ORIGINAL ARTICLE

Value of Preoperative Neutrophil-to-Lymphocyte Ratio in Predicting Prognosis of Surgically Resectable Urinary Cancers: Systematic Review and Meta-Analysis

Zhan Wang, Xu Wang, Wenda Wang,
Guoyang Zheng, Hao Guo, Yushi Zhang*

Department of Urology, Peking Union Medical College Hospital,
Chinese Academy of Medical Sciences & Peking Union
Medical College, Beijing 100730, China

Key words: urinary cancers; neutrophil-to-lymphocyte ratio; inflammatory biomarkers; prognostic factors; meta-analysis

Objective Accumulated evidence has suggested that there is a close association between preoperative neutrophil-to-lymphocyte ratio (NLR) and prognosis of various malignant tumors. However, the relationship between NLR and surgically resectable urinary cancers remains contradictory. Therefore, we performed this systematic review and meta-analysis to explore whether preoperative NLR could predict the prognosis of surgically resectable urinary cancers.

Methods After searching the Embase, PubMed/MEDLINE and Cochrane databases and screening the articles, we finally included 25 studies involving 15 950 patients. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were extracted to assess the association between preoperative NLR and the overall survival (OS) and cancer-specific survival (CSS) of surgically resectable urinary cancers.

Results The pooled results revealed that an elevated preoperative NLR could predict a worse OS ($HR = 1.40$, 95%CI: 1.26–1.54, $P < 0.001$) and CSS ($HR = 1.43$, 95%CI: 1.27–1.59, $P < 0.001$) in urinary cancers. In addition, our analyses also suggested that high preoperative NLR was associated with worse prognosis in renal cell carcinoma (OS: $HR = 2.06$, 95%CI: 1.54–2.76, $P = 0.131$; CSS: $HR = 2.46$, 95%CI: 1.46–4.16, $P = 0.178$), upper tract urothelial carcinoma (OS: $HR = 1.91$, 95%CI: 1.50–2.42, $P = 0.616$; CSS: $HR = 1.84$, 95%CI: 1.41–2.39, $P = 0.001$), bladder cancer (OS: $HR = 1.09$, 95%CI: 1.02–1.17, $P < 0.001$; CSS: $HR = 1.05$, 95%CI: 1.01–1.09, $P = 0.163$) and prostate cancer (OS: $HR = 1.69$, 95%CI: 1.19–2.41, $P = 0.714$). Regardless of the participants'

race or the cutoff value of the preoperative NLR, the results remained valid.

Conclusion Elevated preoperative NLR could predict a worse prognosis in surgically resectable urinary cancers, namely, renal cell carcinoma, bladder cancer, prostate cancer and upper tract urothelial carcinoma.

URINARY cancers are one of the most common malignancies that threaten both men and women worldwide. According to the latest survey, it is estimated that there will be 158 220 new cases and 33 420 deaths in the United States for both sexes, ranking fifth in new cases and sixth in deaths of all malignancies.^[1] Although a set of new preoperative and postoperative adjuvant treatment modalities, such as immunotherapy and molecular targeted drugs, have been developed, a subset of patients still die within a short time after surgery due to the rapid progression or reoccurrence of urinary cancers. Therefore, finding better preoperative prognostic biomarkers could hopefully prolong the survival span and change the postoperative follow-up routines.

Emerging evidence has revealed that the systemic inflammatory reaction (SIR) plays a critical role in the development and progression of various cancers, including malignant tumors of the digestive, respiratory and urological systems. As a marker of SIR, the neutrophil-to-lymphocyte ratio (NLR) has displayed great potential in predicting the prognosis of urinary cancers.^[2-4] However, since the results of different studies remain inconsistent or even contradictory regarding the role of NLR in surgically resectable urinary cancers, we conducted this systematic review and meta-analysis to obtain a more reliable assessment.

MATERIALS AND METHODS

Literature search

We systematically searched the PubMed/MEDLINE, Embase and Cochrane databases for all possible studies without restrictions. The search strategy combined the medical subject heading (Mesh) terms NLR (e.g., "neutrophil-to-lymphocyte ratio" or "neutrophil lymphocyte ratio") with words related to urinary cancers (e.g., "renal cancer", "bladder cancer", "prostate cancer", "urothelial cancer" or "transitional cell carcinoma") and prognosis (e.g., "outcome", "prognosis", "prognostic", "survival", "cancer specific survival" or "overall survival"). The last search was updated on July 18, 2019.

Inclusion and exclusion criteria

Studies were eligible if they met all the following criteria:

(1) Studies evaluated preoperative NLR as a prognostic factor in urothelial cancers, such as renal cell cancer (RCC), bladder cancer (Bca), prostate cancer (Pca) or upper urinary tract urothelial cancer (UTUC); (2) Studies provided survival data on overall survival (OS) and/or cancer-specific survival (CSS); and (3) Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) or *P*-values of CSS or OS can be found or calculated based on information provided in the article.

The exclusion criteria were as follows: (1) review articles, editorial comments, letters, expert opinions, conference abstracts, or case reports; (2) articles containing overlapping or duplicate data; (3) patients who received neoadjuvant treatment such as preoperative chemotherapy or radiotherapy; (4) patients who did not undergo an operation; and (5) incomplete or no survival data regarding OS or CSS.

Data extraction and quality control

For each eligible study, the following items were extracted: first author's name, year of publication, country, tumor type, number of patients, median age, gender composition, NLR cut-off value, median follow-up period, survival outcomes, variate analysis type, and HRs of OS or CSS and 95% CIs. We used the HRs of multivariate analysis if both univariate and multivariate analyses were conducted.

The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of all the enrolled studies. Any included study with a total score of more than 5 was considered good quality. The search was conducted, and the titles and abstracts of all initially identified studies were assessed independently by two authors (WZ and WX). Any discrepancies were solved through group discussion or a third author (ZGY) to establish a consensus.

Statistical analysis

The HRs with their 95% CIs from each study were used to calculate pooled HRs. Cochran's *Q*-test and Higgins *I*² statistics were applied to assess the heterogeneity of the pooled results. *I*² > 50% or *P* < 0.05 was regarded as heterogeneity. The fixed effects model (Mantel-Haenszel method) was used if there was no heterogeneity; otherwise, the random effects model was

applied. In addition, we performed subgroup analysis and sensitivity analysis to identify the source of heterogeneity. Egger's linear regression test was used to evaluate publication bias, and $P < 0.05$ was considered significant. If publication bias existed, we used the Trim and Fill method to assess the influence of publication bias on the effect estimate. All statistical analyses were performed using STATA software version 14.0 (STATA Corporation, College Station, TX, USA). All P values were two-sided.

RESULTS

Characteristics of the included studies

After searching the PubMed/MEDLINE, Embase and Cochrane databases and removing duplicates, we initially found 443 articles. After having read the titles and abstracts, we excluded 383 articles that were reviews, conference abstracts, editorial assessments, letters or studies in which no patients undergoing an operation. Afterward, 60 full-text original articles were screened. As a result, we excluded another 35 articles since 23 provided no or incomplete survival data regarding CCS or OS; 7 focused on neoadjuvant radiotherapy; 3 were related to derived NLR rather than NLR; 2 contained overlapping samples. In the end, 25 studies^[2-26] met our criteria and were included in our final meta-analysis (**Figure 1**). Characteristics of all the included studies are shown in **Table 1**.

The 25 eligible studies contained 15 950 cases from 8 countries (America, Korea, Singapore, Poland, Japan, Italy, China and Austria). Among the 25 studies, 10^[7, 9, 11, 13, 16, 18, 21-23, 25] explored the prognostic role of preoperative NLR in UTUC, which contained 6365 patients; 8 studies^[2, 5, 12, 15, 17, 19, 20, 24] in RCC with 3568 patients; 2^[3, 8] in Pca with 2293 patients; 5^[4, 6, 10, 14, 26] in Bca with 3724 patients. Regarding the survival results, 17 studies^[2-8, 10, 12, 14, 15, 17, 18, 20, 23, 24, 26] focused on the predictive role of NLR in OS, with another 17^[3, 5-7, 9-11, 13, 16, 18, 19, 21-26] on CSS. All 25 studies received scores of more than 5 according to the NOS and were deemed to have good quality.

Overall survival

As shown in **Figure 2** and **Table 2**, it's evident that elevated preoperative NLR could predict a worse prognosis in urinary cancers concerning OS with a pooled HR of 1.40 (95%CI: 1.26–1.54, $P_{\text{heterogeneity}} < 0.001$). Subgroup analysis by cancer type revealed that a

Figure 1. Workflow of our selecting process.

NLR: neutrophil-to-lymphocyte ratio.

higher preoperative NLR was also associated with a poorer OS in RCC^[2, 5, 12, 15, 17, 20, 24] ($HR = 2.06$, 95%CI: 1.54–2.76, $P_{\text{heterogeneity}} = 0.131$), UTUC^[7, 18, 23] ($HR = 1.91$, 95%CI: 1.50–2.42, $P_{\text{heterogeneity}} = 0.616$), Bca^[4, 10, 13, 14, 26] ($HR = 1.09$, 95%CI: 1.02–1.17, $P_{\text{heterogeneity}} < 0.001$) and Pca^[3, 8] ($HR = 1.69$, 95%CI: 1.19–2.41, $P_{\text{heterogeneity}} = 0.714$).

Furthermore, another subgroup analysis by ethnicity suggested that a high preoperative NLR remained a worse predictor for OS in both Asians^[3-5, 7, 8, 12, 14, 15, 17, 18, 20] ($HR = 1.89$, 95%CI: 1.58–2.25, $P_{\text{heterogeneity}} = 0.203$) and Caucasians^[2, 6, 10, 23, 24, 26] ($HR = 1.09$, 95%CI: 1.02–1.16, $P_{\text{heterogeneity}} = 0.001$).

Further analysis stratified by the NLR cut-off value revealed that regardless of whether the NLR cutoff was lower or higher than 2.7, an elevated NLR could still predict a worse prognosis in urinary cancers (NLR < 2.7^[2-5, 7, 8, 12, 20]: $HR = 1.77$, 95%CI: 1.49–2.11, $P_{\text{heterogeneity}} = 0.268$; NLR ≥ 2.7 ^[6, 10, 14, 15, 17, 18, 23, 24, 26]: $HR = 1.15$, 95%CI: 1.05–1.26, $P_{\text{heterogeneity}} < 0.001$).

Cancer-specific survival

As shown in **Figure 3** and **Table 3**, a high preoperative NLR was associated with a worse CSS in urological cancers^[3, 5-7, 9-11, 13, 16, 18, 19, 21-26] ($HR = 1.43$, 95%CI: 1.27–1.59, $P_{\text{heterogeneity}} < 0.001$). Further subgroup anal-

Table 1. Characteristics of all the studies included in our meta-analysis

Author	Year	Country	Tumor type	No. of Patients	Age (yrs)	Gender (M:F)	Cut-off value	Follow-up (months)	Outcomes	Analysis type
Son <i>et al.</i> ^[9]	2018	Korea	UTUC	1137	69 (61-74)*	825:312	3.3	39.1 (18.3-63.8)*	RFS, CSS	UV, MV
Azuma <i>et al.</i> ^[25]	2013	Japan	UTUC	137	69.4 (40-88)	106:31	2.5	60.9 (1.9-187.3)	RFS, CSS	UV, MV
Kohada <i>et al.</i> ^[11]	2018	Japan	UTUC	148	71 (64-78)*	112:36	3	35.5 (12-66)*	RFS, CSS	UV, MV
Tanaka <i>et al.</i> ^[21]	2014	Japan	UTUC	665	70 (62-76)*	493:172	3	28 (14-57)*	RFS, CSS	UV, MV
Cao <i>et al.</i> ^[16]	2017	China	UTUC	656	68 (39-88)	290:366	2.4	46 (12-144)	IVRFS, CSS	UV, MV
Cheng <i>et al.</i> ^[18]	2016	China	UTUC	195	68±10.3	79:116	2.7	36	OS, CSS	UV, MV
Luo <i>et al.</i> ^[22]	2014	China	UTUC	234	N	102:132	3	40.7±23.8	MFS, CSS	UV, MV
Tan <i>et al.</i> ^[7]	2018	China	UTUC	717	67 (59-74)*	408:309	2.5	42 (18-76)*	OS, DFS, CSS, MFS	MV
Dalpiaz <i>et al.</i> ^[23]	2014	Austria	UTUC	202	69.3 (32-85)	122:80	2.7	45 (0-199)	CSS, OS	UV, MV
Vartolomei <i>et al.</i> ^[13]	2017	Austria	UTUC	2274	69 (61-76)	1527:747	2.7	40 (20-76)	RFS, CSS	UV, MV
Byun <i>et al.</i> ^[19]	2016	Korea	RCC	1284	55.9±12.9	913:371	3.7	39 (19-69)*	RFS, CSS	MV
Widz <i>et al.</i> ^[2]	2020	Poland	RCC	196	61 (24-85)*	116:80	2.69	68 (44.5-78)	OS	UV, MV
Agizamhann <i>et al.</i> ^[12]	2018	China	RCC	82	37 (2-71)	33:49	2.45	31 (2-108)	OS, DFS	UV, MV
Chen <i>et al.</i> ^[5]	2019	China	RCC	414	56.3 (24-80)	257:157	2.17	69.2 (1-151)	OS, CSS	MV
Wen <i>et al.</i> ^[20]	2015	China	RCC	327	56 (3-86)	211:116	1.7	43 (0-97)	OS, DFS	UV, MV
Hu <i>et al.</i> ^[15]	2017	China	RCC	484	56 (21-81)	278:206	2.78	36	OS	UV, MV
Gu <i>et al.</i> ^[17]	2016	China	RCC	103	56 (16-79)	71:32	4.1	19.9 (10.8-35.1)*	OS	UV, MV
Pichler <i>et al.</i> ^[24]	2013	Austria	RCC	678	N	N	3.3	44 (0-130)	OS, CSS	UV, MV
Jang <i>et al.</i> ^[3]	2016	Korea	Pca	2067	66 (61-70)	N	1.76	78 (65-6)*	BCRFS, CSS, OS	UV, MV
Sun <i>et al.</i> ^[8]	2018	China	Pca	226	N	N	2.31	24 (1-73)	OS, DFS	UV, MV
Viers <i>et al.</i> ^[26]	2014	USA	Bca	899	69 (62-76)*	723:176	2.7	130.8 (99.6-166.8)*	DFS, CSS, OS	UV, MV
Tan <i>et al.</i> ^[14]	2017	Singapore	Bca	84	67 (37-82)	63:21	2.7	30.1 (3.2-161.7)	DFS, OS	UV, MV
Kang <i>et al.</i> ^[4]	2017	Korea	Bca	1551	65 (57-72)*	1302:249	2	52 (27-82)*	OS	UV, MV
Rajwa <i>et al.</i> ^[10]	2018	Poland	Bca	144	N	N	3	14 (7-40)*	OS, CSS	UV, MV
Vartolomei <i>et al.</i> ^[6]	2018	Italy	Bca	1046	70 (29-91)	864:182	3	26 (10-47)*	OS, DFS, CSS	MV

RCC: renal cell carcinoma; UTUC: upper urinary tract urothelial cancer; Bca: bladder cancer; Pca: prostate cancer; RFS: recurrent free survival; CSS: cancer-specific survival; IVRFS: intravesical recurrence free survival; OS: overall survival; MFS: metastasis free survival; DFS: disease-free survival; BCRFS: biochemical recurrence free survival; UV: univariate; MV: multivariate; *: interquartile range; N: not available.

Figure 2. The forest plot of OS.

A. All the articles enrolled; B. Subgroup analysis by tumor site; C. Subgroup analysis by ethnicity; D. Subgroup analysis by NLR cutoff value.

Table 2. Subgroup analysis of all included articles regarding OS

Subgroups	No. of studies	No. of patients	HR	95%CI	$P_{\text{heterogeneity}}$
Tumor type					
RCC	7	2284	2.06	1.54-2.76	0.131
UTUC	3	1114	1.91	1.50-2.42	0.616
Bca	5	3724	1.09	1.02-1.17	<0.001
Pca	2	2293	1.69	1.19-2.41	0.714
Ethnicity					
Asian	11	3165	1.89	1.58-2.25	0.203
Caucasian	6	6250	1.09	1.02-1.16	0.001
Cut-off value					
< 2.7	8	5580	1.77	1.49-2.11	0.268
≥ 2.7	9	3835	1.15	1.05-1.26	<0.001
Overall	17	9415	1.40	1.26-1.54	<0.001

Figure 3. The forest plot of CSS.

A. All the articles enrolled; B. Subgroup analysis by tumor site; C. Subgroup analysis by ethnicity; D. Subgroup analysis by NLR cutoff value.

Table 3. Subgroup analysis of all included articles regarding CSS

Subgroups	No. of studies	No. of patients	HR	95%CI	P _{heterogeneity}
Tumor type					
RCC	3	2376	2.46	1.46-4.16	0.178
UTUC	10	6365	1.84	1.41-2.39	0.001
Bca	3	2089	1.05	1.01-1.09	0.163
Pca	1	2067	*	*	*
Ethnicity					
Asian	11	7654	2.02	1.67-2.44	0.185
Caucasian	6	5243	1.06	1.00-1.12	0.049
Cut-off value					
< 2.7	5	3991	2.10	1.68-2.61	0.349
≥ 2.7	12	8906	1.19	1.08-1.31	<0.001
Overall	17	12897	1.43	1.27-1.59	<0.001

*As only one study regarding CSS of the Pca was enrolled into the analysis, the analysis could not be conducted.

ysis by tumor site indicated that the NLR remained a prognostic biomarker of UTUC^[7, 9, 11, 13, 16, 18, 21-23, 25] ($HR=1.84$, 95% CI : 1.41–2.39, $P_{\text{heterogeneity}}=0.001$), RCC^[5, 19, 24] ($HR=2.46$, 95% CI : 1.46–4.16, $P_{\text{heterogeneity}}=0.178$), Bca^[6, 10, 26] ($HR=1.05$, 95% CI : 1.01–1.09, $P_{\text{heterogeneity}}=0.163$). Since only one paper explored the CSS of Pca, we didn't perform the subgroup analysis of Pca.

In addition, when stratified by race, the subgroup analysis revealed that elevated NLR could still predict a worse prognosis in urinary cancers (Asian^[3, 5, 7, 9, 11, 16, 18, 19, 21, 22, 25]: $HR=2.02$, 95% CI : 1.67–2.44, $P_{\text{heterogeneity}}=0.185$; Caucasian^[6, 10, 13, 23, 24, 26]: $HR=1.06$, 95% CI : 1.00–1.12, $P_{\text{heterogeneity}}=0.049$).

Another subgroup analysis by NLR cut-off demonstrated that regardless of whether the NLR cutoff was higher or lower than 2.7, preoperative NLR remained a worse prognostic marker ($NLR<2.7$ ^[3, 5, 7, 16, 25]: $HR=2.10$, 95% CI : 1.68–2.61, $P_{\text{heterogeneity}}=0.349$;

$NLR\geq 2.7$ ^[6, 9-11, 13, 18, 19, 21-24, 26]: $HR=1.19$, 95% CI : 1.08–1.31, $P_{\text{heterogeneity}}<0.001$).

Heterogeneity

As shown in **Figures 2 and 3**, there was heterogeneity in our meta-analysis (OS: $I^2=82.8\%$, $P<0.001$; CSS: $I^2=81.8\%$, $P<0.001$). Therefore, we performed sensitivity analysis by sequentially omitting each study (**Figure 4**). The sensitivity analysis results showed that the article of Rajwa *et al.*^[10] and the article of Viers *et al.*^[26] may be the sources of heterogeneity. Therefore, we omitted the two articles and performed the meta-analysis again, and the results regarding OS ($HR=1.78$, 95% CI : 1.53–2.07, $P_{\text{heterogeneity}}=0.135$) and CSS ($HR=1.91$, 95% CI : 1.55–2.37, $P_{\text{heterogeneity}}=0.001$) remained valid.

Publication bias

Egger's test was carried out to identify potential publi-

Figure 4. Sensitivity analysis of all the enrolled articles concerning OS (above) and CSS (below).

cation bias in our enrolled studies. The results showed that there was significant publication bias in the analysis of the pooled OS and CSS ($P_{\text{Egger}} < 0.001$). Therefore, we used the Trim and Fill method to assess the effect of publication bias, and the results showed that the adjusted pooled HRs for OS and CSS were also significant (OS: $HR = 1.209$, 95%CI: 1.095–1.335; CSS: $HR = 1.142$, 95%CI: 1.019–1.280), which was still consistent with the primary results (as presented in **Figure 5**).

DISCUSSION

Although many new therapies have been developed for the treatment of urinary cancers, such as chemotherapy, radiotherapy and molecular-targeted therapy, surgery remains the main therapeutic strategy and can provide a radical cure. Currently, the most widely used preoperative prognostic assessment strategy is the TNM staging system, which is still incomplete and imprecise. The identification of new prognostic factors may contribute to a more precise preoperative assessment, thus promoting survival outcomes and optimising follow-up routines. Recently, enormous evidence has suggested that NLR is closely related to the prognosis of malignant urinary tumors. However, the role of the NLR in surgically resectable

urinary cancers remains unexplored, which is the reason why we performed this meta-analysis. Our studies enrolled 25 studies containing 15 950 patients, which were deemed good quality according to the criterion of the NOS scoring system. From the results of our meta-analysis, we could conclude that elevated preoperative NLR could predict a worse OS and CSS in urinary cancers, namely, RCC, UTUC, Pca and Bca.

However, the deeper underlying mechanism between the NLR and survival is still poorly understood. The most widely accepted hypothesis is the tumor micro-environment theory, which is crucial for the angiogenesis, viability, motility and invasion of tumors.^[27] NLR variations illustrate an elevated neutral-based inflammatory reaction and a weakened lymphocyte-dependent immune response. Cancer cells can create different kinds of cytokines, such as IL-2, IL-6, VEGF and myeloid growth factors, which can increase the count of tumor-infiltrating neutrophils.^[17] In addition, the increased neutrocytes could enhance their ability to secrete potent angiogenesis cytokines, such as vascular endothelial growth factor and reactive oxygen species, thus leading to DNA damage and genetic instability in addition to stimulating tumor proliferation and neo-vascularization in the micro-environment.^[4, 28, 29] On the other hand, the presence of lymphopenia in-

Figure 5. Egger's publication bias plot regarding OS (A) and CSS (C) together with funnel plot used the trim-fill method (B and D, respectively).

icates a relative inefficiency of lymphocytes, and tumor-related lymphocytes have previously been shown to suppress tumour development in some cases.

However, there are still several limitations in our meta-analysis. First, most of the enrolled studies in our meta-analysis were retrospective observational studies. Although the quality has been assessed as good under the criterion of the NOS scoring system, the quality of evidence was still poor. Second, there was significant heterogeneity in some analyses concerning both OS and CSS. Since the tumor site may be a potential source of heterogeneity, we divided the eligible studies into several independent groups to eliminate heterogeneity. However, in the OS of the Bca group and CCS of the UTUC group, heterogeneity also existed. After applying sensitivity analysis to all the articles, we finally identified 2 articles that may affect the stability of our pooled results. Furthermore, we still cannot rule out the possibility that there may be other factors causing the heterogeneity, such as the patients' baseline conditions, the patients' postoperative treatments, and the follow-up period. Since there was only one study concerning the CSS of PCa, we did not perform subgroup analysis on this group, which may be another disadvantage of our meta-analysis. Third, publication bias was detected in our meta-analysis. Studies with positive results are much easier to publish than studies with negative results, which could lead to publication bias. Although we tried our best to acquire as many eligible articles as possible without any restrictions, the Egger's test still suggested significant publication bias in our study. To avoid the effect of potentially negative outcomes, we used the Trim and Fill method to correct our results. However, we still could not completely rule out the possibility of publication bias.

In conclusion, our pooled results revealed that preoperative NLR could act as a potential prognostic marker in malignant urinary tumors. In other words, elevated preoperative NLR was associated with a worse OS and CSS in RCC, Bca, Pca and UTUC, which may help doctors stratify patients and change the postoperative follow-up routines.

Conflict of Interests Statement

The authors declare no competing interests.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69(1):7-34. doi: 10.3322/caac.21551.
2. Widz D, Mitura P, Buraczynski P, et al. Preoperative neutrophil-lymphocyte ratio as a predictor of overall survival in patients with localized renal cell carcinoma. *Urol J* 2020; 17(1):30-5. doi: 10.22037/uj.v0i0.4541.
3. Jang WS, Cho KS, Kim KH, et al. Prognostic impact of preoperative neutrophil-to-lymphocyte ratio after radical prostatectomy in localized prostate cancer. *Prostate Cancer Prostatic Dis* 2016; 19(3):298-304. doi: 10.1038/pcan.2016.20.
4. Kang M, Jeong CW, Kwak C, et al. Preoperative neutrophil-lymphocyte ratio can significantly predict mortality outcomes in patients with non-muscle invasive bladder cancer undergoing transurethral resection of bladder tumor. *Oncotarget* 2017; 8(8):12891-901. doi: 10.18632/oncotarget.14179.
5. Chen Z, Wang K, Lu H, et al. Systemic inflammation response index predicts prognosis in patients with clear cell renal cell carcinoma: a propensity score-matched analysis. *Cancer Manag Res* 2019; 11:909-19. doi: 10.2147/CMAR.S186976.
6. Vartolomei MD, Ferro M, Cantiello F, et al. Validation of neutrophil-to-lymphocyte ratio in a multi-institutional cohort of patients with T1G3 non-muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2018; 16(6):445-52. doi: 10.1016/j.clgc.2018.07.003.
7. Tan P, Xu H, Liu L, et al. The prognostic value of preoperative neutrophil-to-lymphocyte ratio in patients with upper tract urothelial carcinoma. *Clin Chim Acta* 2018; 485:26-32. doi: 10.1016/j.cca.2018.06.019.
8. Sun Z, Ju Y, Han F, et al. Clinical implications of pre-treatment inflammatory biomarkers as independent prognostic indicators in prostate cancer. *J Clin Lab Anal* 2018; 32(3):e22277. doi: 10.1002/jcla.22277.
9. Son S, Hwang EC, Jung SI, et al. Prognostic value of preoperative systemic inflammation markers in localized upper tract urothelial cell carcinoma: a large, multicenter cohort analysis. *Minerva Urol Nefrol* 2018; 70(3):300-9. doi: 10.23736/s0393-2249.18.02914-4.
10. Rajwa P, Życzkowski M, Paradysz A, et al. Evaluation of the prognostic value of LMR, PLR, NLR, and dNLR in urothelial bladder cancer patients treated with radical cystectomy. *Eur Rev Med Pharmacol Sci* 2018; 22(10):3027-37. doi: 10.26355/eurrev_201805_15060.
11. Kohada Y, Hayashi T, Goto K, et al. Preoperative risk classification using neutrophil-lymphocyte ratio and hydronephrosis for upper tract urothelial carcinoma.

- Jpn J Clin Oncol 2018; 48(9):841-50. doi: 10.1093/jjco/hyy084.
12. Agizamhan S, Qu F, Liu N, et al. Preoperative neutrophil-to-lymphocyte ratio predicts the surgical outcome of Xp11.2 translocation/TFE3 renal cell carcinoma patients. BMC Urol 2018; 18(1):60. doi: 10.1186/s12894-018-0374-z.
 13. Vartolomei MD, Mathieu R, Margulis V, et al. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. World J Urol 2017; 35(1):121-30. doi: 10.1007/s00345-016-1848-9.
 14. Tan YG, Eu E, Lau Kam On W, et al. Pretreatment neutrophil-to-lymphocyte ratio predicts worse survival outcomes and advanced tumor staging in patients undergoing radical cystectomy for bladder cancer. Asian J Urol 2017; 4(4):239-46. doi: 10.1016/j.ajur.2017.01.004.
 15. Hu H, Yao X, Xie X, et al. Prognostic value of preoperative NLR, dNLR, PLR and CRP in surgical renal cell carcinoma patients. World J Urol 2017; 35(2):261-70. doi: 10.1007/s00345-016-1864-9.
 16. Cao ZP, Guan B, Zhao GZ, et al. Validation of the pretreatment neutrophil-to-lymphocyte ratio as a prognostic factor in a large cohort of Chinese patients with upper tract urothelial carcinoma. Chin Med J (Engl) 2017; 130(17):2063-8. doi: 10.4103/0366-6999.213414.
 17. Gu L, Ma X, Li H, et al. Prognostic value of preoperative inflammatory response biomarkers in patients with sarcomatoid renal cell carcinoma and the establishment of a nomogram. Sci Rep 2016; 6:23846. doi: 10.1038/srep23846.
 18. Cheng YC, Huang CN, Wu WJ, et al. The prognostic significance of inflammation-associated blood cell markers in patients with upper tract urothelial carcinoma. Ann Surg Oncol 2016; 23(1):343-51. doi: 10.1245/s10434-015-4781-z.
 19. Byun SS, Hwang EC, Kang SH, et al. Prognostic significance of preoperative neutrophil-to-Lymphocyte ratio in nonmetastatic renal cell carcinoma: a large, multicenter cohort analysis. Biomed Res Int 2016; 2016:5634148. doi: 10.1155/2016/5634148.
 20. Wen RM, Zhang YJ, Ma S, et al. Preoperative neutrophil to lymphocyte ratio as a prognostic factor in patients with non-metastatic renal cell carcinoma. Asian Pac J Cancer Prev 2015; 16(9):3703-8. doi: 10.7314/apjcp.2015.16.9.3703.
 21. Tanaka N, Kikuchi E, Kanao K, et al. A multi-institutional validation of the prognostic value of the neutrophil-to-lymphocyte ratio for upper tract urothelial carcinoma treated with radical nephroureterectomy. Ann Surg Oncol 2014; 21(12):4041-8. doi: 10.1245/s10434-014-3830-3.
 22. Luo HL, Chen YT, Chuang YC, et al. Subclassification of upper urinary tract urothelial carcinoma by the neutrophil-to-lymphocyte ratio (NLR) improves prediction of oncological outcome. BJU Int 2014; 113(5b):E144-9. doi: 10.1111/bju.12582.
 23. Dalpiaz O, Ehrlich GC, Mannweiler S, et al. Validation of pretreatment neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. BJU Int 2014; 114(3):334-9. doi: 10.1111/bju.12441.
 24. Pichler M, Hutterer GC, Stoeckigt C, et al. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. Br J Cancer 2013; 108(4):901-7. doi: 10.1038/bjc.2013.28.
 25. Azuma T, Matayoshi Y, Odani K, et al. Preoperative neutrophil-lymphocyte ratio as an independent prognostic marker for patients with upper urinary tract urothelial carcinoma. Clin Genitourin Cancer 2013; 11(3):337-41. doi: 10.1016/j.clgc.2013.04.003.
 26. Viers BR, Boorjian SA, Frank I, et al. 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 2014; 66(6):1157-64. doi: 10.1016/j.eururo.2014.02.042.
 27. Cho H, Hur HW, Kim SW, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009; 58(1):15-23. doi: 10.1007/s00262-008-0516-3.
 28. Fondevila C, Metges JP, Fuster J, et al. p53 and VEGF expression are independent predictors of tumour recurrence and survival following curative resection of gastric cancer. Br J Cancer 2004; 90(1):206-15. doi: 10.1038/sj.bjc.6601455.
 29. Hwang GI, Yoo CH, Sohn BH, et al. Predictive value of preoperative serum CEA, CA19-9 and CA125 levels for peritoneal metastasis in patients with gastric carcinoma. Cancer Res Treat 2004; 36(3):178-81. doi: 10.4143/crt.2004.36.3.178.