor OS and CSS/DSS in bladder cancer, but had no association with RFS. This meta-analysis may provide useful implications for the clinical application of NLR in the treatment of bladder cancer.

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## Disclosure of conflict of interest

None.

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