PARIPEX - INDIAN JOURNAL OF RESEARCH | Volume - 11 | Issue - 01 | January - 2022 | PRINT ISSN No. 2250 - 1991 | DOI : 10.36106/paripex

Journal or p OF	IGINAL RESEARCH PAPER	Surgery
PARIPET CARE	DSPECTIVE STUDY OF PRE-TREATMENT TROPHIL-TO-LYMPHOCYTE RATIO PROGNOSTICATE R SURVIVAL OUTCOMES AND ADVANCED TUMOR TING IN PATIENTS UNDERGOING RADICAL TECTOMY FOR BLADDER CANCER IN A TERTIARY E CENTER.	KEY WORDS: Neutrophil-to- lymphocyte ratio (NLR), Disease – specific survival, Overall survival.
Dr Pritam Sharma	Department of Urology, AJIMS, Mangalore, Karnataka, India.	
Dr U Chowdary Panchumarthi*	Department of Urology, AJIMS, Mangalore, Karnataka, India. *Corresponding Author	
Dr Choubey Devashish	Department of Urology, Father Muller Medical College, Mangalore, Karnataka,India.	
Dr Avinash Reddy	Department of Urology, AJIMS, Mangalore, Karnataka, India.	
Dr E Muneendra Kumar	Department of Urology, AJIMS, Mangalore, Karnataka, India.	
Dr Yogendra Chidrawar	Department of Urology, AJIMS, Mangalore, Karnataka, India.	

Background: We aim to determine the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in patients undergoing radical cystectomy for UCB, in particularly looking at the disease specific survival and overall survival. This will allow us to better identify more suitable candidates for RC or other neoadjuvant or adjuvant therapies.

Methods: This is retrospective study that includes 91 patients that underwent RC for UCB between Jan 2006 to Dec 2015. We excluded 39 patients due to incomplete follow up and neoadjuvant chemotherapeutic treatment. All patients had histological proven UCB via transurethral resection of bladder tumor (TURBT). All patients had undergone staging scans with computed tomographies of the thorax, abdomen and pelvis to confirm the extent of disease. All patients underwent RC and bilateral standard pelvic lymphadenectomies and achieve clear margins on final histology. Outcomes we recorded are Median Disease – specific survival and Median overall survivals.

Results: The Median Disease – specific survival for patients with NLR \geq 2.7 was 20.4 months and with NLR \leq 2.7 was 59.9 months. The Median overall survival for patients with NLR \geq 2.7 was 21.1 months and with NLR \leq 2.7 was 58.2 months. **Conclusions:** These results suggested that NLR could be a novel preoperative factor to stratify and identify patients who might benefit from multimodal therapies in the treatment of UCB.

INTRODUCTION

ABSTRACT

Urothelial carcinoma is the most common type in bladder carcinomas, up to 95% of bladder malignancies are urothelial carcinomas, which are derived from the lining surface epithelium [1-3]. Nearly 75% of patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC), and the remaining patients have muscle-invasive bladder cancer (MIBC) or metastatic disease [4]. A transurethral resection of bladder tumor (TURBT) is the initial step for NMIBC patients, radical cystectomy (RC) is the gold standard therapy for MIBC patients, and cisplatin-based combination chemotherapy is the main treatment for metastatic urothelial carcinoma (mUC) or unresectable urothelial carcinoma patients [4-6].

Adding to the challenge in managing urothelial cancer of the bladder (UCB) is the lack of preoperative risk stratification. While most predictive models are based on pathological data, this information is insufficient to provide detailed prognosis for pre-operative decision making [7,8]. Upstaging of RC on final histology was reported as high as 50% [9]. Given the high recurrence rate and surgical morbidities, newer prognostic factors should be considered to provide a better risk stratification for more informed patient counselling and patient selection for surgery.

On the other hand, there has been increasing evidence supporting the role of inflammation in cancer development and progression [10], and the neutrophil-to-lymphocyte ratio (NLR) has been identified as a marker of tumor activity [11]. A higher NLR has been associated with poorer disease specific and overall survival in gastric, hepatic, nonsmall cell and cervical cancer [12]. This evidence can be relevant in prognosticating UCB, given that inflammation appears to be an important role in the pathogenesis and progression of UCB [10].

Through this paper, we aim to determine the prognostic value of NLR in patients undergoing radical cystectomy for UCB, in particularly looking at the disease specific survival and overall survival. This will allow us to better identify more suitable candidates for RC or other neoadjuvant or adjuvant therapies.

METHODS

This is retrospective study that includes 91 patients that underwent RC for UCB between Jan 2006 to Dec 2015. We excluded 39 patients due to incomplete follow up and neoadjuvant chemotherapeutic treatment. All patients had histological proven UCB via transurethral resection of bladder tumor (TURBT). All patients had undergone staging scans with computed tomographies of the thorax, abdomen and pelvis to confirm the extent of disease.

Haematological and biochemical blood results were collected at a median of 6 days prior to operation. All patients were cleared of any infection or active inflammation at the time of examination. NLR was analysed as a continuous variable and a cut-off point of 2.7 was obtained, with a statistical receiver operating characteristics (ROC) of 0.76 (area under curve).

All patients underwent RC and bilateral standard pelvic lymphadenectomies and achieve clear margins on final histology. Post-operatively, all patients were reviewed

PARIPEX - INDIAN JOURNAL OF RESEARCH | Volume - 11 | Issue - 01 | January - 2022 | PRINT ISSN No. 2250 - 1991 | DOI : 10.36106/paripex

outpatient within 4 weeks after discharge. Given the retrospective nature of this study, follow-ups were not

consistently standardized. Follow-up protocol was, we recommended 3 monthly for the first 2 years post-operatively, 6 monthly for the subsequent 3 years and yearly follow-ups onwards. Evaluations included history and physical examination, urine cytology, repeated computed tomography scans of the thorax, abdomen and pelvis. Outcomes we recorded are Median Disease – specific survival and Median overall survivals.

RESULTS

The patients demographics and tumor characteristics are shown in Table 1. This study included 41 males and 11 females, with a median age of 63 years. 50 patients had muscle invasive bladder cancer, and the remaining 2 patients had persistent BCG-refractory high-grade non-muscle invasive disease. 36 patients had lymph node invasion on final histology.

Table 1: Demographics

Age	63 years
Gender	41
Male	
Female	11
Pathological tumor staging	2
T1	
T2	22
Т3	17
T4	11
Number of tumors	
1	28
2 or more	24
Tumor grade	
Low – Intermediate	7
High	45
Size	
≥ 3 cm	38
< 3 cm	14
Hydronephrosis	
Yes	27
No	25
NLR	
≥ 2.7	33
< 2.7	19
Pathological LN involvement	
Yes	36
No	16

The clinicopathoogic features of patients with NLR < 2.7 and \geq 2.7 are shown in Table 2. Patients with NLR \geq 2.7 were associated with larger tumor size, hydronephrosis, pathological extravesical (T3/4) tumors and lymph node involvement.

Table 2: Clinicopathologic characteristics andpathologicaloutcomes

	NLR < 2.7	$NLR \ge 2.7$
Gender	15	26
Male		
Female	4	7
T staging	19	5
T 1-2		
Т 3-4	10	18
Size	9	5
< 3 cm		
≥ 3 cm	13	25
Number of Tumors	13	15
1		
2 or more	11	13
Tumor grade	4	3
Low - Intermediate		

High	21	24
Hydronephrosis		
Yes	9	18
No	17	8
LN involvement	12	24
Yes		
No	11	5

The Median Disease-specific survival is given in Table 3 and median overall survival is mentioned in Table 4.

Table 3: Median Disease-specific survival.

	Median Disease – specific survival
$NLR \ge 2.7$	20.4 months
NLR < 2.7	59.9 months

Table 4: Median overall survival.

	Median overall survival
$NLR \ge 2.7$	21.1 months
NLR < 2.7	58.2 months

DISCUSSION

A heightened neutrophilic response is associated with increased cytokines, interleukins (IL-1, IL-6) and proangiogenic vascular endothelial growth factor (VEGF) which promote tumor migration and proliferation [13]. Mu"ller et al. [14] also commented that neutrophils release reactive oxygen species, nitric oxide and arginase, all of which compromise T cell function. A relative leukocytopenia could weaken the body's immune response to malignancy, and increase the potential for tumor progression [15]. Henceforth, the combinatory effects of these two cellular mechanisms, or the NLR, can be a strong predictor of tumor biology and outcomes of cancer patients.

The discussion between NLR and bladder cancer has been recent with limited data. Gondo et al. [16] published the first series, correlating NLR >2.5 with worse cancer-specific survival. However, the study was limited by the short follow-up period (median 25 months). Demirtas et al. [17] reported no correlation between NLR >2.5 and overall survival; Krane et al. [18] noted that NLR >2.5 was associated with extravesical disease and worse overall survival, although the study was limited by the small sample size (68 patients) and 15% had neoadjuvant chemotherapy which could have affected the actual NLR value. Hermanns et al. [19] and Viers et al. [20] produced more recent evidence that NLR >3.0 and >2.7 respectively could impact recurrence rate, disease-specific survival and overall survival.

Our analyses expanded on existing data on the validity of NLR in predicting outcomes following RC for UCB. In our study patients with NLR ≥ 2.7 were associated with larger tumor size, hydronephrosis, pathological extravesical (T3/4) tumors and lymph node involvement. We have also demonstrated a significant correlation of NLR ≥ 2.7 with worse disease-specific and overall survivals.

CONCLUSION

This study shows that elevated preoperative NLR was associated with worse disease-specific survival and overall survival and NLR ≥ 2.7 were associated with larger tumor size, hydronephrosis, pathological extravesical (T3/4) tumors and lymph node involvement. These results suggested that NLR could be a novel preoperative factor to stratify and identify patients who might benefit from multimodal therapies in the treatment of UCB.

Acknowledgement: None Conflict of interest: None Funding: None

REFERENCES

1. Wu S, Chen L, Wan Q, Zhang L, Zhao X, Tang X. Inflammatory myofibroblastic

www.worldwidejournals.com

PARIPEX - INDIAN JOURNAL OF RESEARCH | Volume - 11 | Issue - 01 | January - 2022 | PRINT ISSN No. 2250 - 1991 | DOI : 10.36106/paripex

- tumor of the urinary bladder in a patient with the left renal cell carcinoma: A case report. ExpTher Med 2014;7:1010–1012.
- Reuter VE, Grossman HB, Blute ML, Soloway MS, Dinney CPN, Liou LS, Jones JS. The pathology of bladder cancer. Urology 2006;67:11–18.
- Miyazaki J, Nishiyama H. Epidemiology of urothelial carcinoma. Int J Urol 2017;24:1-5.
- Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström PU, Choi W, Guo CC, Lotan Y, Kassouf W. Bladder cancer. Lancet 2016;6736:1–15.
- Lobo N, Mount C, Omar K, Nair R, Thurairaja R, Khan MS. Landmarks in the treatment of muscle-invasive bladder cancer. Nat Rev Urol 2017;14:565-574.
- Abufaraj M, Gust K, Moschini M, Foerster B, Soria F, Mathieu R, Shariat SF. Management of muscle invasive, locally advanced and metastatic urothelial carcinoma of the bladder: a literature review with emphasis on the role of surgery. Transl Androl Urol 2016;5:735–744.
- Shariat SF, Palapattu GS, Karakiewicz PI, Rogers CG, Vazina A, Bastian PJ, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. Eur Urol 2007;51:137e49.
- Ficarra V, Dalpiaz O, Alrabi N, Novara G, Galfano A, Artibani W. Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma. BJU Int 2005;95:786e90.
- Svatek RS, Shariat SF, NovaraG, Skinner EC, Fradet Y, Bastian PJ, et al. Discrepancy between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int 2011;107:898e904.
- Mantovani A, Allavena P, Sica A, Pagani GA. Cancer-related inflammation. Nature 2008;454:436e44.
- Zahorec R. Ratio of neutrophil to lymphocyte countsdrapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5e14.
- 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.
- Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pretreatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009;58:15e23.
- Mu'ller I, Munder M, Kropf P, Ha'nsch GM. Polymorphonuclear neutrophils and T lymphocytes: strange bedfellows or brothers in arms? Trends Immunol 2009;30:522e30.
- 15. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology 2007;121:1e14.
- Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, et al. Prognostic value of neutrophil to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. Urology 2012;79:1085e91.
 Demirtas A, Sabur V, Akinsal EC, Demirci D, Ekmekcioglu O, Gulmez I, et al.
- Demirtas A, Sabur V, Akinsal EC, Demirci D, Ekmekcioglu O, Gulmez I, et al. Can neutrophil-lymphocyte ratio and lymph node density be used as prognostic factors in patients undergoing radical cystectomy? Sci World J 2013;31:703579.http://dx.doi.org/10.1155/2013/703579.
 Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK. Preoperative
- Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK. Preoperative neutrophil lymphocyte ratio predicts overall survival and extravesical disease in patients undergoing radical cystectomy. J Endourol 2013;27:1046e50.
- Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, et al. 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 2014;111:444e51.
- Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, 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):1157e64.