ORIGINAL ARTICLE

Predictive Significance of Neutrophil-To-Lymphocyte Ratio (NLR) among Bladder Carcinoma Patients: A Systematic Review and Meta-Analysis

FAUZAN KURNIAWAN DHANI[1], TAUFIQ NUR BUDAYA[2], HASAN YAHYA[1], MUHAMMAD RIFKI SETIAWAN[1]
[1]Department of Medicine, Universitas Brawijaya, Malang, East Java, Indonesia
[2]Department of Urology, Saiful Anwar Hospital, Malang, East Java, Indonesia
Correspondence to dr. Fauzan Kurniawan Dhani / e-mail : fauzankurniawandhani@gmail.com
Address :Arjuna St 9 Pekanbaru City, Riau Province , Indonesia / phone : +6282388231826

ABSTRACT

Background: Increasing neutrophil-to-lymphocyte ratio (NLR) is recognized to be correlated to the survival of patients with cancer. The predictive significance of NLR, corresponding to prognosis, among bladder carcinoma patients remains inconsistent.
Aim: To assess pre-treatment NLR as an oncological prognostic value for bladder carcinoma patients.
Methods: Relevant studies from databases of Medline/PUBMED, EMBASE and The Cochrane Controlled Trials Register were searched systematically. Hazard ratios (HRs) and confidence intervals (CIs) of 95% were applied to assess the correlations of high vs low pre-treatment NLR for both Cause Specific Survival (CSS) and Recurrence Free Survival (RFS). Multiple variables were analysed accordingly by utilizing STATA (version 13.0) for Windows.
Result: Fourteen studies encompassing a total of 10,184 patients were gathered to assess predictive significance, seen from the CSS and RFS, of pre-treatment NLR amongst Bladder Carcinoma patients. Overall, high pre-treatment NLR predicted worse CSS, as HR = 1.32 (95% CI: 1.16-1.49, P < 0.00), while on RFS, HR = 1.49 (95% CI: 1.26-1.76, P < 0.00).
Conclusion: This meta-analysis indicated that there is a significant correlation between elevated pre-treatment NLR and predicted worse prognosis according to cancer specific survival and the recurrence risk of the disease. The prognostic role of NLR may become a valuable indicator to improve clinical decision in bladder cancer patients.
Keywords: Bladder Cancer, Neutrophil to Lymphocyte Ratio, Prognostic

INTRODUCTION

New cases of bladder malignancy is expected to be as many as 430,000 in 2012, so that it becomes the ninth commonest disease around the world. Over sixty percent of all bladder malignancy and half of all bladder disease were found in developing areas of the world[1]. The type of bladder malignancy is divided into Muscle Invasive Bladder Cancer (MIBC) and Non-Muscle Invasive Bladder Cancer (NMIBC). Adjuvant intravesical instillation treatment after transurethral resection of bladder tumors (TURBT) is the common mainstay treatment of NMIBC [2], while radical cystectomy (RC) becomes the definitive treatment for non-metastatic MIBC. The development of predictive value regarding prognosis of said patients is far from established, albeit advances in treatment approaches have benefited patients with this malignancy.

Increasing number of evidence suggests that inflammation has an essential role in malignancy progression and development[3] and systemic inflammation aggravation is related to a poor prognosis in various malignancy[4]. There is a significant effect regarding tumor development which related to inflammatory cells, thus systemic inflammation markers may become useful prognostic biomarkers[5]. Alteration in NLR could occur in the course of extensive inflammation, resulting from an increase of the neutrophil along with a decrease of the lymphocyte [6]. A higher ratio related to a worsening of disease specific survival and overall survival in hepatic, gastric, non-small cell and cervical cancer[7]. These instances can be significant in prognosticating bladder cancer.

The predictive significance of neutrophil-to-lymphocyte ratio among patients with bladder carcinoma continues to be conflicting. This way the author conducted a meta-analysis as a quantitative study that could epitomize the relationship of preoperative NLR against prognostic measure of Case Specific Survival and Recurrence-Free Survival in primary BC patients.

MATERIALS AND METHODS

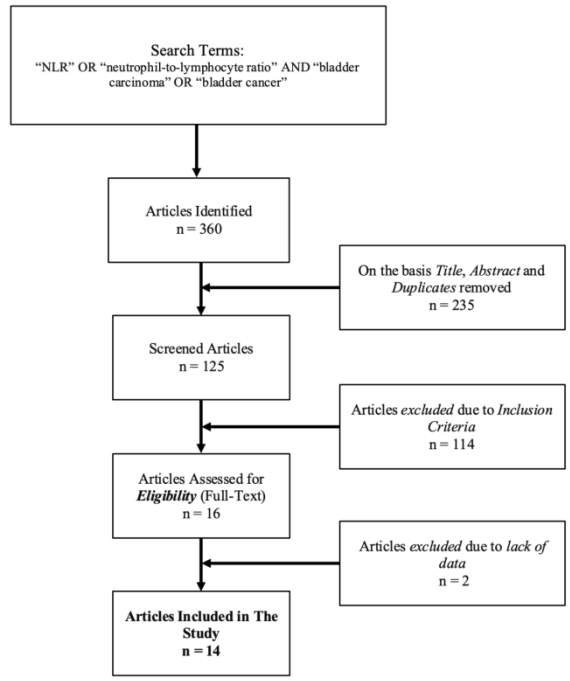
Search Strategy: Collection of studies investigating the predictive significance of NLR among patients with bladder carcinoma was done through database search from PUBMED, Cochrane Controlled Trials Register, and EMBASE. The last updated search was carried out on April 20th, 2020, using keywords of “NLR”, “neutrophil-to-lymphocyte ratio”, “bladder carcinoma”, as well as “bladder cancer”.
Inclusion and Exclusion Criteria: Following the PRISMA approach, inclusion of the study was according to its population, intervention, comparator, outcome, and study design, shortened by PICOS [8]. Studies were qualified if bladder cancer patients who had an increased NLR (P) as a preoperative evaluation for radical cystectomy or TURB (I) was compared with patients who had a decreased NLR (C) to evaluate the predictive significance of NLR indicated by CSS and RFS (O). These studies were analysed in multi variable (S). The latest studies were included in this meta-analysis, in case there was any identical study published at different time or in different journal. The PRISMA flow graph of the study selection and elimination is shown on Fig 1.

Data Extraction: Several items were recorded for all the studies fulfilled the criteria: the authors, time of publication, the total number of patients, country, study design, cancer stage, treatment, NLR cut off, hazard ratios and CI of 95% for neutrophil-to-lymphocyte ratio analysed in multi variable, and follow-ups Table 1 [9-22].

Study Quality: Newcastle-Ottawa Scale [23] regarding cohort study was obtained to review the quality of the study. NOS is consisted of three domains: Selection, Comparability and Exposure. Selection domain has a maximum of 4 stars, 2 stars for Comparability, and 3 stars for Exposure. The total score is 9, while studies are considered high quality if its NOS ≥ 6 (Table 2).

Statistical Analysis: The data were calculated utilizing STATA software (13.0 version). CSS and RFS were analysed using HRs and 95% CIs for included studies to outline pooled HRs. Heterogeneity was statistically defined by Cochrane Chi and I^2. If heterogeneity was detected, pooled estimates were calculated with random effects model or otherwise we utilized fixed effects model. Funnel plot with Begg's Test or Egger's Test was adapted to evaluate publication bias of the studies.

Fig 1. Flow Chart of PRISMA literature search and selection



RESULT

Characteristics of eligible studies: We found 360 articles from PubMed, EMBASE and the Cochrane Controlled Trials Register. Each title and abstract of 360 studies was evaluated. There were a remaining of 125 obtained articles after exclusion of 235 articles based on title and abstract. Full texts were read carefully and more 16 studies exclude due to inclusion criteria. Two studies were also excluded due to lack of data. The final materials eligible for the meta-analysis consisted of 14 studies, with 10,184 patients in total[9-22].

Two studies were researched in Canada and Austria, four in Japan, others in Spain, Italy, Korea, Israel, USA, and Singapore. All eligible studies were published from 2012 - 2017. The range of the sample size was 84 - 4,335 patients and retrospective single center. Five studies conducted patients with NMIBC, two studies conducted with MIBC, and others had patients with type of cancer from all stages. Transurethral Resection of Bladder Tumor (TURB) treatment for NMIBC patients and radical cystectomy, either undergoing preoperative neoadjuvant chemotherapy or not, were the main treatment for the entire patients from other studies.

Predictive Value of Pre-operative Neutrophil-to-Lymphocyte Ratio in Cancer Specific Survival: Based on nine studies included, CSS was predicted to be worse among the increased pre-operative circulating NLR on 1.32 pooled hazard ratio (95% CI: 1.16-1.49, P < 0.00) analysed in multi variable (Fig 2). A random effects model was applied due to heterogeneity of the data based on Cochrane Q Test (Chi^2: 56.09, P < 0.00) and I^2 (I^2: 85.7 %).

Predictive Value of Pre-operative Neutrophil-to-Lymphocyte Ratio in Recurrence Free Survival: Based on ten studies included, RFS was predicted to be poor among the increased pre-operative circulating NLR on 1.492 pooled hazard ratio (95% CI: 1.26-1.76, P < 0.00) analysed in multi variable (Fig 3). A random effects model was applied due to heterogeneity of the data based on Cochrane Q Test (Chi^2: 77.11, P < 0.00) and I^2 (I^2: 88.3 %).

Heterogeneity: Regarding the results, we found heterogeneities between studies, CSS and RFS. Meta-regression was conducted to investigate the potential source of heterogeneities by utilizing the variables of publication year, race (Asian vs. non-Asian), number of patients (≥300 vs. <300), neutrophil-to-lymphocyte ratio cutoff levels (≥ 2.5 vs. < 2.5), patients' treatment (RC vs. TURBT) and type of cancer (Non-Muscle-Invasive BC vs. all stage).

The outcome of heterogeneity for CSS based on each variable are as follows: publication year (P = 0.73), race (P = 0.59), patients (P = 0.36), type of cancer (P = 0.41), treatment (P = 0.41), neutrophil-to-lymphocyte ratio cutoff levels (P = 0.41) (Fig S1).

The outcome of heterogeneity for RFS based on each variable are as follows: race (P = 0.04), patients (P = 0.03), NLR cut-off (P = 0.04) wellspring of heterogeneities, whereas publication year (P = 0.733), treatment (P = 0.34), cancer type (P = 0.34) and neutrophil-to-lymphocyte ratio cutoff levels (P = 0.04) (Fig S2).

Publication Bias : Publication bias of studies was measured using Egger's Test. The entire results were found according to the estimation of funnel plots, CSS (P = 0.00) and RFS (P = 0.00) (Fig S3).

Table 1. The main characteristics of included study

Author	Number of Patients	Year	Country	Study Design	Cancer Stage	Treatment	NLR Cut Off	Statistical Method	Outcome Measure	HR	CI	Follow-up Time (Month)
Bhindi et al. [9]	418	2015	Canada	Retrospective Single Center	pT0-T4, pN0-N+	RC	2,9	Multivariate Cox proportional-hazards regression analysis	CSS	1,47	1,2-1,8	40(14-42)
									RFS	1,52	1.17-1,98	
Buisan et al. [10]	205	2016	Spain	Retrospective Single Center	MIBC	RC	2,5	Multivariate Cox proportional-hazards regression analysis	CSS	1,27	1,11-1,44	31
Favilla et al. [11]	178	2016	Italy	Retrospective Single Center	NMIBC	TURB	3	Multivariate Cox proportional-hazards regression analysis	RFS	2,84	1,5-5,75	53
Hermanns et al. [12]	424	2014	Canada	Retrospective Single Center	pT0-T4;pN0,Npos,Nx	RC;NAC	3	Multivariate Cox proportional-hazards regression analysis	CSS	1,88	1,39-2,54	58.4
									RFS	1,49	1,12-2	
Gondo et al. [13]	189	2012	Japan	Retrospective Single Center	cT1-T4,Nx M0	RC	2,5	Multivariate Cox proportional-hazards regression analysis	CSS	1,946	1,03-3,66	25.1
Hirasawa et al. [14]	136	2016	Japan	Retrospective Single Center	T1-T4	RC	NR	Multivariate Cox proportional-hazards regression analysis	CSS	1,3	1,1-1,5	46.7
Kang et al. [15]	385	2016	Korea	Retrospective Single Center	NMIBC	TURB	2	Multivariate Cox proportional-hazards regression analysis	CSS	1,12	1,01-1,25	52
Mano et al. [16]	107	2015	Israel	Retrospective Single Center	NMIBC	TURB	2,41	Multivariate Cox proportional-hazards regression analysis	RFS	1,75	1,05-2,92	40 (23-51)
Mbeutcha et al. [17]	1578	2016	Austria	Retrospective Multiple Center	NMIBC	TURB	2,5	Multivariate Cox proportional-hazards regression analysis	RFS	1,27	1.05-1.53	64
Morizawa et al. [18]	110	2016	Japan	Retrospective Single Center	MIBC	RC	2,6	Multivariate Cox proportional-hazards regression analysis	CSS	2,6	1,9-5,2	37.5(11-65)
									RFS	2,6	1,1-6	
Ogihara et al. [19]	1136	2016	Japan	Retrospective Single Center	NMIBC	TURB	2,2	Multivariate Cox proportional-hazards regression analysis	RFS	2,08	1,6-2,7	68.8 (4.5-237)
Viers et al. [20]	899	2014	USA	Retrospective Single Center	pT1-T4,pN0-N3	RC	2,7	Multivariate Cox proportional-hazards regression analysis	CSS	1,04	1,01-1,08	130.8 (99.6-166.8)
									RFS	1,04	1,01-1,06	
Tan et al. [21]	84	2017	Singapore	Retrospective Single Center	pT1-T4	RC	2,7	Multivariate Cox proportional-hazards regression analysis	RFS	6,999	1,71-28,60	30.1 (3.2-161.7)
D'Andrea et al. [22]	4335	2016	Austria	Retrospective Single Center	pT1-T4,pN0-N3	RC	2,7	Multivariate Cox proportional-hazards regression analysis	CSS	1,2	1,1-1,4	42.4(18.3-85.1
									RFS	1,2	1,1-1,3	

NMIBC Non Muscle Invasive Bladder Cancer, *MIBC* Muscle Invasive Bladder Cancer, *CSS* Cancer Survival Rate, *RFS* Recurrence Free Survival, *RC* radical cystectomy, *NAC* neoadjuvant chemotherapy, *NR* not reported

Table 2:Newcastle-Ottawa Scale

Author	Selection	Comparability	Exposure	Score
Bhindi et al. [9]	***	**	**	7
Buisan et al [10]	***	**	**	7
Buisan et al [11]	***	**	**	7
Favilla et al [12]	***	**	**	7
Hermanns et al. [13]	***	**	**	7
Hirasawa et al.[14]	***	**	**	7
Gondo et al [15]	***	**	**	7
Hirasawa et al. [16]	***	**	**	7
Kang et al. [17]	***	**	***	8
Mano et al. [18]	***	**	**	7
Mbeutcha et al. [19]	***	**	**	7
Morizawa et al. [20]	***	**	**	7
Tan et al.[21]	***	**	***	8
Ogihara et al [22]	***	**	**	7

Fig. 2: Forest plots describing HR of the association between preoperative NLR and CSS in bladder cancer patients

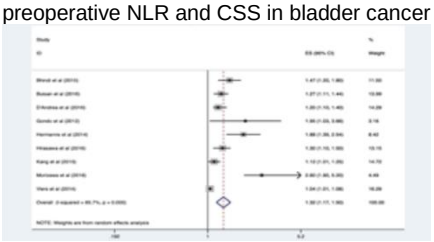


Fig. 3 Forest plots describing HR of the association between preoperative NLR and RFS in bladder cancer patients

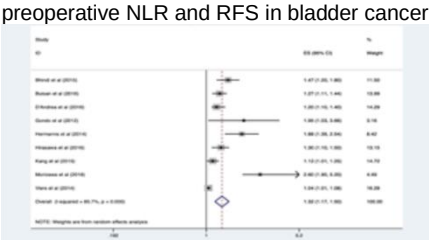


Fig. S1 Heterogeneity for CSS; A: Race; B: Patients; C: NLR; D: Cancer; E: Treatment; F: Year.

A

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Race	.8992631	.1712523	-0.56	0.595	.5732177	1.410763
_cons	1.621626	.5237238	1.50	0.178	.7555909	3.480282

B

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Patients	1.191067	.2153194	0.97	0.366	.7767603	1.826357
_cons	1.067952	.2797284	0.25	0.809	.5748634	1.983986

C

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
NLR	.7778666	.2253899	-0.87	0.419	.3828154	1.580596
_cons	1.851006	.6473391	1.76	0.129	.7866183	4.355634

D

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Cancer	1.249472	.320469	0.87	0.414	.6812907	2.291503
_cons	.8963787	.4354792	-0.23	0.828	.2841721	2.827494

E

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Treatment	1.249472	.320469	0.87	0.414	.6812907	2.291503
_cons	.8963787	.4354792	-0.23	0.828	.2841721	2.827494

F

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
year	.9692524	.0853238	-0.35	0.733	.7871083	1.193546
_cons	2.91e+27	5.17e+29	0.36	0.732	2.0e-155	4.3e+209

Fig. S2 Heterogeneity for RFS; A: Race; B: Patients; C: NLR; D: Cancer; E: Treatment; F: Year.

A

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Race	.6040589	.125476	-2.43	0.041	.3741531	.975235
_cons	3.573683	1.364198	3.34	0.010	1.481886	8.618212

B

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Patients	1.81261	.4339932	2.48	0.038	1.043564	3.1484
_cons	.7512295	.2206946	-0.97	0.359	.3815563	1.479063

C

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
NLR	1.622819	.3395711	2.31	0.049	1.00164	2.629229
_cons	.7991485	.2120627	-0.84	0.423	.4333837	1.473609

D

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Cancer	.7873241	.1882529	-1.00	0.347	.4536218	1.366511
_cons	2.253986	.9055739	2.02	0.078	.8924607	5.692635

E

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Treatment	.7873241	.1882529	-1.00	0.347	.4536218	1.366511
_cons	2.253986	.9055739	2.02	0.078	.8924607	5.692635

F

logor	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
year	1.222968	.1490946	1.65	0.137	.923256	1.619975
_cons	1.0e-176	2.6e-174	-1.65	0.138	0	1.20e+70

Fig. S3Publication Bias of Studies; A: CSS; B: RFS.

Number of studies = 9 Root MSE = .75

A

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0200913	.0157507	-1.28	0.243	-.0573358	.0171532
bias	3.418364	.3549799	9.63	0.000	2.57897	4.257758

Test of H0: no small-study effects P = 0.000

Number of studies = 10 Root MSE = 1.109

B

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0062413	.0152621	0.41	0.693	-.0289532	.0414359
bias	3.089135	.4177933	7.39	0.000	2.125702	4.052568

Test of H0: no small-study effects P = 0.000

DISCUSSION

SIR-related hematological biomarkers are effectively obtained through pre-treatment blood assessment and already provided dependable prognostic data in different sorts of bladder malignant growth in both pre-and post-treatment settings. Potential haematological biomarkers represent to SIR in patient's disease consist of Glasgow Prognostic Score (GPS), C-receptive protein (CRP), albumin, modified GPS (mGPS), and neutrophil-to-lymphocyte ratio (NLR)[24,25]. Presently, NLR already exhibited to have a huge prognostic feature in urologic tumors, for example, prostate[26] and renal malignancy[27]. Past investigations, which assessed the prescient estimation of NLR in bladder malignant growth, were led on muscle-invasive bladder disease patients undergoing radical cystectomy, or non-muscle-invasive tumors undergoing TURB (Table 1)[9-22]. Guoming Hu found that raised NLR was fundamentally connected with decreased RFS in up to 5 years (1, 3, and 5 years, respectively) among essential BC patients who experienced RC [28]. Vartolomei discover NLR in pre-TURBT patients were related to an increased susceptibility of tumor progression as well as the recurrence among NMIBC patients[29]. While Bhindi revealed among CBC biomarkers examined, NLR was the most productive marker for predicting RFS, though NLR and hemoglobin were generally proficient for prognostic CSS. NLR are promising, practical, free biomarkers for predicting oncologic BC results following RC[9]. We direct this research to discover the practicality of NLR as a marker for the oncological outcome among patients with bladder carcinoma.

Our research demonstrated that neutrophil-to-lymphocyte ratio held prognostic significance for bladder carcinoma patients' follow-ups as of Cancer-Specific Survival and Recurrence-Free Survival. Patients who had elevated pre-treatment NLR, also had a significant poor survival rate. More investigations stated that there was a correlation of inflammation against malignancy[30]. The proportion ratio of circling neutrophils (the innate immune system) to lymphocytes (the adaptive immune system), as a proportion of the systemic host response has reaction while assessing the relationship among inflammation and cancer outcome. Indeed, an elevated neutrophil reaction and additionally concealment of lymphocyte prompting a high NLR may advance carcinogenesis and suppressed the anti-tumor response[15]. Likewise, the aggravation would accelerate a malignant growth progression with expanding vascular penetrability and up-controlling lymphatic penetration and stromal intrusion at metastatic locales. NLR has become considerable interest studies over the previous decade as a potential prognostic factor related to the outcome in BC patients and this research summing up these investigations reveal that BC patients with high pre-treatment NLR have worse oncological result, such as CSS and RFS.

We discovered heterogeneity and bias have been found in this investigation. Heterogeneity for CSS and RFS have been observed. The meta-regression demonstrated contributing variable for heterogeneity, for example, the year of distribution, race, the sample size of patients, malignancy type, treatment and NLR cut-off value. We

were unable to discover the source of heterogeneity by these variables for CSS. Significant publication bias was observed in this study. The potential explanation may be that the studies with negative result would have less chance to be published.

Some limitations have been found from this meta-examination. First, 14 studies enrolled in this meta-analysis for evaluating the main oncological outcome for NLR. Second, NLR cut-offs value in included studies were not consistent. Third Heterogeneity has been observed and influenced our final results. Fourth, all of included studies were retrospective, so biases unavoidable. Further investigations are needed to address the above-mentioned shortcomings .Despite the all limitations, our research supports the values of pre-treatment NLR for predicting CSS and RFS in bladder cancer patients.

CONCLUSION

This meta-analysis exhibited that elevated neutrophil-to-lymphocyte ratio significantly associated to poorer prognosis as of case specific survival, and also a higher risk of disease recurrence. The predictive significance of NLR may become a valuable indicator among bladder carcinoma patients. Further investigations are needed in the form of well-designed prospective research with definite NLR cut-off and longer follow-ups.

Acknowledgements We thank the many investigators who shared the data and members who help this study.

Conflict of interest The authors report no conflict of interest.

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

REFERANCE

1. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11. International Agency for Research on Cancer Web site. http://globocan.iarc.fr.
2. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017;71:447–61 http://dx.doi.org/ 10.1016/j.eururo.2016.05.041.
3. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454(7203):436– 44. doi: 10.1038/nature07205
4. de Martino M, Klatte T, Seemann C, Waldert M, Haitel A, Schatzl G, et al. Validation of serum C-reactive
5. protein (CRP) as an independent prognostic factor for disease-free survival in patients with localised renal cell carcinoma (RCC). BJU international. 2013; 111(8):E348–53. doi: 10.1111/bju.12067
6. Steffens S, Kohler A, Rudolph R, Eggers H, Seidel C, Janssen M, et al. Validation of CRP as prognostic marker for renal cell carcinoma in a large series of patients. BMC cancer. 2012; 12:399. doi: 10.1186/ 1471-2407-12-399
7. Formica V, Luccchetti J, Cunningham D et al (2014) Systemic inflammation, as measured by the neutrophil/lymphocyte ratio, may have differential prognostic impact before and during treat- ment with fluorouracil, irinotecan and bevacizumab in metastatic colorectal cancer patients. Med Oncol Northwood Lond Engl 31:166. doi:10.1007/s12032-014-0166-6
8. Jung MR, Park YK, Jeong O, Seon JW, Ryu SY, Kim DY, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol 2011;104:504e10 doi: 10.1002/jso.21986.
9. Moher D, Liberati A, Tetzlaff J, et al. 2009. "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." Br Med J 339:b2535.
10. Bhindi B, Hermanns T, Wei Y et al (2016) Identification of the best complete blood count-based predictors for bladder cancer outcomes in patients undergoing radical cystectomy. Br J Cancer 114:207–212. doi:10.1038/bjc.2015.432
11. Morizawa Y, Miyake M, Shimada K et al (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.e11–257.e17. doi:10.1016/j. urolonc.2016.02.012
12. Favilla V, Castelli T, Urzì D, Reale G, Privitera S, Salici A, et al. Neutrophil to lymphocyte ratio, a biomarker in non-muscle invasive bladder cancer: a single-institutional longitudinal study. Int Braz J Urol Off J Braz Soc Urol 2016;42:685–93.
13. Hermanns T, Bhindi B, Wei Y et al (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. doi:10.1038/ bjc.2014.305
14. Gondo T, Nakashima J, Ohno Y et al (2012) Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preop- erative risk stratification model in bladder cancer patients treated with radical cystectomy. Urology 79:1085–1091. doi:10.1016/j. urology.2011.11.070
15. Hirasawa Y, Nakashima J, Yunaiyama D et al (2016) Sarcope- nia as a novel preoperative prognostic predictor for survival in patients with bladder cancer undergoing radical cystectomy. Ann Surg Oncol. doi:10.1245/s10434-016-5606-4
16. Kang M, Jeong CW, Kwak C, Kim HH, Ku JH. 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; 8:12891–901, http://dx.doi.org/10.18632/oncotarget.14179.
17. Mano R, Baniel J, Shoshany O, Margel D, Bar-On T, Nativ O, et al. Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer e1-7. Urol Oncol 2015;33:67, http://dx.doi.org/10.1016/j.urolonc.2014.06.010.
18. Mbeutcha A, Shariat SF, Rieken M, Rink M, Xylinas E, Seitz C, et al. Prognostic significance of markers of systemic inflammatory response in patients with non-muscle-invasive bladder cancer 483. e17-483.e24. Urol Oncol 2016. http://dx.doi.org/10.1016/j. urolonc.2016.05.013.
19. Morizawa Y, Miyake M, Shimada K et al (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.e11–257.e17. doi:10.1016/j. urolonc.2016.02.012
20. Ogihara K, Kikuchi E, Yuge K, Yanai Y, Matsumoto K, Miyajima A, et al. 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 2016;23:1039–47, http://dx.doi.org/10.1245/ s10434-016-5578-4.
21. Viers BR, Boorjian SA, Frank I et al (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. doi:10.1016/j. eururo.2014.02.042

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 doi: https://doi.org/10.1016/j.ajur.2017.01.004
23. D'Andrea D, Moschini M, Gust K et al. Prognostic role of neutrophil-to-lymphocyte ratio in primary non-muscle-invasive bladder cancer. Clin. Genitourin. Cancer 2017; https://doi.org/10.1016/j.clgc.2017.03.007.
24. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assess- ment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5.
25. Kim H.S., Ku J.H. Systemic Inflammatory Response Based on Neutrophil-to-Lymphocyte Ratio as a Prognostic Marker in Bladder Cancer. Dis Markers. 2016;2016:8345286. doi: 10.1155/2016/8345286.
26. D. Keizman, M. Gottfried, M. Ish-Shalom et al., "Pretreatment neutrophil-to-lymphocyte ratio in metastatic castration-resistant prostate cancer patients treated with ketoconazole: association with outcome and predictive nomogram," Oncologist, vol. 17, no. 12, pp. 1508–1514, 2012. https://doi.org/10.1634/theoncologist.2012-0125
27. D. Keizman, M. Ish-Shalom, P. Huang et al., "The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma," European Journal of Cancer, vol. 48, no. 2, pp. 202–208, 2012. doi: 10.1016/j.ejca.2011.09.001.
28. Hu, G., Xu, F., Zhong, K., Wang, S., Xu, Q., Huang, L., & Cheng, P. (2018). The prognostic role of preoperative circulating neutrophil–lymphocyte ratio in primary bladder cancer patients undergoing radical cystectomy: A meta-analysis. World Journal of Urology, 1–9. https://doi.org/10.1007/s00345-018-2593-z
29. M. D. Vartolomei, D. Porav-Hodade, M. Ferro et al., "Prognostic role of pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with non–muscle-invasive bladder cancer (NMIBC): a systematic review and meta-analysis," Urologic Oncology: Seminars and Original Investigations, vol. 36, no. 9, pp. 389–399, 2018. https://doi.org/10.1016/j.urolonc.2018.05.014
30. Herszényi L, Lakatos G, Hritz I et al (2012) The role of inflam-mation and proteinases in tumor progression. Dig Dis Basel Switz 30:249–254. doi:10.1159/000336914
31. Jaramillo-Reta KY, Velázquez-Dohorn ME, Medina-Franco H (2015) Neutrophil to lymphocyte ratio as predictor of surgi- cal mortality and survival in complex surgery of the upper gas-trointestinal tract. Rev Investig Clin Organo Hosp Enferm Nutr 67:117–121.