World Journal of Urology (2019) 37:1817–1825
https://doi.org/10.1007/s00345-018-2593-z

ORIGINAL ARTICLE

The prognostic role of preoperative circulating neutrophil–lymphocyte ratio in primary bladder cancer patients undergoing radical cystectomy: a meta-analysis

Guoming Hu[1] · Feng Xu[1] · Kefang Zhong[1] · Shimin Wang[2] · Qi Xu[3] · Liming Huang[1] · Pu Cheng[4]

Received: 15 August 2018 / Accepted: 29 November 2018 / Published online: 3 December 2018

Abstract

Background Systemic inflammatory response (SIR) plays important roles in initiation, promotion and progression of tumor. However, the prognostic role of preoperative circulating neutrophil–lymphocyte ratio (NLR) (known as a marker of SIR) in human primary bladder cancer (BC) undergoing radical cystectomy (RC) remains controversial. Hence, we performed this meta-analysis to better understand the role of preoperative circulating NLR in prognosis prediction for primary BC patients undergoing RC.

Methods We searched PubMed, Embase and EBSCO to identify the studies and computed extracted data with STATA 12.0.

Results A total of 11,945 patients with BC from 18 published studies were incorporated into this meta-analysis. We found that elevated NLR was significantly associated with decreased 3-year and 5-year overall survival (OS), 1-year, 3-year and 5-year recurrence-free survival (RFS), but not with 1-year or 10-year OS, or 10-year RFS in primary BC patients who underwent RC. The results also showed that neoadjuvant chemotherapy (NAC) had a significant impact on the negative prognostic effect of NLR. In addition, high NLR significantly correlated with unfavorable clinicopathological features of BC.

Conclusion Elevated preoperative circulating NLR leads to an unfavorable outcome in primary BC undergoing RC, especially in patients without NAC, implicating that it might be a valuable prognostic index for these patients.

Keywords Preoperative circulating neutrophil–lymphocyte ratio · Unfavorable outcome · Primary bladder cancer · Radical cystectomy · Neoadjuvant chemotherapy · Meta-analysis

Abbreviations

NLR	Neutrophil–lymphocyte ratio
SIR	Systemic inflammatory response
BC	Bladder cancer
RC	Radical cystectomy
NAC	Neoadjuvant chemotherapy
OS	Overall survival
RFS	Recurrence-free survival
HR	Hazard rations
OR	Odds ratios
CI	Confidence interval
TNM	Tumor, lymph node, metastasis
NR	Not reported

Co-first authors: Guoming Hu and Feng Xu.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2593-z) contains supplementary material, which is available to authorized users.

✉ Guoming Hu
hgmplj@126.com

✉ Pu Cheng
drchengpu@zju.edu.cn

[1] Department of General Surgery (Breast and Thyroid Surgery), Shaoxing People's Hospital (Shaoxing Hospital, Zhejiang University School of Medicine), Shaoxing 312000, Zhejiang, China

[2] Department of Nephrology, Shaoxing People's Hospital (Shaoxing Hospital, Zhejiang University School of Medicine), Shaoxing 312000, Zhejiang, China

[3] Department of Surgical Oncology, Shaoxing Second Hospital, Shaoxing 312000, Zhejiang, China

[4] Department of Gynecology, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou 310009, China

Background

Although advances in diagnostic and therapeutic strategies have benefited the cancer patients, the progress in prognostic prediction of these patients still remains poor. Over the past decade, it has been shown to depend mainly on tumor characteristics, such as pathological tumor stage, lymph node metastases, etc. Until recently, several systemic inflammatory response (SIR)-related hematological factors have been extensively investigated to risk-stratify cancer patients to improve treatment selection and to predict clinical outcomes in many types of cancers.

The neutrophil–lymphocyte ratio (NLR), known as a marker of the SIR, has gained considerable interest in the past decade as a potential prognostic index associated with clinical outcomes in various cancers [1]. Preoperative circulating NLR, which can easily be measured on the basis of absolute neutrophils and lymphocytes in a differential white blood cell count performed in the clinical setting before operation, has been investigated in recent studies to predict the clinical outcomes in primary bladder cancer (BC) patients who underwent radical cystectomy (RC), but their results were not consistent even controversial. Therefore, an in-depth assessment is warranted. Furthermore, the potential of NLR in peripheral blood before surgery as an effective prognostic index and therapeutic strategy is necessary to be explored.

Herein, we performed this meta-analysis to quantitatively summarize the association between preoperative circulating NLR and clinical outcomes such as overall survival (OS) and recurrence-free survival (RFS) in primary BC patients, and thereby provided more evidence on the clinical value of circulating NLR as a prognostic index for BC.

Methods

Search strategy

We searched PubMed, Embase and EBSCO for studies assessing the NLR in peripheral blood before surgery and survival in BC patients from 1996 to May 31, 2018. The keywords adopted for search were ("neutrophil to lymphocyte ratio" OR "NLR" OR "inflammation") AND ("bladder cancer") AND ("prognosis" OR "survival"). A total of 247, 326 and 658 entries were identified in PubMed, Embase and EBSCO, respectively.

Inclusion and exclusion criteria

Inclusion criteria of the meta-analysis were: studies included must have (1) been published as original articles; (2) evaluated human subjects with histopathologically diagnosed primary BC receiving radical cystectomy; (3) provided hazard ratios (HRs) with 95% confidence interval (CI), or Kaplan–Meier curves of high and low preoperative circulating NLR with overall survival (OS) or recurrence-free survival (RFS); and (4) been published in English.

We excluded studies that were not published as research articles or full texts including commentary, case report and letters to editors and conference abstracts; studies that did not provide sufficient data to estimate hazard ratios (HRs); and studies that detected NLR not in peripheral blood or after surgery.

Endpoints

In this meta-analysis, we recorded OS and RFS as the primary and second endpoints, respectively. Individual studies defined cut-offs of NLR and classified BC patients into high- and low-groups.

Data extraction

Two authors (GM. H. and F. X.) independently reviewed and extracted information including first author's name, publication year, number of patients, median age, gender, time of follow-up and cut-off value to determine high NLR. OS, RFS and clinicopathological data including tumor, lymph node, metastasis (TNM) stage, lymphovascular invasion, etc. were extracted from the text, tables, or Kaplan–Meier curves for both high and low NLR groups.

Quality assessment

The studies included in the meta-analysis were cohort studies. Two independent authors assessed the quality of included individual study with Newcastle–Ottawa Scale (NOS) [2], and achieved consensus for each item under the help of third author. The studies with six scores or more were recorded as high-quality studies.

Statistical analysis

The STATA 12.0 software (Stata Corporation, College Station, TX, USA) was used to combine the extracted data into meta-analyses. Statistical heterogeneity was assessed using the Chi-squared-based Q test or the I^2 method [3]. Data were combined according to the random-effect model

Table 1 Main characteristics of the included studies

Study	Year	No. of patients	Male/female	Median age (range) (year)	Cut-off for NLR	NLR: high/low	Treatment	Tumor stage	Median follow-up date (months)	Survival	Quality Score (NOS)
D'Andrea et al. [7]	2016	4335	3362/836	67 (60, 73)	2.7	2168/2167	RC	I–IV	42.4 (18.3, 85.1)	OS, RFS	7
Kang et al. [9]	2016	385	362/57	65.1 (58.3, 70.4)	2.1	184/201	RC	I–III	38	OS,	8
Viers et al. [10]	2014	899	723/176	69 (62, 76)	2.7	503/396	RC	I–IV	130.8 (99.6, 166.8)	OS, RFS	7
Tan et al. [22]	2017	84	63/21	67 (37, 82)	2.7	45/39	RC	I–IV	30.1 (3.2, 161.7)	OS, RFS	8
Ozcan et al. [19]	2015	286	256/30	60.7 (29, 83)	2.5	144/140	RC	I–IV	28 (0, 144)	OS	6
Zhang et al. [8]	2015	124	100/24	65 (30, 78)	2.1	52/72	RC	I–IV	NR	OS	7
Gondo et al. [23]	2012	189	158/31	68.4 (38, 85)	2.5	104/85	RC	II–III	25.1 (2.1, 127.9)	OS	8
Lucca et al. [32]	2016	4061	3240/821	66.1 ± 10.2	2.7	2546/1515	RC	NR	42 (18, 85)	OS	7
Buisan et al. [27]	2017	19	NR	NR	5.0	NR	NAC + RC	NR	29 (2, 99)	OS	7
van Kessel et al. [26]	2016	123	91/32	61	2.21	55/68	NAC + RC	NR	NR	OS	8
Buisan et al. [20]	2016	75	69/6	NR	2.5	34/41	NAC + RC	NR	NR	OS	7
Krane et al. [28]	2013	68	55/13	67.4 ± 10.1	2.5	NR	RC ± NAC	I–IV	25 (13, 61)	OS	7
Kawahara et al. [16]	2016	74	58/16	≥ 65: 56.8%; < 65: 43.2%	2.38	23/51	RC ± NAC	II–IV	24.2	OS	6
Ojerholm et al. [14]	2016	230	185/45	64.0 (57.2, 68.5)	2.66	NR	RC + NAC	II–IV	223.2	OS	6
Hermanns et al. [15]	2014	424	325/99	70.1 (60.6, 76.3)	3.0	216/208	RC ± NAC	I–IV	58.4 (21.3, 94.5)	OS, RFS	8
Hirasawa et al. [17]	2016	136	112/24	68.6	NR	NR	RC ± NAC	I–IV	46.7	OS	8
Morizawa et al. [21]	2016	110	86/24	72 (65, 76)	2.6	55/55	RC ± NAC	I–IV	37.5 (11, 65)	OS, RFS	7
Yoshida et al. [24]	2016	323	253/70	71 (39, 91)	2.7	147/176	RC ± NAC	I–IV	63.5 (2.2–259.5)	OS	7

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *NR* not reported

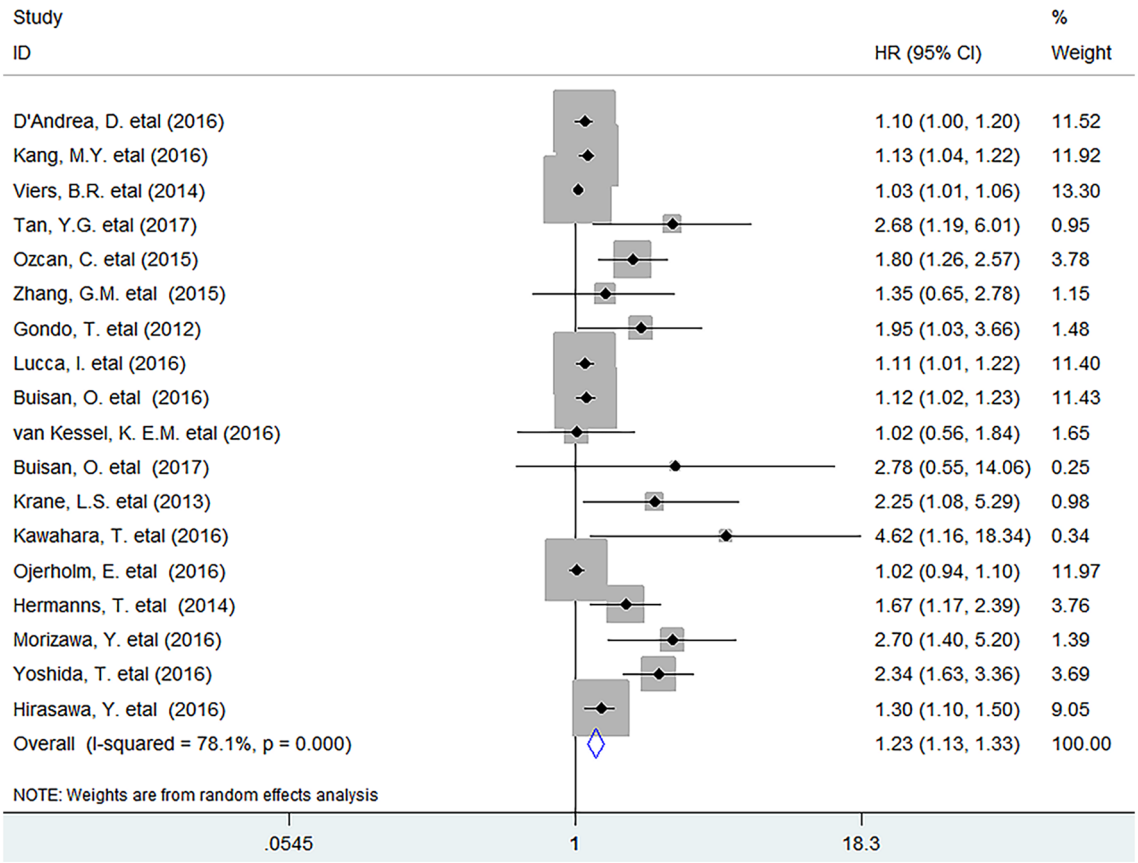

Fig. 1 Forest plots describing HR of the association between preoperative circulating NLR and OS in bladder cancer patients undergoing RC

in the presence of heterogeneity [4]; otherwise, the fixed-effect model was applied [5]. Sensitivity analysis, Begg's funnel plot and Egger's test [6] were employed to investigate the influence of individual studies on the pooled result and potential publication bias, respectively. All *P* values were two-sided and less than 0.05 are considered statistically significant.

Results

Search results and description of studies

1231 records were retrieved and the results were exhibited in Fig. S1. We ultimately identified 18 studies containing 11945 BC patients for the assessment of preoperative circulating NLR [7–30], and then evaluated all these studies with the Newcastle–Ottawa Scale (NOS). Characteristics of included studies that were in accordance with the inclusion criteria and suitable for data consolidation are shown in Table 1 and S1.

Meta-analyses

Overall survival (OS)

The meta-analysis indicated that elevated preoperative NLR in peripheral blood significantly decreased OS (HR 1.23, 95% CI 1.13–1.33, $P=0.000$) in patients with primary BC who underwent RC (Fig. 1). However, in stratified analyses, we found that increased NLR before surgery was significantly associated with decreased 3-year (OR 0.62, 95% CI 0.52–0.74, $P=0.000$) and 5-year survival rate (OR 0.60, 95% CI 0.51–0.71, $P=0.000$), but not with 1-year (OR 0.74, 95% CI 0.55–1.01, $P=0.055$) or 10-year survival rate (OR 0.73, 95% CI 0.51–1.03, $P=0.072$) in BC (Fig. 2).

To investigate whether preoperative treatment such as neoadjuvant chemotherapy (NAC) could influence the association between high preoperative circulating NLR and decreased OS, and the stratified analysis showed that NAC had a significant impact on the prognostic role of NLR in BC patients (HR 1.06, 95% CI 0.99–1.15, $P=0.105$), with little heterogeneity being observed ($I^2=17.2\%$, $P=0.305$); in contrast, elevated preoperative circulating NLR was

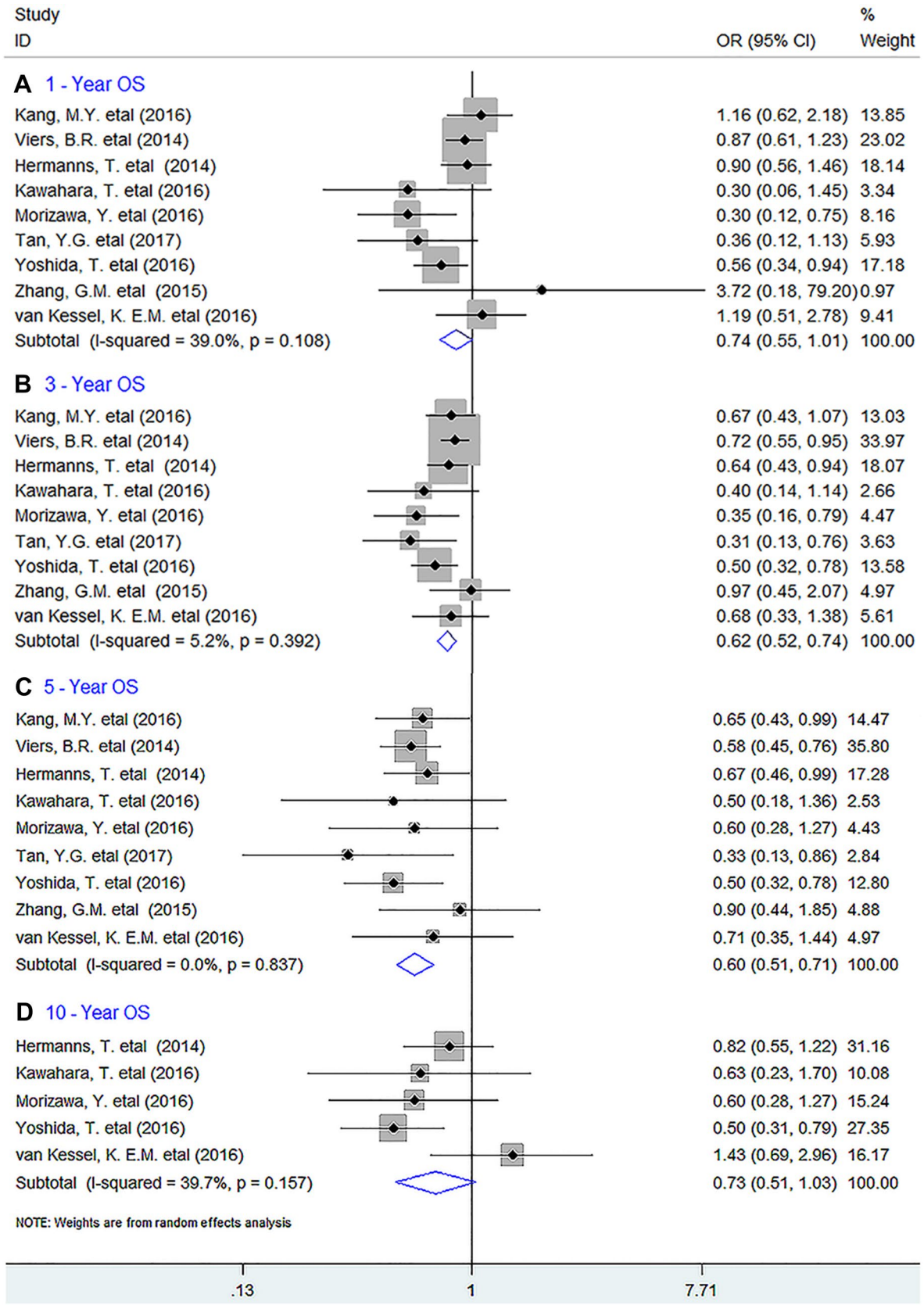

Fig. 2 Stratified analyses describing ORs of the association between preoperative circulating NLR and 1-year, 3-year, 5-year and 10-year survival rate in bladder cancer

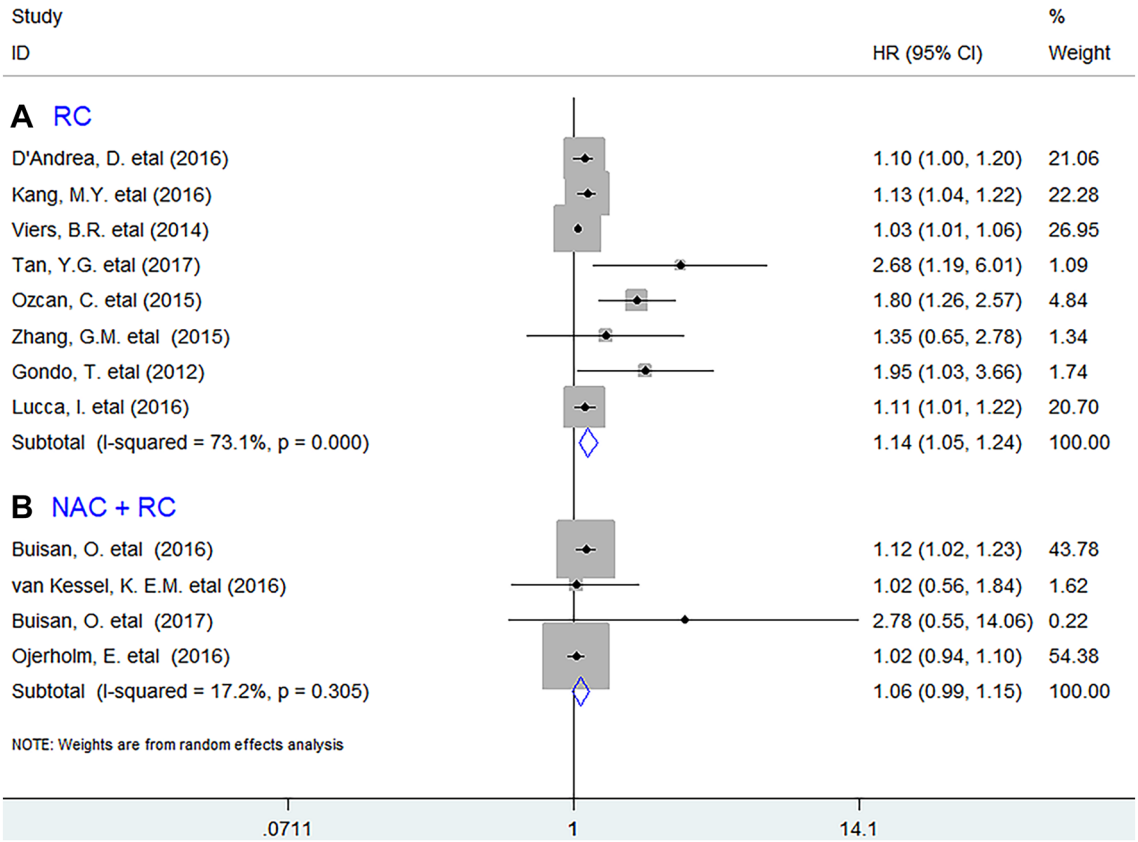

Fig. 3 Stratified analyses describing HRs of the association between preoperative circulating NLR and OS in bladder cancer patients undergoing RC with or without NAC

significantly associated with worse OS in patients who did not receive NAC (HR 1.14, 95% CI 1.05–1.24, $P=0.003$) (Fig. 3).

Recurrence-free survival (RFS)

Meta-analysis revealed that high preoperative circulating NLR was significantly associated with decreased 1-year (OR 0.50, 95% CI 0.34–0.74, $P=0.000$), 3-year (OR 0.52, 95% CI 0.39–0.69, $P=0.000$) and 5-year RFS (OR 0.56, 95% CI 0.42–0.74, $P=0.000$), but not with 10-year RFS (OR 0.59, 95% CI 0.30–1.18, $P=0.138$) in BC patients who underwent RC (Fig. 4).

In addition, we found that high NLR was significantly associated with advanced primary tumor stage (OR 0.67, 95% CI 0.57–0.78, $P=0.000$), lymph node metastasis (OR 1.70, 95% CI 1.31–2.22, $P=0.000$) as well as lymphovascular invasion (OR 1.34, 95% CI 1.16–1.56, $P=0.000$), but not with tumor differentiation (OR 0.54, 95% CI 0.26–1.11, $P=0.092$) of patients (Fig. S2).

Sensitivity analysis

Sensitivity analyses were used to determine the influence of individual studies on the overall HR. As a result, the plots showed that all the individual studies had no important impact on the results for OS or RFS.

Publication bias

Funnel plot and Egger's test indicated that there was no significant publication bias between circulating NLR and OS ($P=0.899$) in patients with BC (Fig. S3).

Discussion

Systemic inflammatory response linked closely with the initiation, promotion and progression of cancer [31]. Although previous study has indicated that high pretreatment NLR decreased OS in urothelial carcinoma [32], the prognostic impact of NLR in human primary BC undergoing RC still remains controversial. In the present meta-analysis, we

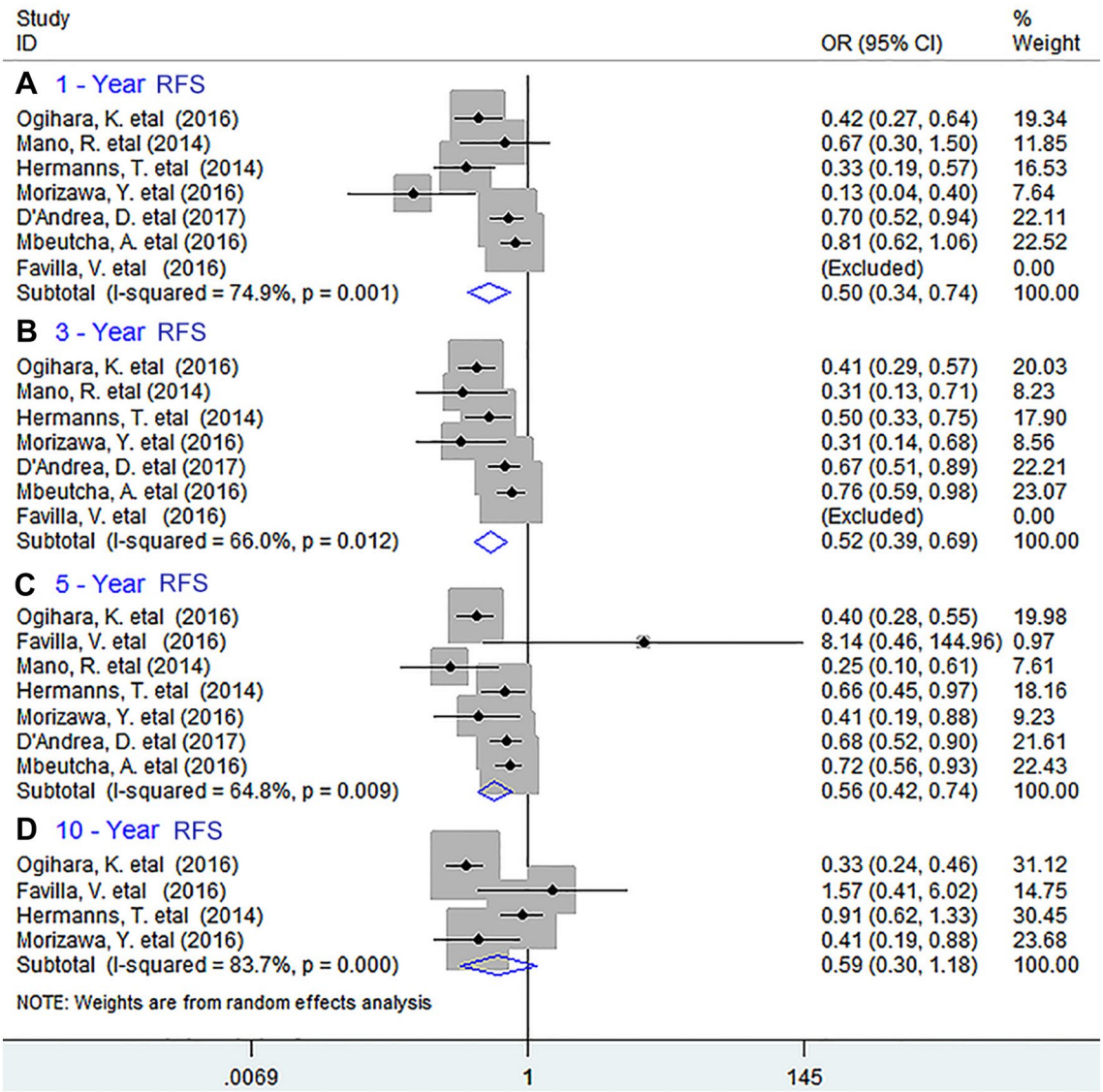

Fig. 4 Forest plots describing ORs of the association between preoperative circulating NLR and 1-year, 3-year, 5-year and 10-year RFS in bladder cancer

found that elevated preoperative circulating NLR was significantly associated with decreased OS, except for 1-year and 10-year survival rate in primary BC patients undergoing RC; which significantly differed from the previous studies [33, 34]. We also found that NAC could significantly affect the association between high NLR and OS in these patients. In addition, high NLR significantly correlated with unfavorable clinicopathological features of BC. We believe that this is the first to provide such distinctive statistical evidence exhibiting the important prognostic value of preoperative circulating NLR in BC patients.

The close association between increased NLR and worse prognosis of BC patients identified in this study may relate to the following reasons: bladder cancer cells can secret granulocyte colony stimulating factor to elicit systemic inflammatory response (SIR) via recruiting myeloid cells and inducing the release of neutrophils from the bone marrow to circulating blood [35], and elevated neutrophils have effect on tumor cells for inducing proliferation, migration and metastasis through producing various pro-angiogenic proteases such as matrix metalloproteinases-9 (MMP-9), cathepsin G and elastase [36]. In addition, increased neutrophils can secret amount of cytokines such as IL-1β, TNF-α, IL-12 to induce a chronic inflammatory state and release arginase-1 to inhibit antitumor immunity mediated by natural killer (NK) cells and effector T cell, therefore, establishing an immune suppressive environment subsequently promoting tumor progression

[37]. Thus, it is reasonable to conclude that the elevated circulating NLR is able to promote tumor progression, therefore, decreasing survival. NAC induces death of bladder cancer cells and inflammatory cells, inhibits hematopoietic function of bone marrow causing neutropenia and finally changes the SIR. However, the cellular (or molecular) mechanisms underlying NAC-mediated impact on the prognostic effect of NLR need be further investigation.

Several limitations should be noted from this meta-analysis. First, cut-offs for NLR adopted in included studies were not consistent. Many papers will define the cut-off values just for the purpose of publications, but we do not know whether these studies had done it in that way. Besides, studies with negative results might not be published, which could cause potential publication bias.

Conclusions

Elevated preoperative circulating NLR leads to an unfavorable clinical outcome in primary BC undergoing RC, especially in patients without NAC, implicating that it might be a valuable prognostic index for these patients and modifying the inflammatory responses may have a potential for effective treatment.

Acknowledgements We thank all the members of the departments who helped in this study.

Author contributions GH contributed to protocol and project development, data collection and manuscript writing; FX, QX and KZ contributed to data collection; SW and LH contributed to data analysis; PC contributed to protocol and project development and the manuscript revision. All authors read and approved the final manuscript.

Funding This work was funded by the National Natural Science Foundation of China (Grant no. 81702803, GMH).

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Research involving human participants and/or animals Human participants.

Informed consent The ethical approval was unnecessary because this study based on summary and analysis of the results of previous studies.

References

1. Albayrak S, Zengin K, Tanik S, Atar M, Unal SH, Imamoglu MA, Gurdal M (2016) Can the neutrophil-to-lymphocyte ratio be used to predict recurrence and progression of non-muscle-invasive bladder cancer? Kaohsiung J Med Sci 32:327–333
2. Stang A (2010) Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25:603–605
3. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
4. Kuritz SJ, Landis JR, Koch GG (1988) A general overview of Mantel–Haenszel methods: applications and recent developments. Annu Rev Public Health 9:123–160
5. DerSimonian R, Kacker R (2007) Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 28:105–114
6. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
7. D'Andrea D, Moschini M, Gust KM, Abufaraj M, Ozsoy M, Mathieu R, Soria F, Briganti A, Roupret M, Karakiewicz PI, Shariat SF (2017) Lymphocyte-to-monocyte ratio and neutrophil-to-lymphocyte ratio as biomarkers for predicting lymph node metastasis and survival in patients treated with radical cystectomy. J Surg Oncol 115:455–461
8. Zhang GM, Zhu Y, Luo L, Wan FN, Zhu YP, Sun LJ, Ye DW (2015) Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumour Biol 36:8537–8543
9. Kang M, Jeong CW, Kwak C, Kim HH, Ku JH (2016) The prognostic significance of the early postoperative neutrophil-to-lymphocyte ratio in patients with urothelial carcinoma of the bladder undergoing radical cystectomy. Ann Surg Oncol 23:335–342
10. Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, Thompson RH, Tollefson MK (2014) Pretreatment neutrophil-to-lymphocyte ratio is associated with advanced pathologic tumor stage and increased cancer-specific mortality among patients with urothelial carcinoma of the bladder undergoing radical cystectomy. Eur Urol 66:1157–1164
11. Ogihara K, Kikuchi E, Yuge K, Yanai Y, Matsumoto K, Miyajima A, Asakura H, Oya M (2016) The preoperative neutrophil-to-lymphocyte ratio is a novel biomarker for predicting worse clinical outcomes in non-muscle invasive bladder cancer patients with a previous history of smoking. Ann Surg Oncol 23:1039–1047
12. Favilla V, Castelli T, Urzi D, Reale G, Privitera S, Salici A, Russo GI, Cimino S, Morgia G (2016) Neutrophil to lymphocyte ratio, a biomarker in non-muscle invasive bladder cancer: a single-institutional longitudinal study. Int Braz J Urol 42:685–693
13. Mano R, Baniel J, Shoshany O, Margel D, Bar-On T, Nativ O, Rubinstein J, Halachmi S (2015) Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer. Urol Oncol 33(67):e1–e7
14. Ojerholm E, Smith A, Hwang WT, Baumann BC, Tucker KN, Lerner SP, Mamtani R, Boursi B, Christodouleas JP (2017) Neutrophil-to-lymphocyte ratio as a bladder cancer biomarker: assessing prognostic and predictive value in SWOG 8710. Cancer 123:794–801
15. Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, Bhatt JR, Almatar A, Jewett MA, Fleshner NE, Zlotta AR, Templeton AJ, Kulkarni GS (2014) Pre-treatment neutrophil-to-lymphocyte ratio as predictor of adverse outcomes in patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Br J Cancer 111:444–451
16. Kawahara T, Furuya K, Nakamura M, Sakamaki K, Osaka K, Ito H, Ito Y, Izumi K, Ohtake S, Miyoshi Y, Makiyama K, Nakaigawa N, Yamanaka T, Miyamoto H, Yao M, Uemura H (2016) Neutrophil-to-lymphocyte ratio is a prognostic marker in bladder cancer patients after radical cystectomy. BMC Cancer 16:185

17. Hirasawa Y, Nakashima J, Yunaiyama D, Sugihara T, Gondo T, Nakagami Y, Horiguchi Y, Ohno Y, Namiki K, Ohori M, Tokuuye K, Tachibana M (2016) Sarcopenia as a novel preoperative prognostic predictor for survival in patients with bladder cancer undergoing radical cystectomy. Ann Surg Oncol 23:1048–1054
18. Kang M, Jeong CW, Kwak C, Kim HH, Ku JH (2017) Preoperative neutrophil-lymphocyte ratio can significantly predict mortality outcomes in patients with non-muscle invasive bladder cancer undergoing transurethral resection of bladder tumor. Oncotarget 8:12891–12901
19. Ozcan C, Telli O, Ozturk E, Suer E, Gokce MI, Gulpinar O, Oztuna D, Baltaci S, Gogus C (2015) The prognostic significance of preoperative leukocytosis and neutrophil-to-lymphocyte ratio in patients who underwent radical cystectomy for bladder cancer. Can Urol Assoc J 9:E789–E794
20. Buisan O, Orsola A, Areal J, Font A, Oliveira M, Martinez R, Ibarz L (2017) Low pretreatment neutrophil-to-lymphocyte ratio predicts for good outcomes in patients receiving neoadjuvant chemotherapy before radical cystectomy for muscle invasive bladder cancer. Clin Genitourin Cancer 15:145–151 e2
21. Morizawa Y, Miyake M, Shimada K, Hori S, Tatsumi Y, Nakai Y, Anai S, Tanaka N, Konishi N, Fujimoto K (2016) Neutrophil-to-lymphocyte ratio as a detection marker of tumor recurrence in patients with muscle-invasive bladder cancer after radical cystectomy. Urol Oncol 34(257):e11–e17
22. Tan YG, Eu E, Lau Kam On W, Huang HH (2017) Pretreatment neutrophil-to-lymphocyte ratio predicts worse survival outcomes and advanced tumor staging in patients undergoing radical cystectomy for bladder cancer. Asian J Urol 4:239–246
23. Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, Yoshioka K, Ohori M, Hatano T, Tachibana M (2012) Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. Urology 79:1085–1091
24. Yoshida T, Kinoshita H, Yoshida K, Mishima T, Yanishi M, Komai Y, Sugi M, Murota T, Kawa G, Matsuda T (2016) Perioperative change in neutrophil-lymphocyte ratio predicts the overall survival of patients with bladder cancer undergoing radical cystectomy. Jpn J Clin Oncol 46:1162–1167
25. Ozyalvacli ME, Ozyalvacli G, Kocaaslan R, Cecen K, Uyeturk U, Kemahli E, Gucuk A (2015) Neutrophil-lymphocyte ratio as a predictor of recurrence and progression in patients with high-grade pT1 bladder cancer. Can Urol Assoc J 9:E126–E131
26. van Kessel KE, de Haan LM, Fransen van de Putte EE, van Rhijn BW, de Wit R, van der Heijden MS, Zwarthoff EC, Boormans JL (2016) Elevated derived neutrophil-to-lymphocyte ratio corresponds with poor outcome in patients undergoing pre-operative chemotherapy in muscle-invasive bladder cancer. Bladder Cancer 2:351–360
27. Buisan O, Orsola A, Oliveira M, Martinez R, Etxaniz O, Areal J, Ibarz L (2017) Role of inflammation in the perioperative management of urothelial bladder cancer with squamous-cell features: impact of neutrophil-to-lymphocyte ratio on outcomes and response to neoadjuvant chemotherapy. Clin Genitourin Cancer 14:e697–e706
28. Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK (2013) Preoperative neutrophil/lymphocyte ratio predicts overall survival and extravesical disease in patients undergoing radical cystectomy. J Endourol 27:1046–1050
29. Mbeutcha A, Shariat SF, Rieken M, Rink M, Xylinas E, Seitz C, Lucca I, Mathieu R, Roupret M, Briganti A, Karakiewicz PI, Klatte T (2016) Prognostic significance of markers of systemic inflammatory response in patients with non-muscle-invasive bladder cancer. Urol Oncol 34:483 e17–483 e24
30. D'Andrea D, Moschini M, Gust K, Abufaraj M, Ozsoy M, Mathieu R, Soria F, Briganti A, Roupret M, Karakiewicz PI, Shariat SF (2017) Prognostic role of neutrophil-to-lymphocyte ratio in primary non-muscle-invasive bladder cancer. Clin Genitourin Cancer 15:e755–e764
31. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140:883–899
32. Li X, Ma X, Tang L, Wang B, Chen L, Zhang F, Zhang X (2017) Prognostic value of neutrophil-to-lymphocyte ratio in urothelial carcinoma of the upper urinary tract and bladder: a systematic review and meta-analysis. Oncotarget 8:62681–62692
33. Lucca I, Jichlinski P, Shariat SF, Roupret M, Rieken M, Kluth LA, Rink M, Mathieu R, Mbeutcha A, Maj-Hes A, Fajkovic H, Briganti A, Seitz C, Karakiewicz PI, de Martino M, Lotan Y, Babjuk M, Klatte T (2016) The neutrophil-to-lymphocyte ratio as a prognostic factor for patients with urothelial carcinoma of the bladder following radical cystectomy: validation and meta-analysis. Eur Urol Focus 2:79–85
34. Tang X, Du P, Yang Y (2017) The clinical use of neutrophil-to-lymphocyte ratio in bladder cancer patients: a systematic review and meta-analysis. Int J Clin Oncol 22:817–825
35. Tachibana M, Miyakawa A, Tazaki H, Nakamura K, Kubo A, Hata J, Nishi T, Amano Y (1995) Autocrine growth of transitional cell carcinoma of the bladder induced by granulocyte-colony stimulating factor. Cancer Res 55:3438–3443
36. Swierczak A, Mouchemore KA, Hamilton JA, Anderson RL (2015) Neutrophils: important contributors to tumor progression and metastasis. Cancer Metastasis Rev 34:735–751
37. Uribe-Querol E, Rosales C (2015) Neutrophils in cancer: two sides of the same coin. J Immunol Res 2015:983698