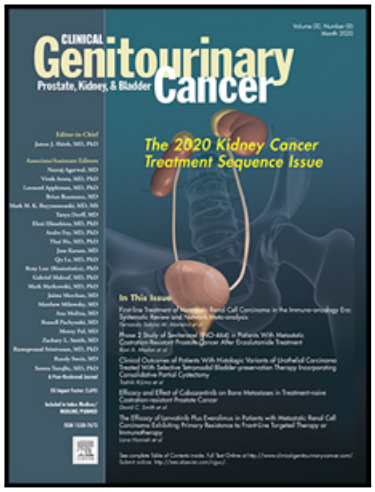
Journal Pre-proof



Systemic Immune-inflammation Index (SII) during Induction has Higher Predictive Value Than Preoperative SII in Non-muscle-invasive Bladder Cancer Patients Receiving Intravesical Bacillus Calmette -Guerin

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Clinical Practice Points

- Urologists are continually devoted to finding a powerful prognostic factor to screen out patients who have no response to BCG and should accept early aggressive treatment. The prognostic value of the ISII remains unclear in NMIBC patients receiving BCG, which might be a power predictor.

- This study respectively collected data from 362 NMIBC patients receiving BCG treatment in our institution to determine and compare the prognostic value of the ISII, PSII and PISII.

- This study first found that ISII could independently predict the prognosis of NMIBC patients receiving BCG.

- ISII was associated with higher prognostic value than PSII and PISII, which might help to select an optimal treatment schedule for patients with NMIBC.

Systemic Immune-inflammation Index (SII) during Induction has Higher Predictive Value Than Preoperative SII in Non-muscle-invasive Bladder Cancer Patients Receiving Intravesical Bacillus Calmette -Guerin

Running Title: SII and non-muscle-invasive bladder cancer.

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Abstract.

Background: The prognostic value of the systemic immune-inflammation index during induction (ISII) remains unclear in non-muscle-invasive bladder cancer (NMIBC) patients receiving Bacillus Calmette-Guérin (BCG). We aimed to determine and compare the prognostic value of the ISII, preoperative systemic immune-inflammation index (PSII) and their dynamic changes (PISII).

Methods: This study respectively collected data from 362 NMIBC patients receiving BCG treatment in our institution. The prognostic values of PSII, ISII and PISII were analyzed by the Kaplan–Meier method and Cox proportional hazard regression models. The concordance index and receiver operating characteristic curve analysis were employed to compare the prognostic value of these three factors.

Results: Our study enrolled 197 patients. These patients included 170 male patients, and the mean age was 64.17 years. During the follow-up time, 85 patients experienced recurrence and 55 patients found progression. According to the results of Cox multivariable analysis, PSII (P=0.001) and ISII (P<0.001) could independently predict the recurrence of NMIBC patients receiving BCG. Meanwhile, PSII (P=0.025) and ISII (P<0.001) were also independent prognostic factors of progression. Compared with PSII, ISII was associated with better accuracy for NMIBC patients receiving BCG.

Conclusions: This study first found that ISII could independently predict the prognosis of NMIBC patients receiving BCG. Furthermore, we also identified that ISII was associated with higher prognostic value than PSII and PISII, which might help to select an optimal treatment schedule for patients with NMIBC.

Keywords: Non-muscle-invasive bladder cancer; Bacillus Calmette-Guérin; Systemic immune-inflammation index;

Micro-abstract

The prognostic value of the systemic immune-inflammation index during induction (ISII) remains unclear in non-muscle-invasive bladder cancer (NMIBC) patients receiving Bacillus Calmette-Guérin (BCG). This study first found that ISII could independently predict the prognosis of NMIBC patients receiving BCG, which might help to select an optimal treatment schedule for patients with NMIBC.

Introduction

Bladder cancer is the 10th most commonly diagnosed carcinoma worldwide and caused 213,000 deaths in 2020 [1]. Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 70% of newly diagnosed bladder cancers and easily recurs and progress after transurethral resection of bladder tumor (TURBT). Fortunately, since Bacillus Calmette-Guérin (BCG) was used clinically, the rates of recurrence and progression have obviously declined in recent decades. Nevertheless, almost 30% of NMIBC patients do not respond to BCG treatment[2]. For patients with BCG failure or high-risk patients, various aggressive therapies are employed to improve their prognosis. For instance, some urologists suggested that patients with BCG failure or high-risk patients might accept early radical cystectomy rather than intravesical therapies[2-4]. However, radical cystectomy has considerable morbidity, even in high-volume centers of excellence and regardless of open versus robotic approaches[3, 5, 6]. Given this condition, urologists must weigh carefully to determine whether aggressive treatments should be performed. Thus, urologists are continually devoted to finding a powerful prognostic factor to screen out patients who have no response to

BCG and should accept early aggressive treatment.

It is widely reported that the preoperative systemic immune-inflammation index (PSII) can independently predict the prognosis of many malignant tumors, such as lung, hepatocellular, kidney and prostate cancers[7]. Recent evidence suggests that PSII can be an independent prognostic factor for NMIBC patients receiving BCG and is associated with pathological features[8-10]. Trained immunity is an important mechanism mediating BCG immunotherapy[11]. Cytokines, including IL-1β, TNF, IL-10 and GM-CSF, are significantly increased after the first BCG instillation[12, 13] and can also predict the recurrence of patients receiving BCG[14]. Neutrophils and lymphocytes are the main components of trained immunity and are significantly increased after the first BCG instillation[12]. Thus, we reasonably assumed that the systemic immune-inflammation index during induction (ISII) might be a powerful prognostic factor for NMIBC patients receiving BCG. However, no study has reported the prognostic value of ISII in patients who received BCG.

To clarify the prognostic value of the ISII, we collected data from NMIBC patients receiving BCG treatment in our institution after approval by ethics committee. The first purpose was to identify the prognostic value of PSII, ISII and their dynamic change (PISII). The second purpose was to compare the prognostic value of these three factors.

Materials and Methods

Patient selection and data collection

We collected the data of NMIBC patients receiving BCG in our hospital from 2014 to 2020 after approval by our institutional ethics committee (approval number: 20201045). Patients included in our study should have blood cell data before surgery and during BCG induction. PSII or ISII=neutrophil count (109/L) *platelet count (109/L)/lymphocyte count (109/L). In detail, PSII should be determined two weeks before surgery, while ISII was generated by blood counts measured during BCG induction. PISII=PSII/ISII. The exclusion criteria for selecting the patients were as

follows: patients with diseases that could affect the results of blood counts (such as prostatitis, cystitis, urinary tract infection, yeast infections, endometriosis and systemic inflammatory disease), those with missing data, other sites of carcinoma, and those who received other intravesical chemotherapy (except immediate single instillation after TURBT).

Experienced pathologists carefully evaluated all specimens included in this study. Pathological information, including tumor stage, World Health Organization (WHO) grade and carcinoma in situ (CIS), was reviewed referring to the 2016 WHO bladder cancer classification[15] and the 2016 American Joint Committee on Cancer[16]. Of these, NMIBC would be considered as histological variant (HV) NMIBC if any HV appeared in the specimens. Moreover, demographic and clinical outcomes were also determined in this study.

Patient management and follow-up

All patients in this study received intravesical BCG therapy. Specifically, induction BCG instillations were performed once a week for 6 weeks. After BCG induction, at least one year of maintenance instillations would be given every fortnight if the patient's condition permits[2]. Patients accepted cystoscopy and urinary cytology every 3 months for the first year, every 6 months 2 to 5 years after TURBT, and then annually. Moreover, imaging and laboratory examination were performed if patients were in need. Recurrence-free survival (RFS) was defined the time from the date of surgery to local or distant recurrence. Progression-free survival (PFS) was defined as an increase in the stage to MIBC and/or metastasis.

Statistical analysis

Categorical and continuous variables between groups were analyzed using Chi-square and Studentôs t-tests, respectively. Fisherôs exact test was applied to estimate categorical variables when one or more of the cell counts in a 2×2 table were less than 5. The best cut-off values of PSII and ISII were generated by the receiver operating characteristic curve (ROC) and Youden index. The prognosis, including RFS and PFS, was validated by the Kaplan–Meier method, and comparisons between

groups were performed by log-rank tests. Univariable and multivariable Cox proportional hazard regression models were employed to evaluate the association of PSII, ISII and PISII with RFS and PFS. For comparison of the prognostic value of PSII, ISII and PISII, the concordance index (C-index) and multiparameter ROC analysis were used to validate the accuracy of different multivariable Cox proportional hazard regression models. A $P<0.05$ was considered significant for all analyses, which were performed using R version 3.6.3 and relative packages.

Results

Demographic and clinicopathologic characteristics

Our study finally selected 197 patients from 362 NMIBC patients receiving BCG. The mean ± standard deviation (SD) follow-up time was 30.18±15.67 months. For PSII and ISII, the optimal cut-off values were 557 and 517, respectively. Then, referring to the cut-off value, all patients were divided into high and low groups. In PISII, patients with PISII>1 were regarded as the high PISII group, and the others were regarded as low PISII group. A total of 21/197 (10.6%) patients exhibited side effects, with cystitis being the most common. To compare the difference between the high and low groups, Table 1 showed that patients in the high ISII group were associated with a large tumor size, and there were more patients with hypertension than in the low ISII group. Patients in the high PISII group were positively correlated with tumor number. The remaining detailed information was provided in Table 1.

The relationship between RFS and PSII, ISII and PISII

There were 85/197 (43.1%) patients who were diagnosed with recurrence during follow-up. The results of the Chi-square analysis showed that patients with high PSII were associated with a significantly higher recurrence rate (Table 1, P=0.006). The correlation between RFS and PSII was also identified by the results of log-rank tests (Figure 1A, P=0.004) and univariable analysis (Figure 2A, P=0.001). Moreover, multivariable analysis demonstrated that PSII was an independent prognostic factor of NMIBC patients receiving BCG (Figure 2B, P=0.005).

For ISII, patients with high ISII were positively related to the recurrence rate according to the results of Chi-square analysis (Table 1, P<0.001). Similarly, the relationship between RFS and ISII was identified by the results of log-rank tests (Figure 1B, P<0.001) and univariable analysis (Figure 2A, P<0.001). Further multivariable analysis illustrated that ISII was an independent prognostic factor of NMIBC patients receiving BCG (Figure 2C, P<0.001). There was no significant difference in RFS between the high and low PISII groups according to the results of the Chi-square analysis (Table 1, P=0.448), log-rank tests (Figure 1C, P=0.308), univariable analysis (Figure 2A, P=0.309) and multivariable analyses (Figure 2D, P=0.854).

The relationship between PFS and PSII, ISII and PISII

The total number of progressions was 55/197 (27.9%) at the end of follow-up. Based on Chi-square analysis, patients with high PSII were positively associated with the recurrence rate (Table 1, P=0.012). It was easier for patients in the high PSII group to progress according to log-rank tests (Figure 1D, P=0.006) and univariable analysis (Figure 3A, P=0.007). Further multivariable analysis indicated that PSII could independently predict the prognosis of NMIBC patients receiving BCG (Figure 3B, P=0.025).

Compared with the low ISII group, the high ISII was positively associated with the progression rate according to the Chi-square analysis (Table 1, P<0.001), log-rank tests (Figure 1E, P<0.001) and univariable analysis (Figure 3A, P<0.001). Furthermore, ISII was an independent prognostic factor for NMIBC patients receiving BCG (Figure 3C, P<0.001). PISII could not be a predicter for progression according to Chi-square analysis (Table 1, P=0.408), log-rank tests (Figure 1F, P=0.089), univariable analysis (Figure 3A, P=0.093) and multivariable analysis (Figure 3D, P=0.537).

Validation of the accuracy and reliability of PSII and ISII

For recurrence, the area under curve (AUC) value of ISII was 0.624, 0.701, and 0.759 in 1, 2, 3 years, respectively (Figure 4A). The AUC value of PSII was lower

than that of ISII, which was 0.622, 0.661, and 0.667 in 1, 2, 3 years, respectively (Figure 4B). Meanwhile, the model including ISII (C-index=0.665, 95% confidence interval (CI)=0.632-0.698) had higher accuracy than PSII (C-index=0.633, 95%CI=0.601-0.664). For progression, the AUC value of ISII (Figure 4C) was higher than that of PSII (Figure 4D). Similarly, ISII showed higher accuracy (C-index=0.737, 95%CI=0.700-0.775) than PSII (C-index=0.685, 95%CI=0.647-0.722).

Discussion

The prognostic value of PSII has widely attracted the attention of doctors. Therefore, urologists also intend to clarify the role of PSII in BCG treatment to screen out NMIBC patients who may fail to response to BCG. In the current study, we not only identified that PSII had independent prognostic ability but also illustrated for the first time that ISII could independently predict the prognosis of NMIBC patients receiving BCG. Furthermore, compared with the PSII and PISII, the ISII was a better prognostic factor for NMIBC patients receiving BCG.

Tumor-related inflammation has been widely studied and listed as a major phenotype of malignant tumors[17]. Meanwhile, inflammatory and immune cells are important parts of the tumor microenvironment and indispensable factors in promoting tumor proliferation, tumor progression, survival and migration[18]. Bladder cancer is an inflammation- and immune-related malignant tumor. The inflammatory and immune environments of peripheral blood and tumors are significantly changed during BCG induction[11]. Therefore, it is important for urologists to clarify the role of peripheral immune cells in NMIBC.

Similar to prostate-specific antigen, a widely recognized cut-off value can significantly promote the clinical application of SII and help doctors select the optimal treatment plan. The optimal cut-off values of PSII and ISII were 557 and 517 in our study, respectively, which were consistent with most studies. Similarly, Ke et al.[10] obtained that the optimal cut-off value of PSII was 439.8 by analyzing NMIBC patients receiving BCG. This value was in agreement with Bi et al.ôs [9] finding,

which suggested that 467.76 was the best cut-off value of PSII by analyzing NMIBC patients receiving BCG. Akan et al. [8] believed that 672 and 624 were the best PSII cut-off values for the recurrence and progression of NMIBC patients receiving BCG, respectively. Moreover, Katayama et al. [19] calculated that the cut-off value of PSII was 580, which enrolled 1117 patients with NMIBC. A study reported that 276.6 was the best cut-off value of PSII in 216 NMIBC patients receiving various chemotherapies[20]. These results suggested that the optimal cut-off value was different among studies. Despite differences, most cut-off values of PSII are usually approximately 500 in patients with NMIBC. This phenomenon was beneficial to the clinical practice of PSII and ISII.

The prognostic value of PSII was first reported in patients undergoing radical cystectomy rather than NMIBC[21]. Subsequent studies also demonstrated the prognostic value of PSII in muscle invasive bladder cancer[22]. An initial objective of the study was to clarify the prognostic value of PSII, ISII and PISII in NMIBC patients receiving BCG. Recently, several studies have reported that PSII could predict the prognosis of patients with NMIBC. For instance, Ke et al[10] illustrated that high PSII was associated with worse RFS according to the results of log-rank tests. This finding was consistent with Zhao et al. [23], who demonstrated that PSII could independently predict the RFS of NMIBC patients receiving various treatments. Similarly, PSII could also independently predict the PFS in patients with NMIBC receiving various chemotherapies by multivariable analysis[19]. This finding was also reported by Akan et al[9] .

Furthermore, high PSII was associated with worse cancer-free survival and overall survival[8]. Consistent with these studies, our study found that patients with high PSII were associated with worse RFS and PFS, again identifying the independent prognostic value of PSII. No study reported the prognostic value of ISII and PISII. In this study, the PISII failed to be an independent prognostic factor for RFS and PFS. In the current study, we first identified that ISII could predict the prognosis of NMIBC patients receiving BCG. Further analysis demonstrated that the model containing the

ISII had higher accuracy than the model including the PISII. ISII was generated by blood tests measured during BCG induction so that NMIBC patients could predict the outcome of BCG immunotherapy early and adjust the treatment plan in time. These results supported that the ISII might help urologists to select an optimal treatment schedule for patients with NMIBC.

A few limitations should be mentioned, including those inherent to the retrospective design of the study. The bias of data might be noticed because the data were derived from a hospital information system. Therefore, we used strict exclusion criteria to avoid possible bias. Additionally, though the number of enrolled patients permits us to perform multivariable analysis, prospective and large-scale studies are still required for more representative samples with higher statistical power.

Conclusion

This study first found that the ISII could independently predict the prognosis of NMIBC patients receiving BCG treatment. Furthermore, compared with the PSII and PISII, the ISII had better prognostic value, which might help select an optimal treatment schedule for patients with NMIBC. Of course, prospective and large-scale studies are still required for more representative samples with higher statistical power.

Author contributions

Conceptualization, DL and QY; formal analysis, DL and DF; funding acquisition, PH; investigation, DL, DF, FZ, RW, QY; methodology, QYand FZ; resources, DF; supervision, PH.; visualization, XS; writing-original draft, DL; writing-review & editing, DF and PH.

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Ethical considerations

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 board of West China Hospital, Sichuan University (No. 20201045) and informed consent was taken from all the patients.

Conflicts of Interest:

The authors declare no conflicts of interest.

Acknowledgments

None.

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Figure Legends

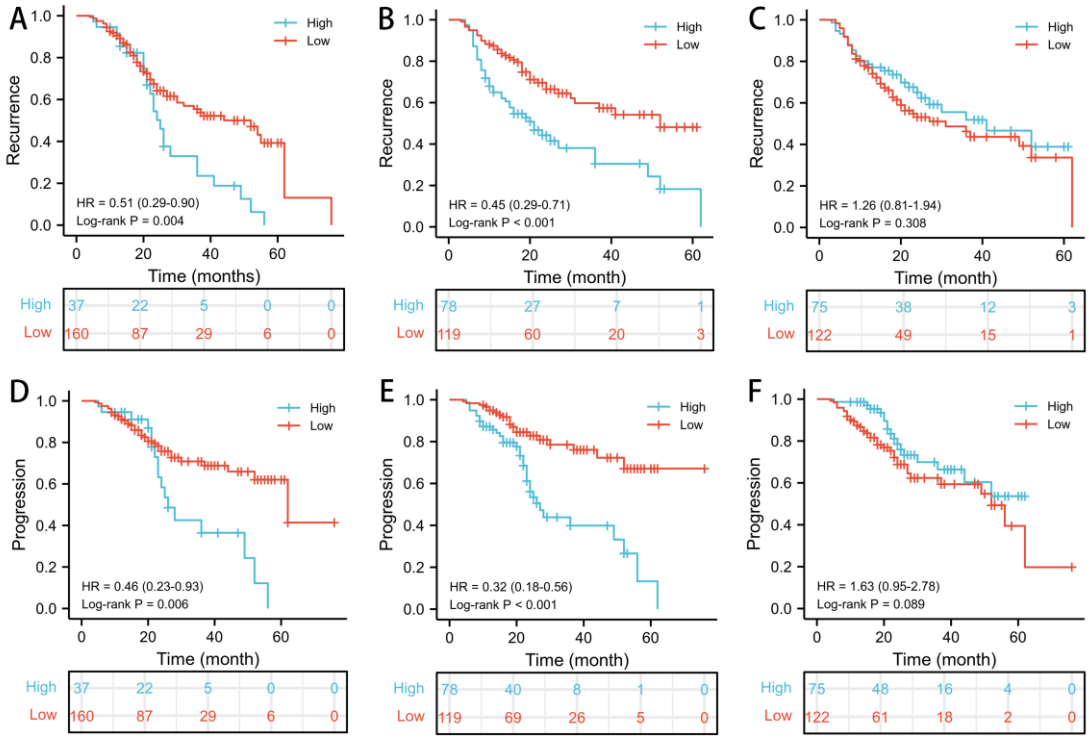

Figure 1. Kaplan-Meier estimates for recurrence and progression

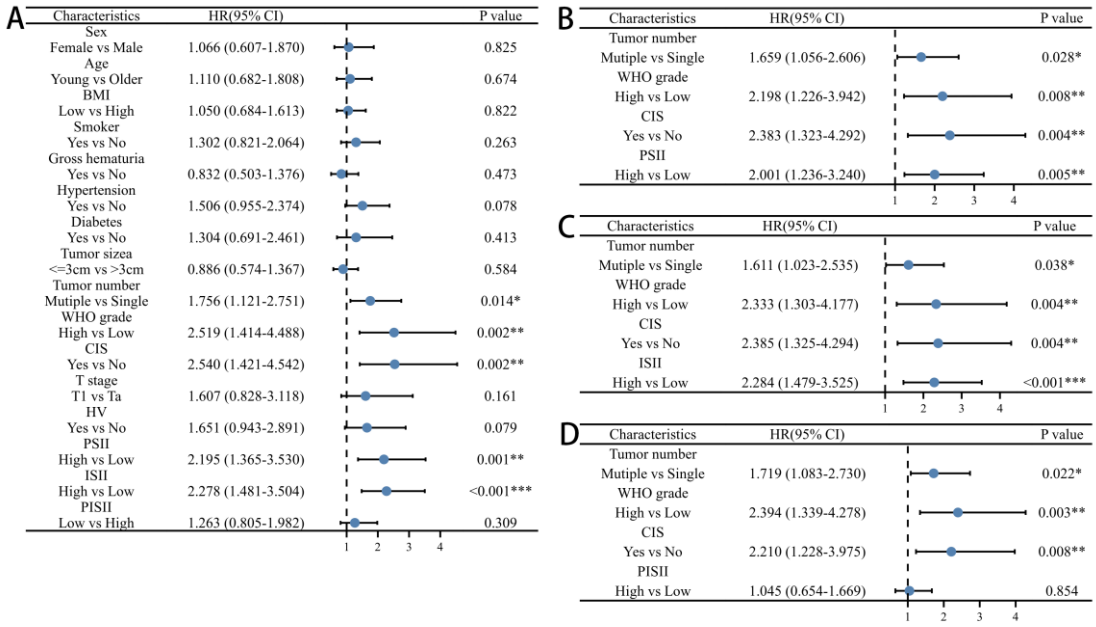

Figure 2. Univariate and multivariate Cox Proportional Hazard model for recurrence: A: univariate results, B: multivariate results with PSII, C: multivariate results with ISII, D: multivariate results with PISII. PSII: Preoperative systemic immune-inflammation index; ISII: Systemic immune-inflammation index during induction; PISII: Preoperative dividing by induction systemic immune-inflammation index; *: P<0.05; **:P<0.01; ***:P<0.001;

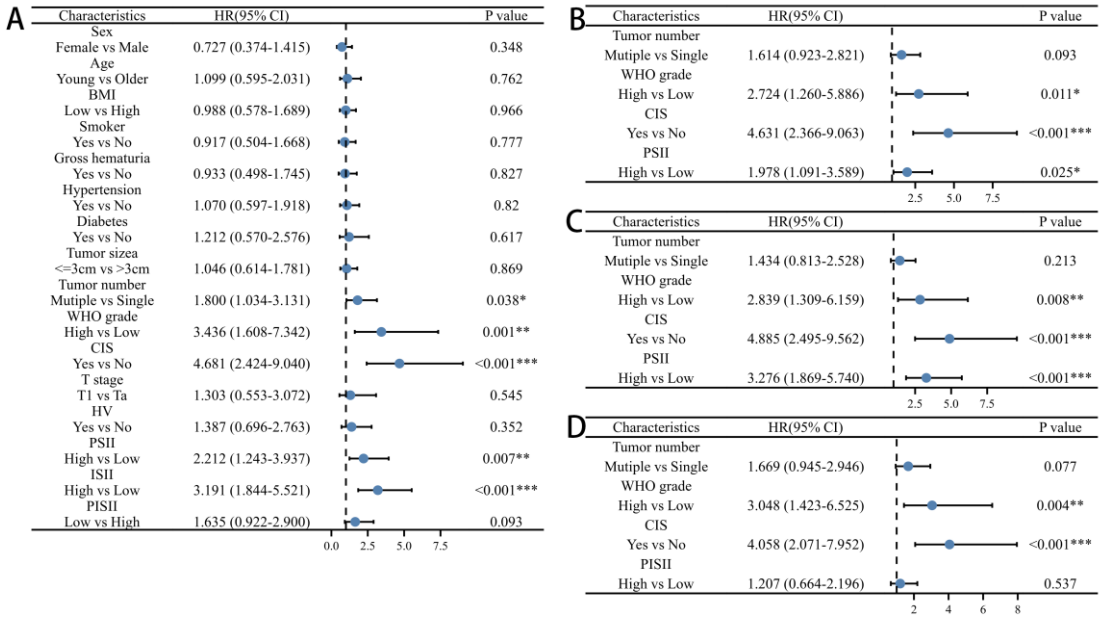

Figure 3. Univariate and multivariate Cox Proportional Hazard model for progression: A: univariate results, B: multivariate results with PSII, C: multivariate results with

ISII, D: multivariate results with PISII. PSII: Preoperative systemic immune-inflammation index; ISII: Systemic immune-inflammation index during induction; PISII: Preoperative dividing by induction systemic immune-inflammation index; *: P<0.05; **:P<0.01; ***:P<0.001;

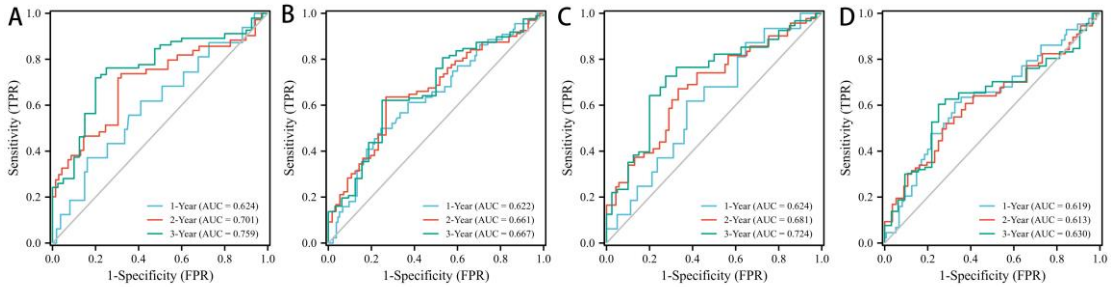

Figure 4. The ROC plots of ISII (A), PSII (B) in recurrence. The ROC plots of ISII (C), PSII (D) in progression. PSII: Preoperative systemic immune-inflammation index; ISII: Systemic immune-inflammation index during induction;

Table 1. Demographic and clinicopathologic characteristics.

	Total	PSII			ISII			PISII		
	197	Low (160)	High (37)	P value	Low (119)	High (78)	P value	Low (75)	High (122)	P value
Sex				0.820			0.936			0.448
Female	27(13.7%)	21 (10.7%)	6 (3%)		17 (8.6%)	10 (5.1%)		8 (4.1%)	19 (9.6%)	
Male	170(86.3%)	139 (70.6%)	31 (15.7%)		102 (51.8%)	68 (34.5%)		67 (34%)	103 (52.3%)	
Age	64.17 ±11.05	64.53 ± 11.0	62.59 ± 11.45	0.339	63.89 ± 11.2	64.59 ± 10.95	0.666	64.77 ± 11.68	63.8 ± 10.73	0.549
BMI	23.65 ±3.04	23.8 ± 2.93	22.98 ± 3.47	0.142	23.97 ± 2.84	23.15 ± 3.3	0.063	23.69 ± 3.28	23.62 ± 2.91	0.864
Smoker				0.6			0.5			0.4

				28			06		76
		112	28		82	58	56	84	
	140(71.1%)	(56.9%)	(14.2%)		(41.6%)	(29.4%)	(28.4%)	(42.6%)	
No		48	9		37	20	19	38	
	57(28.9%)	(24.4%)	(4.6%)		(18.8%)	(10.2%)	(9.6%)	(19.3%)	
Yes									
Gross hematuria				0.623			0.555		0.725
		39	7		30	16	16	30	
	46(23.4%)	(19.8%)	(3.6%)		(15.2%)	(8.1%)	(8.1%)	(15.2%)	
No		121	30		89	62	59	92	
	151(76.6%)	(61.4%)	(15.2%)		(45.2%)	(31.5%)	(29.9%)	(46.7%)	
Yes									
Hypertension				0.470			0.011		0.796
		116	24		93	47	52	88	
	140(71.1%)	(58.9%)	(12.2%)		(47.2%)	(23.9%)	(26.4%)	(44.7%)	
No		44	13		26	31	23	34	
	57(28.9%)	(22.3%)	(6.6%)		(13.2%)	(15.7%)	(11.7%)	(17.3%)	
Yes									
Diabetes				0.177			0.294		0.654
		137	35		101	71	67	105	
	172(87.3%)	(69.5%)	(17.8%)		(51.3%)	(36%)	(34%)	(53.3%)	
No		23			18	7	8	17	
	25(12.7%)	(11.7%)	2 (1%)		(9.1%)	(3.6%)	(4.1%)	(8.6%)	
Yes									
Tumor size[a]				0.670			0.008		0.285
		91	19		76	34	46	64	
	110(55.8%)	(46.2%)	(9.6%)		(38.6%)	(17.3%)	(23.4%)	(32.5%)	
<=3cm			18		43	44	29	58	
	87(44.2%)	69 (35%)	(9.1%)		(21.8%)	(22.3%)	(14.7%)	(29.4%)	
>3cm									
Tumor number				0.179			0.297		0.046
	86(43.7%)	74 (37.6	12 (6.1		56 (28.4	30 (15.2	40 (20.3	46 (23.4	
Single									

		%)	%)		%)	%)		%)	%)	
		86	25			48		35	76	
	111(5	(43.7	(12.7		63	(24.4		(17.8	(38.6	
Multiple	6.3%)	%)	%)		(32%)	%)		%)	%)	
WHO				0.7			0.6			0.1
grade				36			78			36
		46	9		35	20		26	29	
	55(27	(23.4	(4.6		(17.8	(10.2		(13.2	(14.7	
Low	.9%)	%)	%)		%)	%)		%)	%)	
		114	28		84	58		49	93	
	142(7	(57.9	(14.2		(42.6	(29.4		(24.9	(47.2	
High	2.1%)	%)	%)		%)	%)		%)	%)	
				0.3			0.4			0.2
CIS				12			29			21
		146	36		108	74		72	110	
	182(9	(74.1	(18.3		(54.8	(37.6		(36.5	(55.8	
No	2.4%)	%)	%)		%)	%)		%)	%)	
		14	1		11			3	12	
	15(7.	(7.1%	(0.5		(5.6%	4		(1.5	(6.1%	
Yes	6%)	)	%)		)	(2%)		%)	)	
				0.6			1.0			0.4
T stage				54			00			07
		31	9		24	16		18	22	
	40(20	(15.7	(4.6		(12.2	(8.1		(9.1	(11.2	
Ta	.3%)	%)	%)		%)	%)		%)	%)	
		129	28		95	62		57	100	
	157(7	(65.5	(14.2		(48.2	(31.5		(28.9	(50.8	
T1	9.7%)	%)	%)		%)	%)		%)	%)	
Histolog				0.5			0.9			0.1
y				91			29			18
		140	31		104	67		61	110	
	171(8	(71.1	(15.7		(52.8	(34%		(31%	(55.8	
No HV	6.8%)	%)	%)		%)	)		)	%)	
		20			15	11		14	12	
	26(13	(10.2	6		(7.6%	(5.6		(7.1	(6.1%	
HV	.2%)	%)	(3%)		)	%)		%)	)	
							<			
Recurre				0.0			0.0			0.3
nce				06			01			97
		99	13		80	32		46	66	
	112(5	(50.3	(6.6		(40.6	(16.2		(23.4	(33.5	
No	6.9%)	%)	%)		%)	%)		%)	%)	
	85(43	61	24		39	46		29	56	
Yes	.1%)	(31%)	(12.2		(19.8	(23.4		(14.7	(28.4	

			%)		%)	%)	%)	%)	
Progression				0.012		< 0.001			0.261
No	142(72.1%)	122 (61.9 %)	20 (10.2 %)		98 (49.7 %)	44 (22.3 %)	58 (29.4 %)	84 (42.6 %)	
Yes	55(27.9%)	38 (19.3 %)	17 (8.6 %)		21 (10.7 %)	34 (17.3 %)	17 (8.6 %)	38 (19.3 %)	

[a]: For multiple tumors, the diameter of the largest tumor was regarded as tumor size.

BMI: Body mass index; WHO: World Health Organization; CIS: Carcinoma in situ; HV: Histological variant; PSII: Preoperative systemic immune-inflammation index; ISII: Systemic immune-inflammation index during induction; PISII: Preoperative dividing by induction systemic immune-inflammation index.

Abbreviations

PSII: Preoperative systemic immune-inflammation index.

ISII: Systemic immune-inflammation index during induction.

PISII: Preoperative dividing by induction systemic immune-inflammation index.

TURBT: Transurethral resection of bladder tumor.

NMIBC: Non-muscle-invasive bladder cancer.

BCG: Bacillus Calmette-Guérin.

HV: Histological variant.

WHO: World Health Organization.

SD: Standard Deviation.

HR: Hazard ratio.

BMI: Body mass index.

CI: Confidence level.

RFS: Recurrence-free survival;

PFS: Progression-free survival;