

Predictive Value of Prognostic Nutritional index and Systemic Immune-Inflammation Index on Tumor Progression in Bladder Cancer Patients with After Radical Cystectomy

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Research

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Abstract

OBJECTIVES: The purpose of this study was to explore the predictive value of preoperative prognostic nutritional index(PNI) and systemic immune-inflammation index(SII) for local tumor stage in bladder cancer(BC) after radical cystectomy(RC).

METHODS: We researched our database between April 2011 and October 2019. There were 195 BC patients who underwent RC. The PNI and SII were calculated using preoperative blood sample results. The predictive value of SII and PNI was analysed with univariate and multivariate Cox regression models. Significant P was $P < 0.05$.

RESULTS: Of patients, all patients were males with a mean age of 67.94 ± 8.97 years. Mean serum albumin was 42.13 ± 4.28 (g/L), mean PNI score was 51.29 ± 6.09 and mean SII was 661.67 ± 506.22 . Multivariable Cox regression analysis demonstrated that PNI scores and SII could not play a significantly predictive factor between muscle invasive bladder cancer(MIBC) and non-muscle-invasive bladder cancer(NMIBC). While we also found PNI was an independent risk factors for predicting tumor stage($pT \geq 3a$ and $pT \geq 3a$).

CONCLUSIONS: Our research revealed that preoperative low PNI but not SII could be used as an independent factor to predict worse pathological stage($pT \geq 3a$). We still need future studies with large cohorts to identify our results.

Introduction

Bladder cancer(BC) is currently one of the most common urinary system tumors affecting human health. BC is also the eighth leading cause of cancer death in men[1]. About 75% of patients with newly diagnosed bladder cancer are confined to the mucosa or urothelial tissue[2]. Radical cystectomy(RC) is the clinically accepted gold standard for the treatment of muscular invasive bladder cancer(MIBC) and non-muscle invasive bladder cancer(NMIBC) that is not effective by intravesical therapy[3, 4]. Tumor-related inflammation may affect the tumor cell gene expression to promote local tumor progression, metastasis, and reduce the effectiveness of tumor therapy[5]. Recently, many studies have found that some immune cells in the blood, including neutrophils, lymphocytes and monocytes, affect the tumor microenvironment through some signaling pathways, which may affect the local progression and metastasis[6]. The inflammatory cell markers neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) have been used to assess tumor recurrence and survival rates[7, 8]. The systemic immune-inflammation index(SII) has also recently been considered to represent systemic inflammation levels to better predict the prognosis of tumors including gastric cancer, colorectal cancer, esophageal cancer, and other tumors[9–11]. The Prognostic Nutritional Index (PNI) indicator was calculated from serum albumin and the total number of lymphocytes, and was first proposed in 1980[12]. So far, PNI has played an important role in predicting the prognosis of some urinary tumors[13, 14].

Currently, few studies have shown the relationship between PNI, SII and the pathological stage of BC. Therefore, in order to study the predictive value of preoperative PNI and SII for pathological staging of BC

after RC, we performed this study

Patients And Methods

The institutional review board and medical ethics committee of XXXX approved the research protocol of this study. We collected the medical data of 195 BC patients with RB in XXXX from April 2011 and October 2019. Participants were in this study if they (a) were pathologically diagnosed BC; (b) with complete data and laboratory results; The participants were excluded (a) who already had clinical evidence of inflammatory diseases such as infection; (b) using nonsteroidal anti-inflammatory drugs (c) without complete medical records and laboratory results. Each participant signed the informed consent for the data to be utilized in our study. The following demographic, clinical, and pathology data were collected from patient medical records. Pathologists assessed the tumor grade and stage according to the 2004 WHO classification system and tumor, lymph node, metastasis (TNM) rubric. The counts of neutrophil, lymphocyte, platelet and the albumin level was obtained with the hepatic function data before operation. The definitions of PNI, SII, NLR, and PLR were shown as follows: PNI = albumin (g/L) + 5×total lymphocyte counts ($10^9/L$); SII = platelet × neutrophil/lymphocyte counts; NLR = neutrophil/lymphocyte counts; and PLR = platelet/lymphocyte counts. The study protocol was approved by the institutional Ethics Committee.

Statistical analysis

SPSS 22.0 was used for all statistical analyses. $x \pm s$ was used to evaluate continuous variables; frequency and scale were used to evaluate categorical variables. Chi-square test is used to analyze categorical variables. Receiver operating characteristic (ROC) curves were generated and areas under the curves (AUCs) were determined. Univariate and multivariate Cox regression analyses were performed to calculate corresponding odds ratios (ORs) and 95% confidence interval (CI). P values < 0.05 were considered statistically significant.

Results

Our study included 195 participants totally according to the inclusion criteria. And all patients were male in this study, with the 67.94 ± 8.97 years. Among these patients, 38(19.5%) patients had diabetes, 67(34.4%) patients had hypertension, 40(20.5%) patients had coronary heart disease. 69(35.4%) patients were diagnosed the NMIBC, 126(64.6%) patients had MIBC. 90(46.1%) patients had pT \geq 3a, 105(53.9%) patients had pT \geq 3a. 37(18.9%) patients had incident prostate cancer after RC. the mean PNI was 51.29 ± 6.09 , the mean serum albumin was 42.13 ± 4.28 (g/L), and the mean SII score was 661.67 ± 506.22 . Demographic and clinicopathological characteristics of the patients are summarized in Table 1. According to whether muscle-invasive or not, we divided the patients into NMIBC group and MIBC group. Clinicopathological characteristics of the patients are summarized in Table 2. In univariate analysis, we found that PNI, SII, NLR and PLR were all statistically significant for the incidence of MIBC. However, multivariate analysis showed that PNI, SII, NLR and PLR could not be used as independent factors to

predict the risk of MIBC in Table 3. According to tumor stage, we divided the patients into pT<3a group and pT ≥ 3a group in Table 4. In univariate analysis, we found that PNI, SII, NLR and PLR were all statistically significant for the incidence of worse stage. In multivariate analysis, we only found that preoperative PNI could be used as an independent predictor of tumor stage in Table 5(p = 0.014). ROC curve indicated that a PNI of 52.225 had

Table 1
Characteristics of the study cohort

	Mean ± SD and n (%)
Age(years) mean ± SD	67.94 ± 8.97
Gender, no. (%)	
Male	195(100)
Female	-
BMI, mean ± SD	24.11 ± 3.41
Diabetes, no. (%)	
Asent	56(80.5)
Present	38(19.5)
Hypertension, no. (%)	
Asent	128(65.6)
Present	67(34.4)
Coronary heart disease, no. (%)	
Asent	155(79.5)
Present	40(20.5)
PNI, mean ± SD	51.29 ± 6.09
SII, mean ± SD	661.67 ± 506.22
NLR, mean ± SD	2.95 ± 2.00
PLR, mean ± SD	138.8 ± 69.85
Albumin, mean ± SD	42.13 ± 4.28
Bladder cancer(NMIBC or MIBC), no. (%)	
NMIBC	69(35.4)
MIBC	126(64.6)
pT,no.(%)	
T<3a	105(46.1)

BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index, NMIBC non-muscle-invasive bladder cancer, MIBC muscle-invasive bladder cancer

	Mean ± SD and n (%)
T ≥ 3a	90(53.9)
pN,no. (%)	
N ₀	68(34.9)
N ₊	22(11.3)
N _x	105(53.8)
Incidental PCa, no.(%)	
Asent	158(81.1)
Present	37(18.9)
BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index, NMIBC non-muscle-invasive bladder cancer, MIBC muscle-invasive bladder cancer	

Table 2
Characteristics of the study between NMIBC and MIBC

	NMIBC(n = 69)	MIBC(n = 126)	p value
Age(years) mean ± SD	68.04 ± 8.38	67.88 ± 9.34	0.904
Gender, no. (%)			
Male	69(100)	126(100)	
Female	-	-	
BMI, mean ± SD	23.74 ± 3.00	24.33 ± 3.61	0.241
Diabetes, no. (%)			0.866
Asent	56(81.2)	101(80.2)	
Present	13(18.8)	25(19.8)	
Hypertension, no. (%)			0.518
Asent	48(69.6)	80(63.5)	
Present	21(30.4)	46(36.5)	
Coronary heart disease, no. (%)			0.06
Asent	60(87.0)	95(75.4)	
Present	9(13.0)	31(24.6)	
PNI, mean ± SD	52.74 ± 6.5	50.49 ± 5.75	0.014*
SII, mean ± SD	497.41 ± 277.94	751.62 ± 578.62	0.001*
NLR, mean ± SD	2.32 ± 1.07	3.30 ± 2.29	0.001*
PLR, mean ± SD	118.45 ± 46.59	149.95 ± 77.95	0.003*
Albumin, mean ± SD	42.61 ± 4.25	41.87 ± 2.31	0.253
pT,no.(%)			
Tis or T1	69(100)	-	

BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index, NMIBC non-muscle-invasive bladder cancer, MIBC muscle-invasive bladder cancer

* Statistically significant

	NMIBC(n = 69)	MIBC(n = 126)	p value
T2	-	36(28.6)	
T3	-	63(50)	
T4	-	27(47.4)	
pN,no. (%)			
N ₀	23(33.3)	45(34.9)	
N ₁	-	22(17.1)	
N _x	46(66.7)	59(48)	
Incidental PCa, no.(%)			
Asent	54(78.3)	104(82.9)	0.293
Present	15(21.7)	22(17.1)	
BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index, NMIBC non-muscle-invasive bladder cancer, MIBC muscle-invasive bladder cancer			
* Statistically significant			

Table 3

Univariate and Multivariate analysis for the association between muscle-invasive and patients and tumor characteristics

Variables		Univariate analysis			Multivariate analysis		
		OR	95CI%	p value	OR	95CI%	p value
Age	(continuous)	0.998	0.966–1.031	0.904			
BMI	(continuous)	1.055	0.966–1.154	0.235			
Albumin	(continuous)	0.96	0.896–1.029	0.252			
PNI	(continuous)	1.054	1.027–1.082	0.016*	0.987	0.972–1.001	0.077
SII	(continuous)	1.002	1.001–1.003	0.001*	1.001	0.999–1.003	0.382
PLR	(continuous)	1.009	1.003–1.015	0.003*	1.001	0.992–1.01	0.877
NLR	(continuous)	1.492	1.167–1.906	0.001*	1.204	0.801–1.81	0.372
Diabetes	(presence vs absence)	1.066	0.506–2.247	0.866			
Hypertension	(presence vs absence)	1.232	0.655–2.319	0.518			
Coronary heart disease	(presence vs absence)	2.175	0.968–4.887	0.06			
BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index,							
* Statistically significant							

Table 4
 Characteristics of the study between pT ≥ 3a and pT<3a

	pT<3a(n = 105)	pT ≥ 3a(n = 90)	p value
Age(years) mean ± SD	67.87 ± 8.51	68.01 ± 9.58	0.914
BMI, mean ± SD	23.83 ± 3.22	24.44 ± 3.62	0.209
Diabetes, no. (%)			0.354
Asent	83(79.1)	74(77.9)	
Present	22(20.9)	16(22.4)	
Hypertension, no. (%)			0.488
Asent	70(66.7)	58(61)	
Present	35(33.3)	32(39)	
Coronary heart disease, no. (%)			0.037*
Asent	89(84.8)	66(69.5)	
Present	16(13.2)	24(30.5)	
PNI, mean ± SD	52.24 ± 6.33	50.19 ± 5.66	0.019*
SII, mean ± SD	548.54 ± 354.76	793.66 ± 617.79	0.001*
NLR, mean ± SD	2.45 ± 1.25	3.54 ± 2.51	<0.001*
PLR, mean ± SD	127.14 ± 56.3	152.4 ± 81.47	0.012*
Albumin, mean ± SD	42.48 ± 4.31	41.72 ± 4.27	0.223
BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index			
* Statistically significant			

Table 5
Univariate and Multivariate analysis for the association between pathologic stage(pT \geq 3a) and patients and tumor characteristics

Variables		Univariate analysis			Multivariate analysis		
		OR	95CI%	p value	OR	95CI%	p value
Age	(continuous)	1.002	0.971–1.034	0.917			
BMI	(continuous)	1.055	0.97–1.147	0.209			
Albumin	(continuous)	0.96	0.898–1.025	0.223			
PNI	(continuous)	0.944	0.9–0.991	0.021*	0.983	0.97–0.997	0.014*
SII	(continuous)	1.001	1.000–1.002	0.001*	1.001	0.999–1.002	0.421
PLR	(continuous)	1.006	1.001–1.011	0.016*	0.996	0.988–1.004	0.317
NLR	(continuous)	1.427	1.171–1.740	<0.001*	1.332	0.936–1.896	0.111
Diabetes	(presence vs absence)	0.816	0.399–1,669	0.577			
Hypertension	(presence vs absence)	1.056	0.583–1.914	0.857			
Coronary heart disease	(presence vs absence)	2.023	0.996–4.107	0.051			
BMI body mass index, NLR neutrophil to lymphocyte ratio, PLR platelets to lymphocyte ratio, PNI prognostic nutritional index, SII systemic immune inflammation index,							
* Statistically significant							

maximum Youden index value (Fig. 1) (sensitivity = 64.4%, Specificity = 54.3%).

Discussion

Inflammation plays an important role in tumor occurrence, tumor progression and distant metastasis, and can also predict the prognosis of tumor patients[15]. We included the PNI, SII, NLR, PLR into this study, and found that PNI, SII, PLR, NLR could not predict the occurrence of muscular invasive BC, but on the other hand, our results revealed that PNI could be used as an independent predictor to predict whether the

tumor has invaded beyond the bladder($pT \geq 3a$), the lower the PNI may indicate the worse the pathological results.

Many studies have found that using inflammatory cell counts to calculate relevant inflammation markers, including NLR, PLR, LMR, has a meaningful relationship with the prognosis of tumors[7, 8]. NLR revealed the response level and defense ability of the human immune system, which can reflect the body's immune surveillance and immunosurveillance to tumors[16]. Dalpiaz et al reported that preoperative high NLR had a worse cancer-specific- as well as overall mortality after radical surgery for upper tract urothelial carcinoma (UTUC)[17]. Gondo et al also suggested that NLR could be used as an independent predictor to predict disease-specific survival(DSS)in BC patients with RC[18]. In addition to the prognosis of patients with BC, NLR was also related to the pathological stage of the BC. In Tazeh et al's study, they described the significant association between the high NLR before transurethral resection of bladder tumor(s) (TURBT)and postoperative advanced tumor stage[19]. However, our study found that there was no statistical significance between NLR and the pathological stage of the tumor, which may be caused by the different surgical methods and the inclusion criteria.

SII based on lymphocyte, neutrophil, and platelet counts. Compared with NLR, the appearance of SII is more representative of the level of human inflammatory response. Increased levels of inflammation represented by SII may indicate increased tumor burden or tumor progression[20]. Zhang et al proposed their research in 2019 which demonstrated that SII can play as an independent predictor of overall survival (OS) in patients who have undergone radical cystectomy for bladder cancer, their research considered SII might to be a better predictor of prognosis than NLR, PLR[21]. Since many studies have found that SII plays an important role in predicting the prognosis of different tumors, we also analyzed level of SII and the incidence of worse pathological stage in BC patients after RC for the first time, although univariate analysis found that SII may be statistically related to the pathological stage after RC, SII could not be used as an independent influencing factor to predict pathological stage.

PNI based on serum albumin and lymphocyte count which has been used as a significant predictor for prognosis of several urological cancers[22–24]. PNI not only indicates the level of inflammation in the human body, but also represents the nutritional level of the human body. Many studies on malnutrition associated with malignant tumors may lead to a poor prognosis. The composition of the human immune mechanism is inseparable from the support of nutrition. cancer-related malnutrition will disrupt the immune mechanism and break the normal immune balance, thereby reducing the inhibitory effect on tumor cells and promoting the proliferation of tumor cells, and the proliferation of tumor cells would also increase the consumption of human nutrition, such a vicious cycle would eventually lead to a poor prognosis[25, 26]. Xue et al thought low preoperative PNI was associated with worse survival outcomes in patients with UTUC[24]. Recently, Karsiyakali et al research 164 primary BC patients who underwent TURBT and found that PNI is a potential predictor of preoperative tumor staging and an independent risk factor for predicting tumor staging[27]. Their results also indicated that PNI could significantly predict poor tumor stage, which is similar to the conclusion obtained by our research, but we believed that PNI could mainly predict the incidence of $pT \geq 3$, and could not predict whether the tumor invades the

muscular layer. their study only found that PNI could predict the incidence of pT₁ after TURBT. The reason for this difference might be due to the different clinical stages of the patients and the different surgical methods.

A few limitations of our study should be considered. First, This study is an independent, single-center retrospective study. The clinical data collected may be biased, affecting the results. Besides, due to the small number of samples included in this study, The research results need to be further confirmed.

Conclusion

In conclusion, patients with low PNI had worse tumor stage($pT \geq 3a$). PNI is an independent predictor of oncologic outcomes in patients with BC after RC. Therefore, we suggested that Preoperative PNI can be combined with clinical bladder MRI to further increase the accuracy of clinical staging of BC, especially in pT3a.

Declarations

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Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Further information

Not applicable.

Authors' contributions

Conception and Design: JZ and RL; Extraction of Data: XX and JZ;

Drafting the Article: JZ and RL; Revising It for Intellectual Content: JZ, RL; Final Approval of the Completed Article: JZ, RL. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

Statement of Ethics

All procedures performed in studies involving human participants were following the ethical standards of the institution and/or national research committee. This article does not contain any studies with animals performed by any of the authors.

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Figures

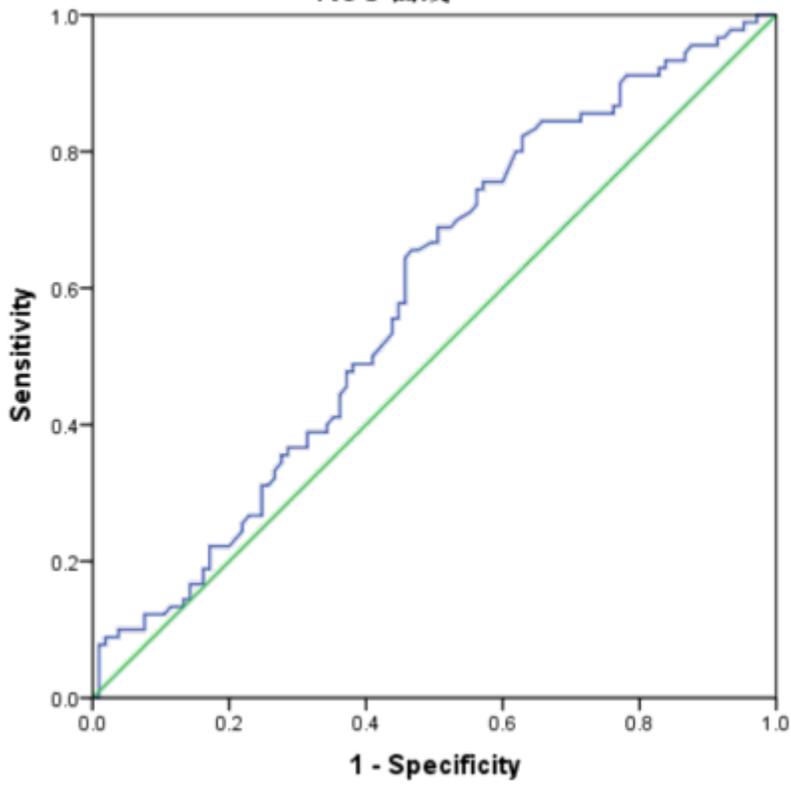


Figure 1

ROC curves in predicting $pT \geq 3a$ by PNI (continuous, AUC = 0.589). ROC receiver operating characteristic, AUC area under curve