



A high monocyte-to-lymphocyte ratio predicts poor prognosis in patients with radical cystectomy for bladder cancer

Heng Shi^{1,2#}, Keyi Wang^{1#}, Jing Yuan^{1#}, Weipu Mao^{1,2}, Zonglin Wu², Qunlong Liu¹, Jinbo Xie¹, Bo Peng^{1,2^}

¹Department of Urology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, China; ²Department of Urology, People's Hospital of Putuo District, Shanghai, China

Contributions: (I) Conception and design: H Shi, J Xie, B Peng; (II) Administrative support: B Peng; (III) Provision of study materials or patients: W Mao, Z Wu, Q Liu; (IV) Collection and assembly of data: H Shi, J Yuan; (V) Data analysis and interpretation: H Shi, K Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Bo Peng; Jinbo Xie. Department of Urology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, No. 301, Yanchang Road, Jing'an District, Shanghai 200072, China. Email: pengbo6908@163.com; doctorjinbox@outlook.com.

Background: At present, it is well known that many hemogram parameters were related to the prognosis of a variety of cancers. Among them, monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have attracted more and more attention. The purpose of this study was to investigate the prognostic value of MLR, NLR, PLR, especially MLR, in patients with bladder cancer (BC) treated with radical cystectomy (RC).

Methods: Between January 2009 and October 2018, 203 BC patients who underwent RC participated in the survey, and various clinical and hematological parameters were recorded. The optimal cutoff of MLR, NLR and PLR were determined by X-tile software, and Cox regression analysis was performed to investigate the effect of MLR, NLR and PLR on the overall survival (OS) and disease-free survival (DFS).

Results: The optimal cutoff values of MLR, NLR and PLR were 0.54, 4.10 and 164.63, respectively. Patients with high MLR (>0.54) predicted shorter OS [hazard ratio (HR): 2.30; 95% confidence interval (CI): 1.36–3.89; P=0.002] and DFS (HR: 2.13; 95% CI: 1.21–3.75; P=0.009) compared with patients with low MLR (≤0.54). Multivariate Cox regression analysis showed that only MLR was an independent risk factor for OS and DFS in MLR, NLR and PLR. In addition, receiver operating characteristic (ROC) analysis showed that at most time points, the area under the curve (AUC) of MLR was greater than that of NLR and PLR used to predict OS and DFS.

Conclusions: Our results show that MLR can be independently used as a poor prognostic factor for OS and DFS in BC patients with RC. The prognosis of BC patients after RC can be predicted by measuring the level of MLR.

Keywords: Bladder cancer (BC); monocyte-to-lymphocyte ratio (MLR); radical cystectomy; prognosis; biomarker

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[^] ORCID: 0000-0001-5656-2115.

Introduction

Bladder cancer (BC) is the 11th most commonly diagnosed cancer worldwide, and the worldwide age-standardized incidence rates (per 100,000 person/year) are 9.0 for men and 2.2 for women (1). It is reported that in 2019, the incidence of BC will be the fourth most common malignant tumor in American men, and the mortality rate will be the eighth (2). Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta and CIS) or submucosa (stage T1) (3). In addition, 70–85% of patients with BC were initially diagnosed as non-muscle invasive bladder cancer (NMIBC), while 15–30% were diagnosed as muscle invasive bladder cancer (MIBC) (4).

Nowadays, radical cystectomy (RC) is the most important method for the treatment of MIBC, because of the complexity of the operation, the incidence of postoperative complications in patients with MIBC was higher, and the 5-year survival rate was still low (5,6). In addition, neoadjuvant chemotherapy, adjuvant chemotherapy and lymph node dissection also play an important role in the treatment of bladder cancer (7). Even if the clinical diagnosis of patients is the same, the prognosis of patients is not the same, therefore, it is necessary to explore some indicators to predict the prognosis.

Recent studies have shown that the proliferation, invasion, metastasis, and angiogenesis of tumor cells are affected by inflammation. The commonly used inflammatory indexes include MLR, NLR, PLR, C reactive protein and so on (8–10). Currently, some studies have shown that MLR, NLR and PLR can be used as prognostic indicators of gastric cancer, breast cancer, lung cancer and so on (11–14). There are few studies investigated the prognostic value of MLR, NLR, PLR, especially MLR, in patients with BC treated with RC. The purpose of this study is to analyze the effect of MLR on the prognosis of patients undergoing RC.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-1060>).

Methods

Patients

From January 2009 to October 2018, 278 patients with BC who underwent RC were invited to participate in the study

of urology in Shanghai Tenth People's Hospital. The supine position was taken after general anesthesia, laparoscopic resection of bladder cancer was performed, routine pelvic lymph node dissection was performed sequentially, the resected tissue was removed, and ileal orthotopic bladder was performed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Tenth People's Hospital of Shanghai (SHSY-IEC-KY-4.0/18-68/01) and informed consent was taken from all the patients.

Inclusion criteria: the diagnosis of BC was confirmed by cystoscopy and pathological examination; patients undergoing RC; older than 18.

Exclusion criteria: patients with a history of other malignant tumors (2 cases); infection before surgery (8 cases); radiotherapy or chemotherapy before surgery (5 cases); mental abnormalities (0 cases); incomplete experimental data (46 cases); lost follow-up data (14 cases). Finally, 203 patients participated in the study.

Data collection

The clinical data of the patients were collected, including age, sex, body mass index (BMI), comprehensive complication index (CCI), T-stage, N-stage, M-stage and tumor grade. Laboratory data such as neutrophils, lymphocytes, monocytes, and platelets were collected 3 days before operation. MLR, NMR and PLR were calculated as absolute monocyte count divided by absolute lymphocyte count, absolute neutrophil count divided by absolute lymphocyte count, and absolute platelet count divided by absolute lymphocyte count.

Follow-up

In this study, patients who participated in the study were followed up after operation. The patients were followed up every 3 months in the first 2 years after operation and then every 6 months thereafter. The last follow-up date was January 20, 2019. The postoperative tumor recurrence and survival status of the patients were collected during each follow-up. If the patients were dead, the date of death and causes were recorded. The end point of follow-up was the time of the last follow-up or the time of death of the patient. Survival time is from the patient's operation to

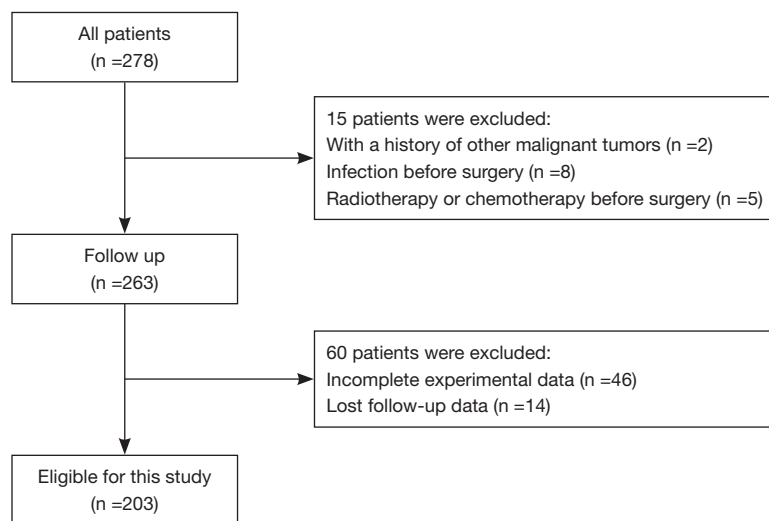


Figure 1 Research flow diagram.

death or to the patient's last follow-up.

Statistical analysis

Continuous variables are described as median (quartile range) and classification variables are described as frequency (percentage). X-tile software was used to calculate the optimal cutoff value of MLR, NLR and PLR. The baseline characteristics between groups were compared using independent sample t-test and chi-square test as appropriate. Overall survival (OS) and disease-free survival (DFS) curves were drawn by the Kaplan-Meier method and evaluated using the log-rank test. The relationship between OS, DFS and potential confounding variables (including age, sex, BMI, CCI, TNM stage and tumor grade, as well as NLR, LMR and PLR) was determined by Cox proportional risk regression model. Medcalc software was used to draw receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) >0.5 indicates that it has clinical diagnostic value, and the higher the AUC value, the higher the diagnostic value. $P < 0.05$ was considered statistically significant. Statistical analyses were performed by SPSS version 24.0 software (IBM Corporation, Somers, NY, USA).

Results

Patient characteristics

According to the inclusion criteria, a total of 203 BC patients who underwent RC in Shanghai Tenth People's

Hospital agreed to participate in the study (Figure 1). The baseline characteristics of the patient are shown in Table 1. In this study, the median age of the patients was 66 years [interquartile range (IQR): 60.0–73.0]. The median BMI of the patient was 23.1 kg/m² (IQR: 21.3–25.3). The majority of patients were male (176, 86.7%), CCI ≤2 (128, 63.1%), high-grade tumors (191, 94.1%), and the patient's TNM stage was at mostly N0 (168, 82.8%), M0 (194, 95.6%). In addition, the median MLR, NLR, and PLR of the patients were 0.28 (IQR: 0.19–0.44), 3.09 (IQR: 2.02–5.76), and 130.14 (IQR: 88.98–183.19), respectively.

Clinical characteristics of the patients according to MLR, NLR and PLR

The optimal cutoff values for MLR, NLR and PLR are 0.54, 4.10, and 164.63, respectively (Figure 2). The patient was divided into higher and lower groups according to the cutoff value. The clinical characteristics of the patient are shown in Table 2. The median age of the higher MLR group was higher than the lower MLR group (69.0 vs. 65.0 years, $P = 0.028$). The patient's median BMI was lower in the higher MLR group (23.4 vs. 22.3 kg/m², $P = 0.033$) and higher NLR group (23.9 vs. 22.4 kg/m², $P < 0.001$). Other clinical characteristics were not significantly different between groups.

Factors predicting OS and DFS

As shown in Table 3, univariate analysis showed that higher

Table 1 Baseline characteristics of the study population

Characteristics	Median (IQR) or N (%)
Age (years)	66.0 (60.0–73.0)
BMI (kg/m ²)	23.1 (21.3–25.3)
Sex	
Male	176 (86.7)
Female	27 (13.3)
CCI	
≤2	128 (63.1)
>2	75 (36.9)
T-stage	
T1	80 (39.4)
T2	43 (21.2)
T3	41 (20.2)
T4	39 (19.2)
N-stage	
N0	168 (82.8)
N+	35 (17.2)
M-stage	
M0	194 (95.6)
M1	9 (4.4)
Grade	
Low grade	12 (5.9)
High grade	191 (94.1)
MLR	0.28 (0.19–0.44)
NLR	3.09 (2.02–5.76)
PLR	130.14 (88.98–183.19)

Percentages may not total 100 because of rounding. IQR, interquartile range; BMI, body mass index; CCI, comprehensive complication index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

T stage, N+, M1, MLR >0.54, NLR >4.10, and PLR >164.63 were associated with poor prognosis in patients (Figure 3A,B,C). However, multivariate analysis showed that only the TNM, MLR [MLR >0.54 vs. MLR ≤0.54; hazard ratio (HR): 2.30; 95% CI: 1.36–3.89; P=0.002] were independent factors for OS. Similarly, we also analyzed the factors associated with DFS (Table 4). Univariate analysis showed that factors associated with DFS were T stage,

N stage, M stage, MLR, NLR and PLR (Figure 3D,E,F). However, in multivariate analysis, among the three indicators of MLR, NLR and PLR, only MLR was an independent risk factor for DFS, and high MLR (HR: 2.13; 95% CI: 1.21–3.75; P=0.009) indicated poor survival.

Time-dependent ROC analysis for MLR, NLR, and PLR according to OS and DFS

As indicated by ROC analysis (Figure 4), at most time points, the area under the curve (AUC) of the MLR was greater than the NLR and PLR used to predict OS and DFS. Moreover, MLR could better predict patients' OS [area under the curve (AUC): 0.635; 95% CI: 0.554–0.717; P=0.001] and DFS (AUC: 0.617; 95% CI: 0.530–0.703; P=0.008) than NLR and PLR (Table 5).

Discussion

It was reported that hemogram parameters can be used to predict the prognosis of cancer and provide a basis for judging the prognosis of cancer (15,16), and inflammation is related to the occurrence and development of cancer (17,18). A series of inflammatory indexes have been reported to participate in tumor progress, such as MLR, NLR and PLR.

So far, there have been many studies on the relationship between MLR, NLR, PLR and tumor prognosis. Zhang *et al.* (19) reported that elevated NLR and PLR were associated with poor prognosis in patients with gastric cancer, while NLR was an independent prognostic factor for OS. However, it has been reported that NLR and PLR are not independently related to the prognosis of gastric cancer, and preoperative LMR was an independent prognostic factor for postoperative patients with gastric cancer (20). Moon *et al.* (11) reported that elevated NLR may be an independent prognostic factor for advanced recurrence of breast cancer. Although the results are not the same, MLR, NLR and PLR have significant diagnostic and prognostic value in a variety of cancers (21–23).

At present, only a few studies have reported the relationship between MLR, NLR, PLR and the prognosis of patients undergoing radical resection of BC. It has been reported that PLR was the most effective index to predict CSS and OS (24). Other studies have shown that LMR and NLR can be used as independent factors to predict cancer-specific survival (CSS) and OS in patients with BC after RC (25,26). Rajwa (26) has reported that LMR, PLR, NLR

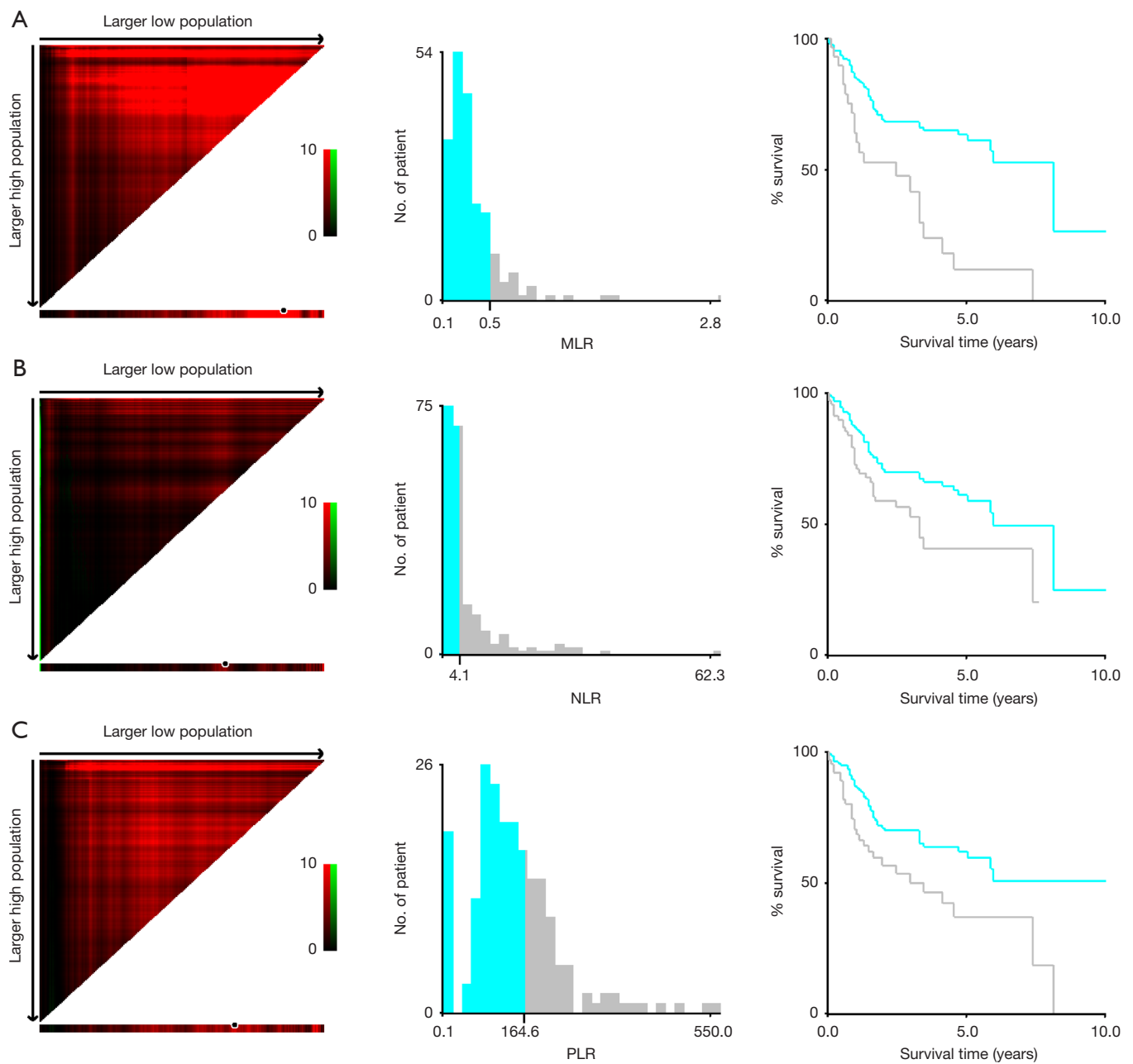


Figure 2 Estimation of the cut-off value for the MLR (A), NLR (B) and PLR (C) stratification as determined by the X-tile software. MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

is associated with the prognosis of BC patients receiving RC. And LMR is a comprehensive index, which can better predict the prognosis of cancer patients. It is reported that MLR has prognostic value in several malignant tumors (27). There are still few reports about the predictive effect of MLR on the prognosis of patients with BC.

In our study, based on a study of 203 patients with BC

who underwent RC, we found that MLR is an independent risk factor for OS and DFS in MLR, NLR, and PLR, and MLR predicts patient prognosis better than NLR and PLR. Patients with high MLR (>0.54) predicted shorter OS (HR: 2.30; 95% CI: 1.36–3.89; $P=0.002$) and DFS (HR: 2.13; 95% CI: 1.21–3.75; $P=0.009$) compared with patients with low MLR (≤ 0.54).

Table 2 Clinical characteristics of the patients according to MLR, NLR, NLR and PLR

Characteristics	MLR			NLR, median (IQR)			PLR, median (IQR)			P value
	≤0.54 (n=174)	>0.54 (n=29)	P value	≤4.10 (n=134)	>4.10 (n=69)	P value	≤164.63 (n=138)	>164.63 (n=65)	P value	
Age (years), median (IQR)	65.0 (58.8–72.0)	69.0 (63.5–78.5)	0.028	65.0 (59.0–72.0)	68.0 (63.0–75.5)	0.094	65.0 (58.0–73.0)	68.0 (62.0–73.5)	0.080	
BMI (kg/m ²), median (IQR)	23.4 (21.5–25.7)	22.3 (20.2–24.1)	0.033	23.9 (22.0–26.0)	22.4 (20.7–23.8)	<0.001	23.2 (21.7–25.4)	23.0 (20.9–25.2)	0.241	
Sex, n (%)			0.933			0.166			0.875	
Male	151 (86.8)	25 (86.2)		113 (84.3)	63 (91.3)		120 (87.0)	56 (86.2)		
Female	23 (13.2)	4 (13.8)		21 (15.7)	6 (8.7)		18 (13.0)	9 (13.8)		
CCI, n (%)			0.342			0.091			0.536	
≤2	112 (64.4)	16 (55.2)		90 (67.2)	38 (55.1)		89 (64.5)	39 (60.0)		
>2	62 (35.6)	13 (44.8)		44 (32.8)	31 (44.9)		49 (35.5)	26 (40.0)		
T-stage, n (%)			0.467			0.632			0.395	
T1	72 (41.4)	8 (27.6)		51 (38.1)	29 (42.0)		54 (39.1)	26 (40.0)		
T2	37 (21.3)	6 (20.7)		32 (23.9)	11 (15.9)		33 (23.9)	10 (15.4)		
T3	33 (19.0)	8 (27.6)		26 (19.4)	15 (21.7)		28 (20.3)	13 (20.0)		
T4	32 (18.4)	7 (24.1)		25 (18.7)	14 (20.3)		23 (16.7)	16 (24.6)		
N-stage, n (%)			0.595			0.223			0.131	
N0	145 (83.3)	23 (79.3)		114 (85.1)	54 (78.3)		118 (85.5)	50 (76.9)		
N+	29 (16.7)	6 (20.7)		20 (14.9)	15 (21.7)		20 (14.5)	15 (23.1)		
M-stage, n (%)			0.781			0.498			0.122	
M0	166 (95.4)	28 (96.6)		129 (96.3)	65 (94.2)		134 (97.1)	60 (92.3)		
M1	8 (4.6)	1 (3.4)		5 (3.7)	4 (5.8)		4 (2.9)	5 (7.7)		
Grade, n (%)			0.145			0.961			0.070	
Low grade	12 (6.9)	0 (0.0)		8 (6.0)	4 (5.8)		11 (8.0)	1 (1.5)		
High grade	162 (93.1)	29 (100.0)		126 (94.0)	65 (94.2)		127 (92.0)	64 (98.5)		

Percentages may not total 100 because of rounding. IQR, interquartile range; BMI, body mass index; CCI, comprehensive complication index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 3 Univariate and multivariate analyses of factors associated with OS

Characteristics	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤65	Reference			
>65	1.53 (0.97–2.44)	0.070		
BMI (kg/m ²)				
≤24	Reference			
>24	0.78 (0.48–1.26)	0.312		
Sex				
Male	Reference			
Female	1.01 (0.52–1.96)	0.989		
CCI				
≤2	Reference			
>2	0.93 (0.59–1.49)	0.767		
T-stage				
T1	Reference		Reference	
T2	2.28 (1.11–4.68)	0.025	2.17 (1.05–4.48)	0.036
T3	3.82 (1.97–7.41)	<0.001	2.70 (1.35–5.39)	0.005
T4	5.56 (2.86–10.81)	<0.001	3.18 (1.49–6.78)	0.003
N-stage				
N0	Reference		Reference	
N+	3.42 (2.07–5.66)	<0.001	2.09 (1.17–3.73)	0.012
M-stage				
M0	Reference		Reference	
M1	2.91 (1.17–7.24)	0.020	2.74 (1.06–7.06)	0.037
Grade				
Low grade	Reference			
High grade	1.90 (0.68–5.28)	0.221		
MLR				
≤0.54	Reference		Reference	
>0.54	2.97 (1.78–4.93)	<0.001	2.30 (1.36–3.89)	0.002
NLR				
≤4.10	Reference		Reference	
>4.10	1.77 (1.11–2.82)	0.016	–	0.777
PLR				
≤164.63	Reference		Reference	
>164.63	1.93 (1.21–3.08)	0.006	–	0.396

HR, hazard ratio; OS, overall survival; CI, confidence interval; BMI, body mass index; CCI, comprehensive complication index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

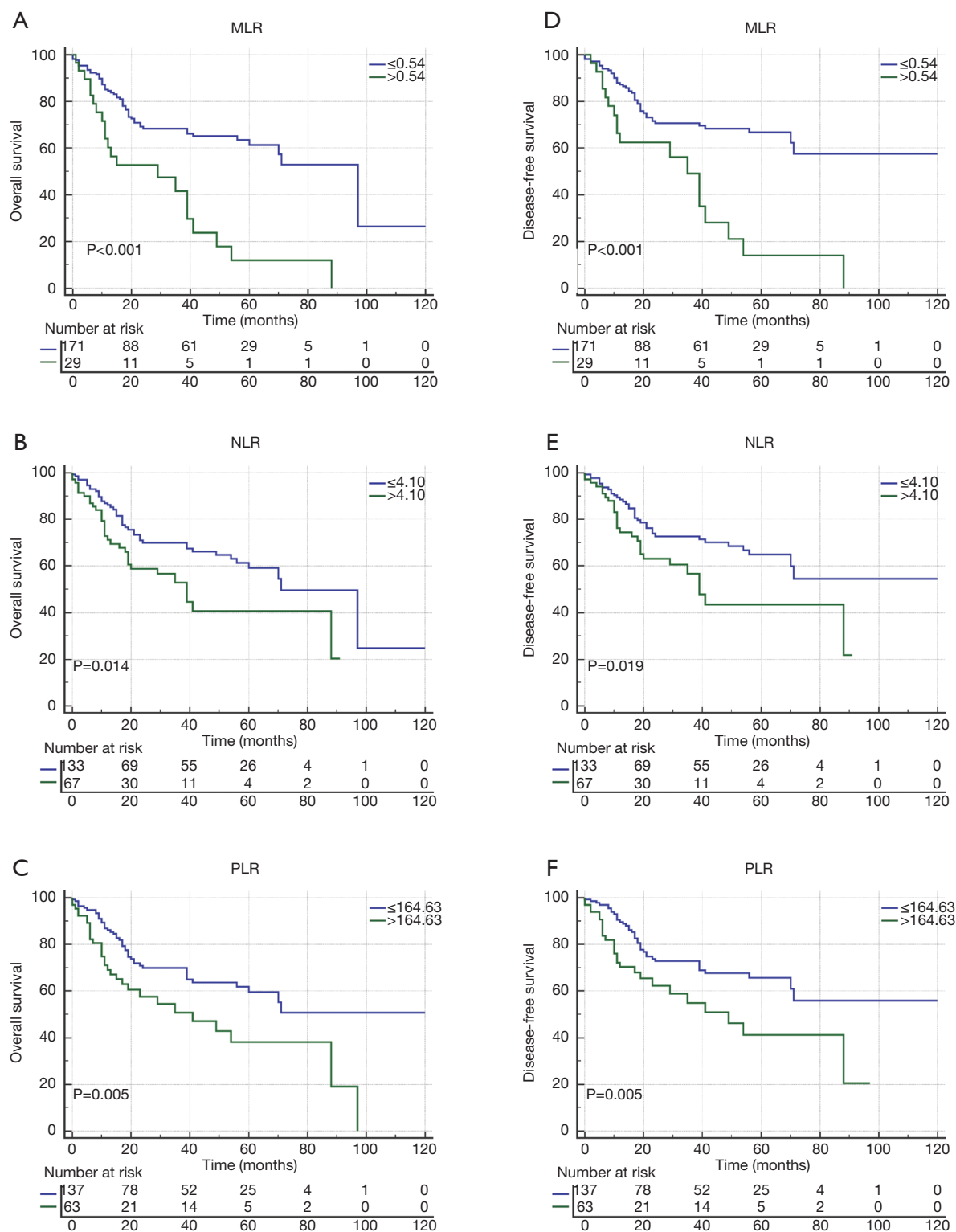


Figure 3 Overall survival and disease-free survival curves of BC patients with RC. (A,B) Overall survival and disease-free survival in high and low MLR group. (C,D) Overall survival and disease-free survival in high and low NLR group. (E,F) Overall survival and disease-free survival in high and low PLR group. BC, bladder cancer; RC, radical cystectomy; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 4 Univariate and multivariate analyses of factors associated with DFS

Characteristics	Univariate analyses		Multivariate analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
≤65	Reference			
>65	1.51 (0.91–2.49)	0.108		
BMI (kg/m ²)				
≤24	Reference			
>24	0.65 (0.38–1.11)	0.114		
Sex				
Male	Reference			
Female	0.92 (0.44–1.93)	0.821		
CCI				
≤2	Reference			
>2	0.83 (0.50–1.39)	0.481		
T-stage				
Ta/Tis /T1	Reference		Reference	
T2	4.12 (1.72–9.85)	0.001	4.00 (1.67–9.60)	0.002
T3	6.73 (2.97–15.25)	<0.001	4.76 (2.05–11.08)	<0.001
T4	9.59 (4.20–21.92)	<0.001	5.46 (2.20–13.58)	<0.001
N-stage				
N0	Reference		Reference	
N+	3.79 (2.22–6.45)	<0.001	2.16 (1.18–3.96)	0.013
M-stage				
M0	Reference		Reference	
M1	3.55 (1.42–8.90)	0.007	3.46 (1.32–9.08)	0.012
Grade				
Low grade	Reference			
High grade	2.02 (0.63–6.49)	0.236		
MLR				
≤0.54	Reference		Reference	
>0.54	2.92 (1.69–5.06)	<0.001	2.13 (1.21–3.75)	0.009
NLR				
≤4.10	Reference		Reference	
>4.10	1.80 (1.09–2.96)	0.021	–	0.784
PLR				
≤164.63	Reference		Reference	
>164.63	2.03 (1.23–3.35)	0.006	–	0.371

HR, hazard ratio; DFS, disease-free survival; CI, confidence interval; BMI, body mass index; CCI, comprehensive complication index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

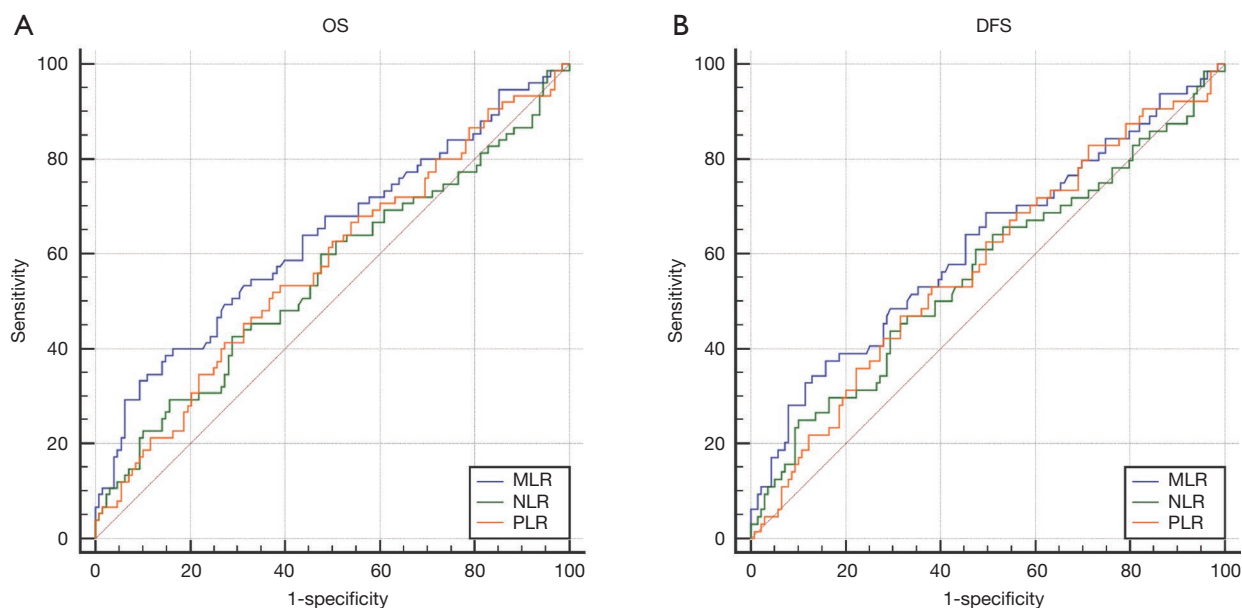


Figure 4 Receiver operating characteristic (ROC) curves for overall survival (A) and disease-free survival (B).

Table 5 Analysis of predictive accuracy through the evaluation of AUC

Ratio	OS			DFS		
	AUC	P value	95% CI	AUC	P value	95% CI
MLR	0.635	0.001*	0.554–0.717	0.617	0.008*	0.530–0.703
NLR	0.554	0.198	0.469–0.639	0.562	0.160	0.473–0.650
PLR	0.575	0.075	0.493–0.657	0.575	0.087	0.490–0.660

*, $P < 0.05$. AUC, area under the curve; OS, overall survival; DFS, disease-free survival; CI, confidence interval; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Immunotherapy is a rising tumor therapy program in recent years (28). At present, people have a deeper understanding of the anti-tumor effect of the immune system. After recognizing tumor-associated antigens, the body can induce the activation, proliferation and migration of cytotoxic T cell (cytotoxic T lymphocyte, CTL) and other effector cells, and kill tumor cells, thus giving full play to the anti-tumor effect of the immune system (29). Lymphocytes are a kind of white blood cells and an important cellular component of the immune response function of the body. And it is helpful for the body to resist the invasion of tumor (30). Lymphocytes can induce apoptosis and inhibit tumor growth, and kill tumor cells through cytotoxicity (31,32). The number of lymphocytes in patients with invasive BC is significantly lower than that in patients with superficial BC (33). And a higher number of

tumor infiltrating cytotoxic T lymphocyte (TILs) can better improve the prognosis of patients with BC (34). This shows that the decrease of lymphocytes can lead to abnormal immune function, and then reduce the immunity of the body to tumor.

At present, monocytes have become an important regulator of the development and progression of cancer (35). Tumor cells induce monocytes to differentiate into tumor-related macrophages (TAMs), by secreting cytokines and chemokines to coordinate the recruitment and function of other immune cells, thus promoting tumor proliferation and migration (36,37).

As a comprehensive index, MLR can well reflect the expression of monocytes and lymphocytes *in vivo*. When MLR increases, it indicates that monocytes increase, lymphocytes relatively decrease, and tumors are easy to

proliferate and migrate. On the other hand, the immunity of the body is relatively weakened. Therefore, there is a certain relationship between MLR and the prognosis of patients, which is consistent with our results. All in all, according to our study, compared with NLR and PLR, MLR is a better predictor of prognosis in patients with BC and can be a potential risk predictor.

We admit our research has some limitations. First of all, as a retrospective study, our study inevitably has selective bias. In addition, the factors affecting the prognosis of BC include the effectiveness of surgery and adjuvant treatment after operation, which are not taken into account. In the follow-up study, we hope to conduct larger, multicenter, and prospective studies to further verify the results through more abundant and perfect data analysis.

Conclusions

Our results show that compared with NLR and PLR, elevated MLR is an independent prognostic biomarker of DFS and OS in patients with BC after RC. The application of easily available MLR is helpful to determine the patients with higher DFS and OS. The patients with higher MLR should be reexamined more frequently and receive more active treatment before operation.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-1060>).

[org/10.21037/tcr-20-1060](http://dx.doi.org/10.21037/tcr-20-1060)). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Tenth People's Hospital of Shanghai (SHSY-IEC-KY-4.0/18-68/01) and informed consent was taken from all the patients.

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