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Prognostic role of pretreatment derived neutrophil to lymphocyte ratio in urological cancers: A systematic review and meta-analysis

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ABSTRACT

Background: To investigate the possible prognostic role of pretreatment derived neutrophil-lymphocyte ratio (dNLR) in urological cancers, including renal cell carcinoma (RCC), prostate cancer (PCa), and urothelial cancer (UCa).

Materials and methods: Eligible studies were comprehensively searched from PubMed, Embase, Cochrane Library and Web of Science, up to April 2019. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the relationships.

Results: A total of 12 studies embracing 6585 patients were included in the meta-analysis. Our results indicated that a higher pretreatment dNLR was associated with a decreased cancer-specific survival (CSS, HR 2.67, 95% CI 1.06–6.71, P = 0.037) and disease-free survival (DFS, HR 2.02, 95% CI 1.03–3.94, P = 0.040) in RCC, but not for overall survival (OS, HR 1.05, 95% CI 0.71–1.53, P = 0.818). A higher dNLR was associated with an inferior biochemical recurrence-free survival (BRFS, HR 1.70, 95% CI 1.00–2.87, P = 0.049) and OS (HR 1.35, 95% CI 1.20–1.51, P < 0.001) in PCa. A higher dNLR was associated with a worse OS (HR 1.29, 95% CI 1.03–1.61, P = 0.029) and CSS (HR 1.51, 95% CI 1.06–2.15, P = 0.024) in UCa, but not for DFS (HR 1.44, 95% CI 0.89–2.34, P = 0.139).

Conclusion: A higher dNLR level was negatively associated with OS, CSS, DFS and BRFS, forecasting that it could be an independent prognosis predictor in urological cancers.

1. Introduction

Urological cancers, mostly embraced renal cell carcinoma (RCC), prostate cancer (PCa), and urothelial cancer (UCa) are common types of malignancies with universal adding incidence and mortality [1]. Based on the latest cancer statistics for the United States, urological cancers make up more than 32% of all types of malignancies in 2019 [2]. Moreover, during the last decades, PCa is the most common malignance for men, which accounted for 20% of estimated new incidences with about 174, 650 new cases and 10% of estimated deaths with about 31,620 deaths [2]. Due to the extensive application of radiological imaging techniques and new methods of examinations, the increasingly small and localized masses have been identified [3]. Moreover, because of the progress in treatment modalities such as immunotherapy [4] and the advance of molecular-targeting agents [5,6], prognosis of urological cancers has gained a great improvement. Nevertheless, there is still a large part of patients experienced late-stage diseases, and long-term survival for them remains unsatisfactory. Hence, it is meaningful to investigate the prognostic factors for these patients, so as to preferably comprehend the underlying mechanisms and contribute to optimally treating urological cancers.

Mounting evidence supports a vital role of the systemic inflammatory response in formation and progression of types malignances. Several markers of the immune response, such as C-reactive protein [7], platelet count [8], as well as neutrophil-lymphocyte ratio (NLR) [9], lymphocyte-monocyte ratio (LMR) [10], platelet-lymphocyte ratio (PLR) [11], have been proposed as potential prognostic factors for patients with RCC, PCa and UCa. Recently, derived neutrophil-lymphocyte ratio (dNLR), which is made up of the neutrophil count to (white cell count minus neutrophil count), has been implemented Proctor et al. [12]. This simplified blood index has been considered as prognostic factor in types malignances including urological cancers, and was demonstrated to have similar prognostic value as the classical NLR. After that, there is increasing studies to examine the prognostic value of dNLR in urological cancers, and reported inconsistent results. Therefore, we aim to systematically review the related publication and

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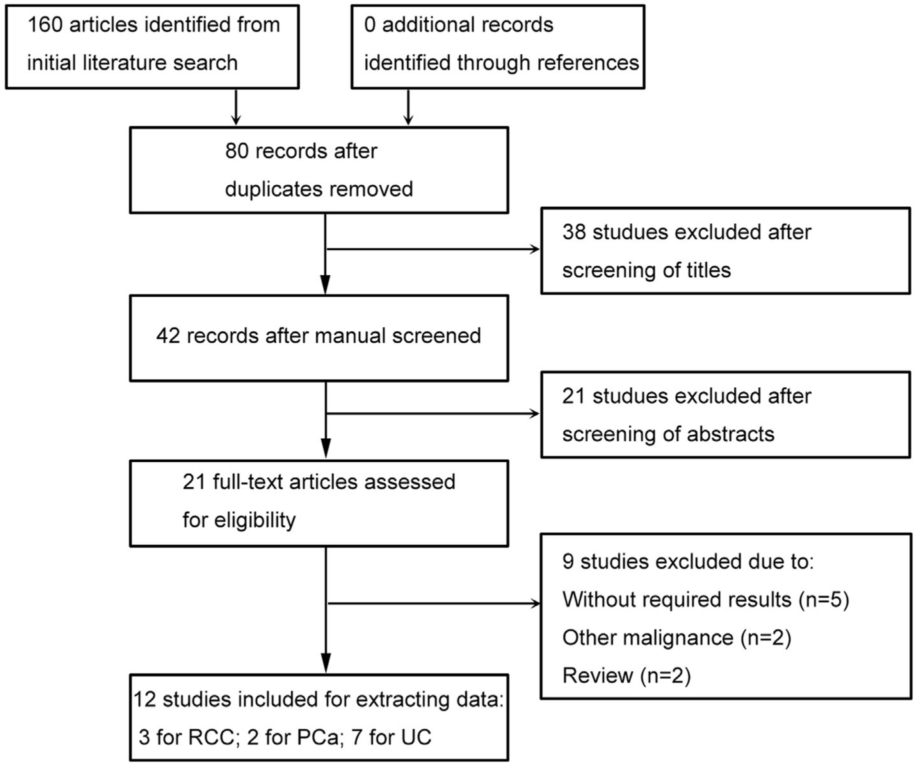

Fig. 1. The flow diagram of literature selection.

perform this meta-analysis to evaluate the relationship between dNLR and survival of urological cancer patients.

2. Materials and Methods

2.1. Literature search

A systematic literature search of PubMed, Embase, Cochrane Library and Web of Science was performed in April 2019. Major terms for search strategy were: "urological cancer" (e.g., "kidney cancer", "bladder cancer", "prostate cancer", "urothelial cancer" or "transitional cell carcinoma"), "dNLR" (e.g., "derived neutrophil to lymphocyte ratio", "derived neutrophil lymphocyte ratio", "derived neutrophil-to-lymphocyte") and "prognosis" (e.g., "prognosis," "survival," "outcome," "mortality," "recurrence" "progression," "metastasis"). A manual search of literature references was also performed to retrieve potentially related studies. This meta-analysis was conducted following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and Assessing the methodological quality of systematic reviews (AMSTAR) criteria. The protocol for this study was registered on PROSPERO (CRD 42019131641).

2.2. Inclusion criteria and study eligibility

All candidate literatures were independently reviewed by two researchers. Discrepancies were resolved by discussion. Literatures were eligible for our analysis when they met the following criteria [1]: studied patients with renal cell carcinoma (RCC), prostate cancer (PCa), or urothelial cancer (UCa), which were diagnosed with pathological examination [2]; reported the correlation of pretreatment dNLR with overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), and biochemical recurrence-free survival (BRFS) [3]; reported hazard ratios (HRs) and 95% confidence interval (CI) directly, or had sufficient data for calculating HRs and 95% CI [4]; published in peer-review journals.

Studies were excluded when they met the following criteria [1]: basic research [2]; conference abstracts, editorials, letters, expert opinions, review articles, case reports or series less than ten patients [3]; studied dNLR as a continuous variable, or didn't clearly reported the cut-off value [4]; studies which can't obtain HRs with their corresponding 95% CIs [5]; not written in English. The quality of literatures were evaluated in the light of the Newcastle-Ottawa Scale [13].

2.3. Data extraction

The following data were collected [1]: first author's name, year of publication, country, design of study (retrospective or prospective, single center or multi-institutional), sample size, median or mean age [2]; cancer related data including type of tumor, site, stage, treatment, endpoints of survival [3]; dNLR related data including cut-off value, and corresponding judgment methods. HRs of dNLR for OS, CSS, DFS, BRFS, and related 95% CIs were also obtained. If available, HRs and 95% CIs were preferentially obtained from multivariate results. Otherwise, they were extracted from univariable outcomes or calculated according to the method of Tierney et al. [14]. Subgroup analyses of OS and CSS for urothelial carcinoma were also performed, the grouping variables embraced publication year, region, site of carcinoma, sample size, value of cut-off, and HR source.

2.4. Statistical analysis

HRs with related 95% CIs from each publication were merged to evaluate the importance of prognostic role of dNLR for patients with urological cancers. For each meta-analysis, the Higgins I-squared statistic and Cochran's Q test were applied to assess the heterogeneity of the included literatures. $I^2 > 50\%$ and/or $P < 0.1$ were considered as a measure of marked heterogeneity. If severe heterogeneity existed, the random-effect model was used to calculated the pooled HRs and 95% CIs. Otherwise, the fixed-effect model was performed. When a meta-analysis embraced five or more literatures, publication bias was visually assessed by funnel plots, and quantitatively checked by Egger's and Begg's tests. Sensitivity analysis was undertaken by precluding any single study by turn to assess robustness of the results. Subgroup analyses and meta-regression were performed to examine the relationships of dNLR with grouping variables for urothelial carcinoma. All statistical analyses were carried out with Stata 12.0 software (STATA Corporation, College Station, TX, USA).

3. Results

3.1. Literature searching and features of studies

The flow diagram for the study searching was presented in Fig. 1. The primary search strategy obtained a total of 160 publications. After removing duplicates and screening titles and abstracts, 21 full-text articles were evaluated for eligibility. Of them, nine studies were precluded due to the following concerns: five didn't provide sufficient data; two focused on other malignances; two were review articles. Lastly, 12 literatures [3,15–25] published between 2014 and 2018 were included in the present study. Of them, 3 focused on renal cell carcinoma, 2 investigated prostate cancer, and 7 evaluated urothelial cancer.

The features of the 12 literatures were outlined in Table 1. Four studies were from South Korea, three studies were from China, two studies were from Austria, one from Poland, one from Netherlands, and one (two cohorts) from Multiple countries. These studies contained totally 6585 subjects, and the median sample size was 331 (IQR 128–561). The median or mean age of patients belonging to included studies range from 56 to 72.6 years. Of seven studies on UCa, 4 focused on bladder urothelial cancer, 3 investigated upper urinary tract urothelial cancer. Most of HRs and related 95% CIs were obtained from multivariate results.

3.2. dNLR and OS, CSS, DFS in RCC

There were 3 studies investigating the relationship between pretreatment dNLR and patient survival in RCC [3,20,22]. All of them contained data of OS, the merged results were shown in Fig. 2A. Taken that no marked heterogeneity was found among the three studies, a fixed-effect model was preformed (I^2 = 0.0%, P = 0.428). There was no significant correlation between pretreatment dNLR level and OS (hazard ratio [HR] 1.05, 95% confidence interval [CI] 0.71–1.53, P = 0.818) for RCC. However, Dalpiaz et al. [3] identified that a higher dNLR was associated with a worse CSS (HR 2.67, 95% CI 1.06–6.71, P = 0.037) and DFS (HR 2.02, 95% CI 1.03–3.94, P = 0.040) for RCC patients.

3.3. dNLR and BRFS, OS in PCa

There were 3 cohorts investigating the relationship between pretreatment dNLR and patient survival in PCa [16,23]. The merged results were shown in Fig. 2B. Taken that no marked heterogeneity was found among these cohorts, a fixed-effect model was applied (I^2 = 0.0% and 0.0%, P = 0.582 and 0.380). The results showed that a higher dNLR was associated with an inferior BRFS (HR 1.70, 95% CI 1.00–2.87, P = 0.049) and OS (HR 1.35, 95% CI 1.20–1.51, P < 0.001) for PCa patients.

3.4. dNLR and OS, CSS, DFS in UCa

There were 7 studies investigating the relationship between pretreatment dNLR and patient survival in UC [15,17–19,21,24,25]. The merged results were shown in Fig. 3. Since severe heterogeneity was identified among these studies, a random-effect model was applied (I^2 = 49.8%, 58.1% and 59.5%, P = 0.063, 0.049 and 0.116). The results showed that a higher dNLR was associated with a worse OS (HR 1.29, 95% CI 1.03–1.61, P = 0.029) and CSS (HR 1.51, 95% CI 1.06–2.15, P = 0.024) for UCa patients. However, there was no significant correlation between pretreatment dNLR level and DFS (HR 1.44, 95% CI 0.89–2.34, P = 0.139). Subgroup analyses of OS and CSS for UCa were presented in Table 2. The HR of dNLR on OS was 1.22 (95% CI 1.13–1.31, P < 0.001) for bladder UC, 1.78 (95% CI 1.20–2.65, P = 0.004) for upper urinary tract UCa patients. The HR of dNLR on CSS was 1.14 (95% CI 1.04–1.25, P = 0.005) for bladder UCa, 1.88 (95% CI 1.33–2.67, P < 0.001) for upper urinary tract UCa patients. Though some subgrouping variables changed the results for OS and CSS, meta-regression didn't identified the reasons of heterogeneity.

3.5. Publication bias

Funnel plots were presented for the included cohorts in UCa

Table 1
Characteristics of all the studies.

Study	Year	Country	Study Design	Case Number	Age (Years)	Site	Stage	Treatment	Cut-off value	Determine the cut-off value	Cox	Survival Analysis	SQ
Renal cell carcinoma													
Hu	2017	China	RTP, MI	484	56 (21–81)[R]	-	All	Surgery	2.05	ROC curve	Mul	OS	8
Dalpiaz	2017	Austria	RTP, SC	587	65 (20–88)[R]	-	Localized	Surgery	2.0	Reported	Mul	OS, CSS, DFS	8
Gu	2016	China	RTP, SC	103	56 (16–79)[R]	-	All	Surgery	2.57	ROC curve	Mul	OS	7
Prostate cancer													
Shu	2018	China	RTP, SC	440	-	-	Localized	Surgery and ADT	1.3/1.8	ROC curve	Uni	BRFS	7
van Soest	2015	Multiple	PRO, MI	1224	68 (40–88)[R]	-	Metastatic	Chemotherapy	2.0	Median	Mul	OS	8
van Soest	2015	Multiple	PRO, MI	1006	68 (36–92)[R]	-	Metastatic	Chemotherapy	2.1	Median	Mul	OS	8
Urothelial carcinoma													
Yuk	2018	South Korea	RTP, SC	385	72.6 ± 10.6	Bladder	NMI	Surgery and BCG	1.2	ROC curve	Mul	OS, CSS	8
Rajwa	2018	Poland	RTP, SC	144	-	Bladder	Localized	Surgery	1.95	ROC curve	Mul	OS, CSS	6
Kang	2017	South Korea	RTP, SC	90	62 (54–68)	UUT	Localized	Surgery and chemotherapy	2.0	ROC curve	Uni	OS, CSS	7
Kang	2017	South Korea	RTP, SC	1551	65 (57–72)	Bladder	NMI	Surgery	1.5	ROC curve	Mul	OS	8
van Kessel	2016	Netherlands	RTP, MI	123	61[M]	Bladder	MI	Chemotherapy and surgery	2.21	ROC curve	Uni	OS, DFS	7
Kim	2015	South Korea	RTP, SC	277	64 (57–71)	UUT	Localized	Surgery	2.0	Not reported	Mul	CSS, DFS	8
Dalpiaz	2014	Austria	RTP, SC	171	69 ± 10.1	UUT	Localized	Surgery	1.5	ROC curve	Uni	OS, CSS	7

SQ = study quality according to the Newcastle-Ottawa scale; RTP = retrospective; SC = single center; MI = multi-institutional; UUT = upper urinary tract; All = localized and metastatic; NMI = non-muscle invasive; MI = muscle invasive; ADT = androgen deprivation therapy; BCG = Bacillus Calmette-Guerin; OS = overall survival; CSS = cancer-specific survival; DFS = disease-free survival; BRFS = biochemical recurrence free survival.
[R] Median (range).
[M] Mean.

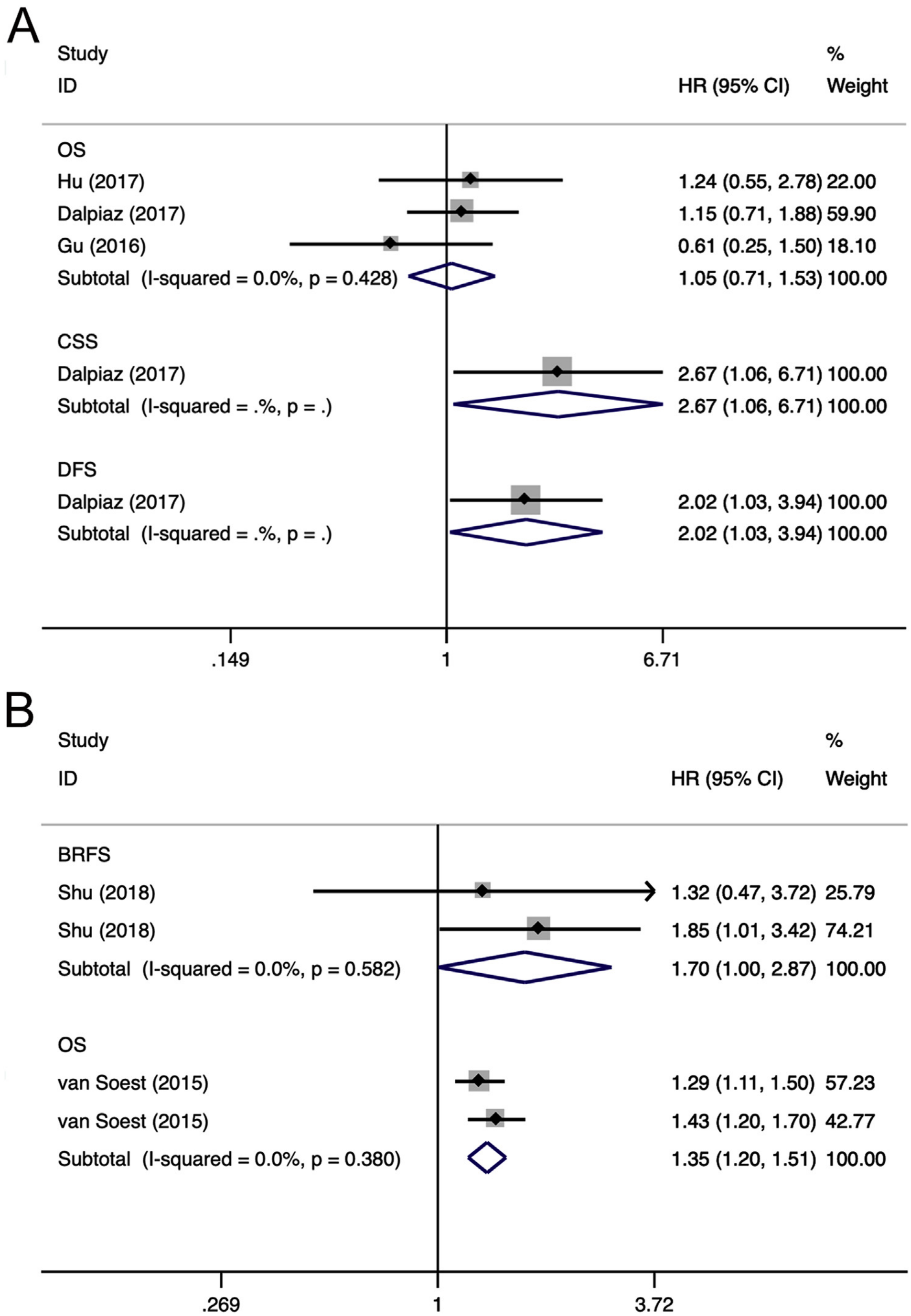

Fig. 2. Forest plot reflects the association between dNLR and oncologic outcomes for RCC and PCa. **(A)** dNLR and OS, CSS, DFS in RCC; **(B)** dNLR and BRFS, OS in PCa.

patients, which showed asymmetry for OS and CSS (Fig. 4). The P values of Begg's and Egger's test showed that no publication bias existed in OS (P = 0.548 and 0.700) and CSS (P = 1.000 and 0.134) among these included studies.

3.6. Sensitivity analysis

A single study was deleted each time, and the corresponding pooled HRs for dNLR and OS/CSS in UCa patients were not materially changed (Fig. 5).

4. Discussion

Urological cancers had constituted a large part of all cancer and the approximated new cases of RCC, PCa, UCa were 73,820, 84,400, and 174,650 respectively in USA, 2019 [2]. Distant metastasis or post-operative recurrence were common events occurred in these urological cancers. For high-risk bladder cancer, approximately 75% of them would experience recurrence, progression, or death within ten years [26]. Furthermore, for RCC patients, nearly 20% of them might experience local disease recurrence or distant metastasis ultimately [27]. Less than 10% of metastatic RCC can survival for ten years [28]. Hence, it is meaningful to discover the prognostic factors for urological cancers. As far as we know, our study is the first systematic review and

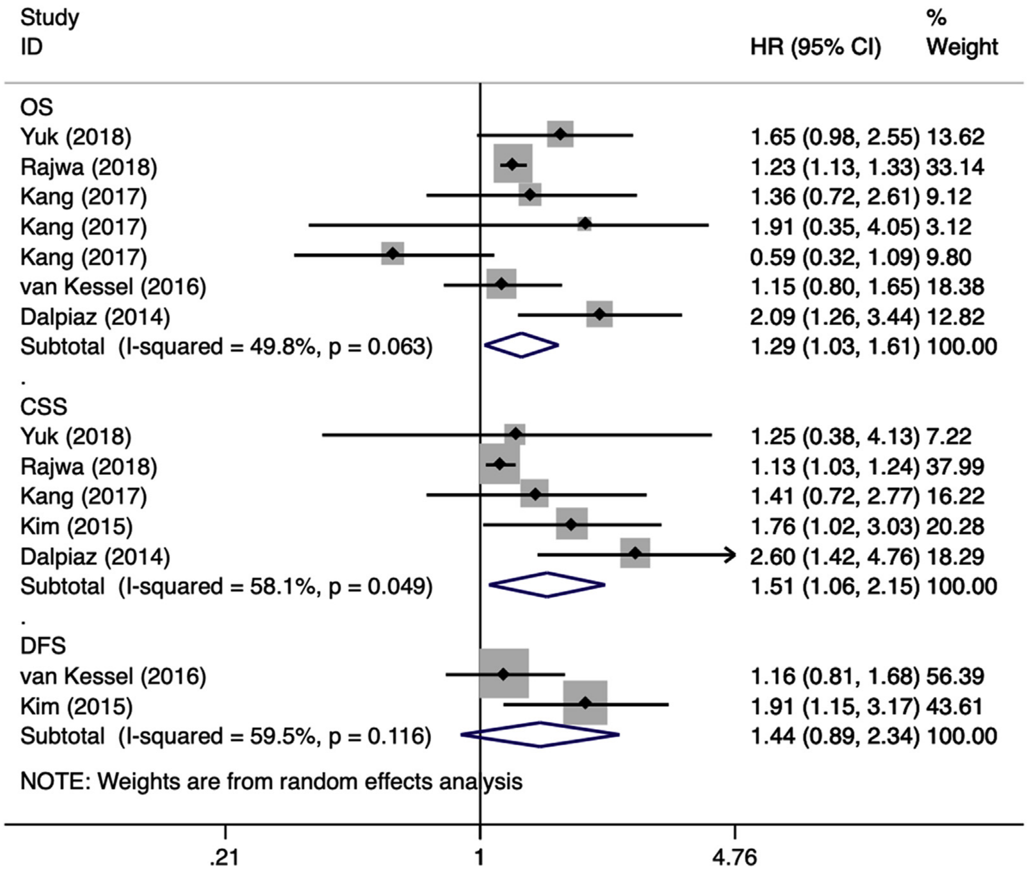

Fig. 3. Forest plot reflects the association between dNLR and oncologic outcomes for UCa.

meta-analysis to assess the prognostic value of dNLR in patients with urological cancers.

Increasing evidence have proposed that systemic inflammatory response exerted a vital role in the process of oncogenesis and tumor progression. Recently, many researches had revealed that many systemic inflammatory biomarkers can be prognostic factors in various urological cancers. Hu et al. [7] have conducted a systematic review and found that a high C-reactive protein level was correlated with poorer survival in RCC patients. In 2014, Wei et al. [29] have carried out a meta-analysis and assess the prognostic value of NLR in urological cancers. They have found that elevated NLR was a poor predictor for RCC, bladder cancer and urothelial carcinoma. Gu et al. [10] have performed a comprehensive systematic review to quantify the prognostic impact of LMR in various cancer. A decreased LMR has been found to imply poor prognosis in RCC and urothelial carcinoma. As for PLR, high pretreatment PLR has been confirmed to be correlated with inferior OS in patients with urological malignances [30].

A promising blood marker, dNLR, has been extensively researched in types of urological cancers. In the present study, we initially systematically reviewed the related publication and performed a meta-analysis to assess the prognostic role of dNLR in urological cancers. Based on the merged data, we have found that a higher pretreatment dNLR was associated with a poorer CSS and DFS in RCC, a worse BRFS and OS in PCa, an inferior OS and CSS in UCa. Subgroup analyses by publication year, site of carcinoma, sample size, value of cut-off and HR source obtained the similar results. Publication bias also proved the robustness of the findings.

Since only neutrophil and leukocyte counts needed to be documented, this simplified index, dNLR might be more convenient in clinical practice. The propose of dNLR based on the assumption that the white cell is chiefly consist of neutrophils and lymphocytes. According to this, the absolute count of leukocytes minus the absolute neutrophil count may approximate to lymphocyte count. In 2012, Proctor et al. [12] firstly proposed the dNLR, and tested the possible prognostic value of this blood index compared to NLR in 12000 more cases with various types of malignance. Both dNLR and NLR were found to be independent prognostic factors in different cancers, and they have similar prognostic value. The authors proposed that dNLR mixed two cells with potential opposing predictive effects, namely lymphocytes and monocytes. Though there might be a decrease in the absolute percentage of lymphocytes and a raise in the absolute percentage of monocytes in patients with cancer, the ratio of lymphocytes to monocytes is close to 6:1 in normal range, the absolute count of leukocytes minus neutrophil count is mainly decided by lymphocytes. Hence, it is reasonable that the dNLR is probably highly approximated to NLR, and the possible error brought by monocytes is negligible [12].

In the present study, we try our best to search the mainstream databases and get the comprehensive data, so as to provide the integrated and reliable results for this topic. However, the publications investigating the prognostic value of dNLR in urological cancers remain insufficient. Though RCC, PCa and UCa are all belong to urological cancer, they indeed are of different mechanisms of genesis and progression. So the meta-analysis was performed separately according to the type of cancer, which may lead to inadequate data in some analyses. For CSS and DFS in RCC, there was only one article for all [3]. In that research, Dalpiaz et al. [3] have examined the prognostic value of the pretreatment dNLR in a large RCC cohort. According to this comprehensive and rigorous study, the independently predictive role of dNLR in CSS and DFS for RCC was proved.

There are strengths for our study. However, before fully understanding the results, several limitations should be pay attention to. Firstly, because most of included studies were retrospective and single-center designed and part of HRs and 95% CIs were extracted from univariable results, uncontrollable bias may exist. Secondly, due to the

Table 2
Subgroup analyses of overall survival and cancer-specific survival for urothelial carcinoma.

Subgroup	Studies	HR (95% CI)	P value	Meta-regression P value	Heterogeneity	
					I^2 (%)	P value
Urothelial Carcinoma-OS						
Year of publication				0.540		
2017–2018	5	1.22 (1.13–1.32)	< 0.001		47.3	0.108
2014–2016	2	1.51 (0.90–1.62)	0.166		72.3	0.057
Region				0.683		
Asia	4	1.20 (0.70–2.06)	0.502		60.5	0.055
Non-Asia	3	1.32 (1.02–1.71)	0.032		55.4	0.106
Site of carcinoma				0.226		
Bladder	5	1.22 (1.13–1.31)	< 0.001		47.2	0.109
Upper Urinary Tract	2	1.78 (1.20–2.65)	0.004		6.1	0.302
Sample size				0.725		
> 150	4	1.38 (0.76–2.50)	0.297		72.3	0.013
< 150	3	1.22 (1.13–1.32)	< 0.001		0.0	0.897
Cut-off value				0.725		
> 1.5	3	1.22 (1.13–1.32)	< 0.001		0.0	0.897
≤ 1.5	4	1.38 (0.76–2.50)	0.297		72.3	0.013
Source of HR				0.514		
Multivariable	4	1.18 (0.81–1.71)	0.391		59.9	0.058
Univariate	3	1.40 (1.07–1.83)	0.013		44.7	0.164
Urothelial Carcinoma-CSS						
Year of publication				0.073		
2018	2	1.14 (1.04–1.25)	0.005		0.0	0.883
2014–2017	3	1.88 (1.33–2.67)	< 0.001		0.0	0.383
Region				0.979		
Asia	3	1.56 (1.05–2.33)	0.029		0.0	0.819
Non-Asia	2	1.63 (0.73–3.65)	0.234		85.9	0.008
Site of carcinoma				0.073		
Bladder	2	1.14 (1.04–1.25)	0.005		0.0	0.883
Upper Urinary Tract	3	1.88 (1.33–2.67)	< 0.001		0.0	0.383
Sample size				0.073		
> 150	3	1.99 (1.35–2.91)	< 0.001		0.0	0.454
< 150	2	1.14 (1.04–1.25)	0.004		0.0	0.545
Cut-off value				0.198		
> 1.5	3	1.16 (1.06–1.26)	0.001		24.4	0.266
≤ 1.5	2	2.24 (1.31–3.85)	0.003		15.0	0.278
Source of HR				0.275		
Multivariable	3	1.15 (1.05–1.26)	0.002		14.4	0.311
Univariate	2	1.98 (1.26–3.11)	0.003		44.5	0.180

HR = hazard ratio; CI = confidence interval; OS = overall survival; CSS = cancer-specific survival.

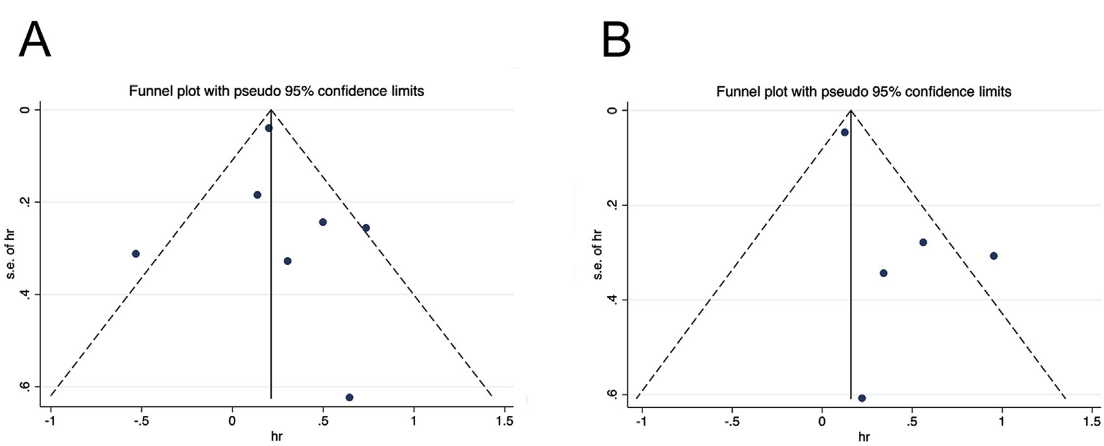

Fig. 4. Funnel plot for publication bias. **(A)** Correlation of dNLR with OS in UCa; **(B)** correlation of dNLR with CSS in UCa.

inclusion of published literatures only, publication bias might exist. Lastly, we try to obtain the comprehensive and extensive data, however, related articles were too few in some specific endpoints, especially for RCC and PCa. The deficiency in studies made us only detect publication bias and perform sensitivity analysis in some of the meta-analyses.

5. Conclusion

In summary, despite the above limitations, the results of this meta-analysis showed that a higher dNLR level was negatively correlated with OS, CSS, DFS and BRFS, forecasting that it could be an independent prognosis predictor in urological cancers. Further multicentric investigation were still required to confirm our findings.

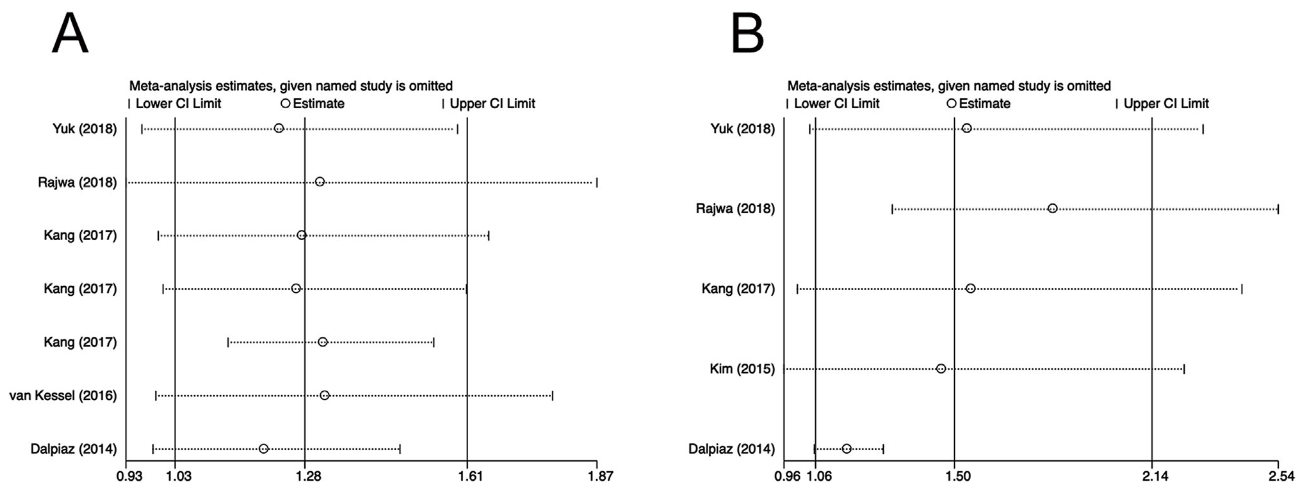

Fig. 5. Results of sensitivity analysis. **(A)** Correlation of dNLR with OS in UCa; **(B)** correlation of dNLR with CSS in UCa.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

Inapplicable.

Ethical approval

Inapplicable.

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Author contribution

Study design: Chao Li.
Data collections: Shiqiang Su and Lizhe Liu.
Data analysis: Shiqiang Su, Jin Zhang and Shen Li.
Writing: Shiqiang Su.
Supervision: Chao Li.

Research registration number

The protocol for this study was registered on PROSPERO (CRD 42019131641).

Guarantor

Chao Li.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.10.043.

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