

Preoperative Prognostic Nutritional Index and Systemic Immune-Inflammation Index for Predicting the Long-Term Recurrence-Free Survival of Patients with High-Risk Non-Muscle-Invasive Bladder Cancer After Transurethral Resection of a Bladder Tumour: A Cohort Study

Huifeng Bi

Department of Urology, Xuanwu Hospital Capital Medical University. 2:Department of Urology, Jincheng General Hospital

Chunsong Jia

Department of Urology, Xuanwu Hospital Capital Medical University

Zhenhua Shang

Department of Urology, Xuanwu Hospital Capital Medical University

Zhongwen Feng

Department of Urology, Jincheng General Hospital

Xinrong Ning

Broadgreen Hospital Department of Urology

Tongwen Ou (✉ outongwen1967@126.com)

Xuanwu Hospital <https://orcid.org/0000-0001-8055-9418>

Research

Keywords: Prognostic nutritional index, Systemic immune-inflammation index, Recurrence-free survival, Non-muscle-invasive bladder cancer, Transurethral resection of bladder tumour, Bacillus Calmette-Guerin

Posted Date: May 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-463437/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background The predictive values of preoperative prognostic nutritional index (PNI) and systemic immune-inflammation index (SII) for long-term recurrence-free survival (RFS) in high-risk non-muscle-invasive bladder cancer (NMIBC) have not been fully elucidated. Hence, this study aimed to examine the associations between PNI and SII as well as RFS in patients with high-risk NMIBC who received intravesical instillation of Bacillus Calmette–Guerin (BCG) after transurethral resection of bladder tumour (TURBT).

Methods We retrospectively collected data on 387 high-risk NMIBC patients between January 2004 and December 2014. Preoperative PNI was calculated as albumin concentration (g/L)+5×total lymphocyte count ($10^9/L$), while preoperative SII was defined as neutrophil count ($10^9/L$)×platelet count ($10^9/L$)/lymphocyte count ($10^9/L$). The optimal cut-off values of PNI and SII were determined via a receiver operating characteristic analysis. RFS was evaluated via a Kaplan–Meier analysis. Between-group differences were compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed to assess the predictive values of PNI and SII for RFS.

Results Patients were divided into two groups according to the cut-off values of PNI (<50.17 vs ≥ 50.17) and SII (<467.76 vs ≥ 467.76). Kaplan-Meier analyses revealed that low PNI and high SII were associated with poor RFS in patients with high- and higher-risk NMIBC. Furthermore, based on univariate and multivariate Cox regression analyses, PNI and SII were independent predictive factors of RFS in patients with high-risk NMIBC.

Conclusion Preoperative PNI and SII are simple, noninvasive, inexpensive and useful tools for predicting long-term RFS among patients with high-risk NMIBC who received intravesical instillation of BCG after TURBT.

Background

Bladder cancer (BC) has been identified as the 7th most frequent cancer in the male population and 11th when considering both genders [1]. It ranks as the ninth leading cause of cancer deaths in the male population worldwide as BC is more common in men than in women, with respective incidence and mortality rates of 9.6 and 3.2 per 100,000 [2]. The mortality and morbidity of BC vary across countries and regions due to differences in related risk factors, detection and diagnostic practices and availability of treatments. BC is classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) subtypes according to distinct clinical recurrence, progression and prognosis. Approximately 75% of BC patients present with a disease confined to the mucosa or submucosa and are eventually diagnosed with NMIBC [3]. The NMIBC subtype can be further distinguished as Ta (non-invasive papillary carcinoma), T1 (tumour invading subepithelial connective tissue) or carcinoma in situ (CIS, ‘flat tumour’). The European Association of Urology (EAU) Guidelines 2019 defined the high-risk NMIBC group as follows: (1) T1 tumours; (2) G3 (high-grade [HG]) tumours; (3) CIS and (4) multiple,

recurrent and large (>3 cm) TaG1G2/low-grade tumours (all features must be present) [4]. In addition, based on prognostic factors, the highest-risk NMIBC subgroup includes T1G3/HG tumours associated with concurrent bladder CIS; multiple and/or large T1G3/HG and/or recurrent T1G3/HG tumours; T1G3/HG tumours with CIS in the prostatic urethra; some forms of variant histology of urothelial carcinoma; and lymphovascular invasion.

Transurethral resection of bladder tumour (TURBT) is a typical first line treatment for NMIBC patients. Meanwhile, low-risk NMIBCs only undergo TURBT, whereas for intermediate- and high-risk NMIBCs, TURBT with Bacillus Calmette-Guerin (BCG) immunotherapy or chemotherapy is the standard treatment. The clinical behaviour of NMIBC is largely unpredictable, and even patients treated in accordance to EAU recommendations have a heterogeneous prognosis. Often, high-risk NMIBC patients have high rates of disease recurrence and progression to MIBC and BCG treatment failure [5]. As the highest-risk subtype of NMIBC, high-grade T1 (HGT1) BC presents an almost 40% rate of recurrence and 20% of progression at 5 years [6]. Recurrence-free survival (RFS) rates were 54.9%, 55.3% and 60.4% for primary, concomitant and secondary CIS, respectively, at 5-year follow-up. Progression-free survival rates at 5-year follow-up were 65.8%, 72.1% and 77% for primary, concomitant and secondary CIS, respectively [7]. Thus, the stratification of risk groups based on recurrence and progression is a strategy that attempts to individualise and standardise BC patients.

A patient's nutritional and immune status has an important impact on oncological outcomes [8]. The prognostic nutritional index (PNI) was first introduced by Onodera et al. [9] in 1984. It was used to evaluate the risk of postoperative complications among patients with gastric cancer according to baseline nutritional status. Growing evidence has shown that a low PNI score is significantly associated with major postoperative complications and poor prognosis [10,11]. The systemic immune-inflammation index (SII) was first used to evaluate hepatocellular carcinoma and was considered a predictor of several solid tumours, particularly prostate cancer and metastatic non-clear cell renal cell carcinoma [12,13]. The preoperative PNI and SII are identified as effective tumour biomarkers that have important significance in the prognosis of many malignant tumours [14,15]. Considering that the recurrence and progression factors of high-risk NMIBC cannot be precisely identified before or after surgery, which often results in missed timeframes for appropriate and effective clinical therapy, an urgent need arises for new markers predicting the recurrence risks of high-risk NMIBC patients. We have found no relevant research reports on PNI or SII for predicting the long-term recurrence risks of high-risk NMIBC patients. Therefore, this study was conducted to evaluate PNI and SII in predicting the long-term RFS of high-risk NMIBC patients who received intravesical instillation of BCG after TURBT.

Methods

Patient Selection

We retrospectively collected and examined the medical data of 387 patients who met the high-risk NMIBC group criteria and received intravesical instillation of BCG after TURBT at the Department of Urology of

Xuanwu Hospital Capital Medical University, National Clinical Research Centre for Geriatric Diseases from January 2004 to December 2014. Patients who met the following criteria were included in our study: (1) complete clinical and pathological records; (2) conformity to the stratification of high-risk NMIBC; (3) receipt of BCG therapy after TURBT; (4) absence of autoimmune diseases; (5) absence of cancers in other systems; (6) absence of preoperative radiotherapy and neoadjuvant chemotherapy; (7) absence of distant metastasis before surgery and (8) complete follow-up medical data.

Data Collection and Definitions

Clinicopathological data, including gender, age, smoking status, body mass index (BMI), recurrence, tumour number, tumour size, tumour grade, T stage, lymphovascular invasion (LVI), concomitant CIS and preoperative routine laboratory data, were obtained from patients' medical records. The albumin concentration was obtained using the hepatic function test, while the neutrophil, platelet and lymphocyte counts were determined through a routine blood test performed before breakfast within 1-2 weeks before TURBT. PNI was calculated as albumin concentration (g/L) + 5 × total lymphocyte count ($10^9/L$) and SII as neutrophil count ($10^9/L$) × platelet count ($10^9/L$)/lymphocyte count ($10^9/L$).

Follow-up

All 387 patients were regularly followed up with physical examination, blood tests, biochemical tests, urine routine tests and cystoscopy every 3 months for the first 2 years, every 6 months in the following 3 years and annually thereafter. Computed tomography or contrast-enhanced computed tomography was performed every year to assess recurrence in the bladder and upper urinary tract. BCG was performed after TURBT according to the following schedule: induction therapy (weekly BCG instillation for the first 6 weeks) and maintenance therapy for up to 3 years (3 weekly maintenance instillations at 3, 6, 12, 18, 24 and 36 months).

Statistical Analysis

The SPSS software version 25.0 (IBM, Armonk, NY, USA), Sigma Plot version 14.0 for Windows (SysTest Software, Inc., San Jose, CA, USA) and GraphPad Prism version 8.4.2 for Windows (GraphPad Software Inc., San Diego, CA, USA) were used in statistical analyses. Continuous data are shown as the mean ± standard deviation (SD) or median with interquartile range. Categorical variables are presented as frequencies and percentages and were compared using Pearson's chi-squared test. Receiver operating characteristic (ROC) curve analysis was then applied to identify the optimal cut-off values of PNI and SII with the highest Youden's index for predicting the 5-year overall survival (OS). The end point of this retrospective cohort study was the RFS. The Kaplan–Meier method and log-rank test were used to analyse RFS and compare RFS curves. A Cox proportional hazards regression model was used to analyse various independent predictors of postoperative RFS. Univariate analysis was used to assess various factors related to patients' clinicopathological characteristics. Multivariate analysis was performed for variables with $p < 0.1$ in univariate analysis. In two-tailed tests, $p < 0.05$ was considered statistically significant.

Results

Clinicopathological Characteristics of all Patients

In total, 387 high-risk NMIBC patients who were diagnosed after surgery, received intravesical instillation of BCG after TURBT and met the inclusion criteria were enrolled in our study. Of all 387 patients, 277 (71.58%) were male and 158 (40.83%) were current or ex-smokers. The mean \pm SD age and BMI were 69.49 ± 10.84 years and 24.07 ± 3.35 kg/m 2 , respectively. Over half (53.49%) of these patients experienced recurrence, with 214 (55.30%) diagnosed with multifocal tumours. The tumours of 303 (78.29%) patients were <3 cm. Most patients ($n = 263$, 67.96%) were determined to have a high pathological grade, and 260 (67.18%) had T1 stage. Among all 387 patients, 31 (8.01%) had LVI, and 24 (6.20%) had concomitant CIS. Meanwhile, 194 (50.12%) experienced recurrence in the bladder, 13 (3.36%) had recurrence in the upper urinary tract, 82 (21.19%) presented tumour progression and 42 (10.85%) underwent radical cystectomy. The 5-year recurrence rate of all 387 high-risk NMIBC patients and the 5-year recurrence rate of the 90 highest-risk NMIBC patients were 41.86% and 65.56%, respectively. The 5-year cancer-specific mortality and 5-year overall mortality for all 387 patients were 11.78% and 16.80%, respectively. Furthermore, the 5-year cancer-specific mortality and 5-year overall mortality for the highest-risk NMIBC patients were 42.17% and 46.67%, respectively. The median (range) follow-up duration was 108 (5–191) months. The mean \pm SD values of PNI and SII were 51.64 ± 11.67 and 447.46 ± 139.39 , respectively (Table 1).

The Optimal Cut-off Values of PNI, SII and Other Indexes for Estimating Prognosis

The optimal cut-off values of PNI and SII for predicting 5-year OS were determined by ROC curve analysis. As shown in Figure 1, the areas under the curve for 5-year OS were 0.668 (95% CI: 0.599–0.738) and 0.671 (95% CI: 0.604–0.753) for PNI and SII, respectively. The corresponding optimal cut-off values were 50.17 for PNI and 467.76 for SII based on the maximum Youden index. Similarly, the optimal cut-off values for age, BMI, albumin concentration and lymphocyte, neutrophil and platelet counts were 63.5 years, 22.31 kg/m 2 , 42.19 g/L, 1.78×10^9 /L, 4.36×10^9 /L and 235×10^9 /L, respectively. Based on the chosen optimal cut-off values, the 387 patients were divided into the following groups: low PNI group (<50.17; $n = 116$) or high PNI group (≥ 50.17 ; $n = 271$) and low SII group (<467.76; $n = 242$) or high SII group (≥ 467.76 ; $n = 145$).

Correlations Between PNI, SII and Clinicopathological Parameters

The correlations between preoperative PNI and SII and patient clinicopathological parameters are provided in Table 2. We have found that patients with low PNI (<50.17) were associated with a younger age ($p = 0.009$), lower BMI ($p = 0.006$), higher recurrence frequency ($p = 0.002$), higher tumour number ($p = 0.048$), larger tumour size ($p < 0.001$), higher tumour grade ($p = 0.001$), more advanced T stage ($p < 0.001$), more common LVI ($p = 0.006$) and concomitant CIS ($p = 0.002$). Patients with high SII (≥ 467.76) were more likely to have lower BMI ($p = 0.007$), higher recurrence frequency ($p = 0.005$), higher tumour number ($p = 0.007$), larger tumour size ($p < 0.001$), higher tumour grade ($p = 0.033$), more advanced T

stage ($p = 0.005$), more common LVI ($p = 0.004$) and concomitant CIS ($p = 0.009$). However, no significant relationships were observed in terms of gender ($p > 0.05$) or smoking status ($p > 0.05$). Interestingly, no association between SII and age ($p > 0.05$) was observed in this cohort study.

Associations between PNI and SII as well as RFS in Patients with High- and Highest-risk NMIBC

Patients were divided into two groups based on preoperative PNI (<50.17 vs ≥ 50.17) and SII (<467.76 vs ≥ 467.76). RFS was significantly lower in the low PNI group than in the high PNI group, and a low SII was correlated with better RFS, as shown in Figures 2A and 2B.

We further examined whether PNI and SII were associated with RFS in patients with highest-risk NMIBC. Notably, RFS was significantly lower in the high PNI group (≥ 50.17) than in the low PNI group, and a high SII (≥ 467.76) was associated with poor RFS, as shown in Figures 3A and 3B.

Significant Predictors of RFS by Cox Univariate and Multivariate Regression Analyses

The results of univariate and multivariate Cox regression analyses of clinicopathological factors related to RFS are presented in Table 3. Univariate Cox regression analysis revealed that PNI ($p = 0.001$), SII ($p = 0.005$), age ($p = 0.025$), BMI ($p = 0.004$), tumour number ($p < 0.001$), tumour size ($p < 0.001$), tumour grade ($p < 0.001$), T stage ($p = 0.002$), LVI ($p < 0.001$) and concomitant CIS ($p = 0.004$) were independent predictors of RFS. Furthermore, multivariate Cox regression analysis showed that PNI ($p = 0.017$), SII ($p = 0.014$), tumour number ($p = 0.023$), tumour size ($p = 0.001$), tumour grade ($p = 0.027$), T stage ($p = 0.039$), LVI ($p = 0.009$) and concomitant CIS ($p = 0.024$) were independent predictive factors for RFS, after adjusting for other confounding factors.

Discussion

Urothelial carcinomas are identified as malignant tumours that arise from the urothelial epithelium and may involve the bladder and upper urinary tract. As the most common malignancy of the urinary tract, BC accounts for 90%–95% of all urothelial carcinomas characterised by multiple, multifocal recurrences throughout the genitourinary tract. In China, the incidence of BC is increasing in men, although mortality is decreasing in both genders [16]. According to distinct clinical recurrence, progression and prognosis, BC is classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Recently, most patients with BC have been diagnosed with NMIBC [4], and approximately 53% experience progression to life-threatening MIBC [17]. Given the very high recurrence rate, the prediction of recurrence is particularly important in NMIBC. According to the probabilities of recurrence and progression defined in the European Organisation for Research and Treatment of Cancer Genitourinary Cancer Group risk scoring system, patients were divided into low-, intermediate- and high-risk groups [4]. Given the extremely high recurrence and progression risk in NMIBC patients, the clinical management of high-risk NMIBC is identified to be challenging. Early detection of recurrences and accurate identification and prediction of the likely progression of tumours are especially vital. BCG followed by maintenance therapy remains the golden standard of care for high-risk patients [18].

Generally, tumour-related pathological factors such as tissue type, grade, stage and LVI have been used to predict recurrence, progression, metastasis and prognosis in a majority of cancer cases. However, this standard evaluation system ignores demographic and other clinical features, such as immune and inflammatory status, which may contribute to its heterogeneity. Malnutrition is a common comorbidity and a consequence of the increase in inflammatory cytokines associated with cancer and metabolic alterations in most patients with malignant tumours [19]. Cancer malnutrition or cachexia, reflected by hypoalbuminemia and hyperlymphocytosis, is associated with increasing morbidity and mortality in patients with cancer [20,21]. In addition, several studies have shown that malnutrition is associated with recurrence and interferes with the patient's response to cancer treatment [22, 23]. Albumin concentration and lymphocyte count, which are the common indicators of nutritional status, are important predictors of nutritional risk and postoperative complications. PNI, which is calculated using serum albumin concentration and absolute lymphocyte count, is considered an essential predictive indicator of different types of human cancers [24,25,26]. As a hallmark of cancer that fosters recurrence, progression and metastasis, tumour-associated systemic inflammation has been extensively reviewed in recent years [27]. Systemic inflammatory response (SIR) markers such as lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and derived neutrophil-to-lymphocyte ratio have been used to evaluate inflammatory responses and predict tumour prognosis in several types of malignancies, including urological cancer [28,29]. However, these inflammation-based markers integrated only two types of inflammatory cells. SII, which is based on neutrophil, platelet and lymphocyte counts, was first used in hepatocellular carcinoma and was considered a predictor of several types of solid tumours [12,13,30]. In this study, we investigated the preoperative nutrition- and inflammation-based factors, PNI and SII, in high-risk NMIBC patients who received intravesical instillation of BCG after TURBT. To the best of our knowledge, this is the first study to investigate the predictive values of PNI and SII for long-term RFS and the relationships of these indices, gender, age, smoking status, BMI, smoking status and pathological parameters with the RFS outcomes of high-risk NMIBC.

The optimal cut-off values of PNI and SII for predicting RFS outcomes vary across studies. Lee *et al.* [31] reported a PNI of 45 for follicular lymphoma, whereas Car *et al.* [32] reported a PNI of 46 as the optimum cut-off value for OS in patients with metastatic colorectal cancer. Additionally, Tang *et al.* [33] reported an SII of 463.56 for BC with total cystectomy. However, Akan *et al.* [34] determined an SII of 672.75 as cut-off value for high-risk NMIBC with intravesical instillation of BCG after surgery. Our PNI value was slightly higher than those in previous studies, whereas the SII value was similar to that of Tang *et al.* [33]. The difference could have been influenced by the different types of tumours, differences in risk group stratification and clinicopathological stages for BC, heterogeneous patient status and different statistical methods.

Preoperative nutrition- and inflammation-based indicators are reported to be associated with postoperative complication and tumour prognosis [35]. In our study, low PNI and high SII were to be associated with lower BMI, higher recurrence frequency, higher tumour number, larger tumour size, higher tumour grade, more advanced T stage, more common LVI and concomitant CIS, all indicating more aggressive tumour phenotypes. The results of our study were consistent with those of previously

published reports [36,37,38]. However, no associations were found between PNI and gender or smoking status. Furthermore, no relationships between SII and gender, age or smoking status were found. These findings may have been affected by certain influential factors, such as the limited number of patients, a bias resulting from patient selection, differences in patients in terms of risk stratification and pathological stages of BC.

Our study identified several noteworthy findings. Significant correlations were made between PNI or SII and RFS in all 387 patients in this study. Lower PNI and higher SII were found to be related to worse RFS, whereas elevated PNI and decreased SII were independently associated with better RFS. In addition, univariate analysis demonstrated that PNI, SII, age, BMI, tumour number, tumour size, tumour grade, T stage, LVI and concomitant CIS were significantly associated with RFS. However, some results obtained varied from those of previous studies. No relationship between gender or smoking status and RFS was found in univariate analysis. Moreover, PNI, SII, tumour number, tumour size, tumour grade, T stage, LVI and concomitant CIS were significantly associated with RFS in multivariate analysis. Incidentally, we found that older age, which is significantly associated with BC, was not an independent predictor of RFS, which was inconsistent with previous studies [37,39]. From a mechanistic view, lower BMI may be related to the patients' low nutritional status and decreased immune response. However, in this study, BMI was not an effective predictor of RFS. Contradictory results have been reported as to whether BMI can predict clinical outcomes for BC [40,41]. These results may be due to biases related to the limited patient pool, varying clinicopathological stages of patients and risk stratification.

According to the EAU Guidelines 2020, sub-stratifying high-risk group patients and identifying those who are at highest risk of disease progression based on prognostic factors are necessary. An analysis of the highest-risk NMIBC subgroup showed that low PNI and elevated SII were significantly associated with poorer RFS. Unfortunately, due to the limited number of patients who met the highest-risk NMIBC group criteria, evaluating the relative predictive factors by univariate and multivariate analyses was insufficient.

The mechanism by which low nutritional status and increased SIR influence the biological features of tumours was not sufficiently understood and thus need further study. The association between low PNI or elevated SII and poor RFS in high-risk NMIBC patients could be elucidated at the physiological level. Patients with low PNI and high SII often have hypoalbuminemia, lymphopenia, neutrophilia and thrombocytosis. Malnutrition, reflected by hypoalbuminemia, creates a favourable microenvironment for tumour recurrence [42]. In addition, a poor nutritional status leads to tumour progression through the suppression of adaptive immunity against cancer cells [43]. Although the causes of tumour-induced lymphocytopenia remain to be elucidated in detail, one potential reason is the enhanced lymphocyte apoptosis and impaired lymphocyte homeostasis in cancer [44]. As part of the inflammatory response, neutrophils play a fundamental role in generating high levels of reactive oxygen species, tumour necrosis factor- α and macrophage migration inhibitory factor [45]. It can also cause the secretion of large amounts of arginase, and nitric oxide, which results in the disorder of T cell activation and the production of vascular endothelial growth factor [46,47]. Elevated platelet counts could also stimulate tumour angiogenesis and protect tumour-related cells from cytolysis, which contributes to tumour recurrence and

progression. Evidence suggests that circulating platelet–tumour cell aggregates may favour cancer metastasis development [48]. Furthermore, platelets induce tumour cells to form cytoskeletal connections, thereby promoting cancer migration [49].

This present study had several limitations. First, it was based on retrospective data from a single institution representing one region. Second, this study has a retrospective cohort design, which may have promoted selection bias during patient selection and data collection. Third, the assessment of other reported inflammation- and nutrition-based indicators, such as Glasgow Prognostic Score, Naples Prognostic Score, Controlling Nutritional Status score, Carlson Comorbidity Index, mid-upper arm muscle area, Dietary Inflammatory Index and C-reactive protein/albumin ratio were not included in this study. Fourth, although laboratory data were all collected before surgery, the timing of blood withdrawal was variable. Finally, the specificities of PNI and SII may not be high. Therefore, further prospective studies with external validation are needed to confirm the findings of this study.

Conclusions

PNI and SII can be potential valuable independent predictors of RFS in high-risk NMIBC patients. Preoperative PNI and SII are simple, non-invasive and inexpensive but could evaluate long-term recurrence in high-risk NMIBC.

List Of Abbreviations

PNI, Prognostic nutritional index; SII, Systemic immune-inflammation index; RFS, Recurrence-free survival; NMIBC, Non-muscle-invasive bladder cancer; BCG, Bacillus Calmette–Guerin; TURBT, Transurethral resection of bladder tumour; ROC, Receiver operating characteristic ; BC , Bladder cancer; MIBC, Muscle-invasive bladder cancer; PFS, Progression-free survival; SIR, Systemic inflammatory response; LMR, Lymphocyte-to-monocyte ratio; PLR, Platelet-to-lymphocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; dNLR, Derived neutrophil/lymphocyte ratio; SD, Standard deviation; BMI, Body mass Index; LG, Low grade; HG, High grade; LVI, Lymphovascular invasion; CIS, Carcinoma in situ; ALB, Albumin; LYMP, Lymphocyte; NEUT, Neutrophil; PLT, Platelet; AUCs, Areas under the curve; HR, Hazard ratio; CI, Confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EAU, European Association of Urology; ROS, Reactive oxygen species; TNF- α , Tumour necrosis factor alpha; VEGF, Vascular endothelial growth factor; GPS, Glasgow prognostic score; NPS, Naples prognostic score; CONUT, Controlling Nutritional Status; CCI, Charlson Comorbidity Index; MUAMA, Mid-upper arm muscle area; DII, Dietary inflammatory index; CRP/ALB, C-reactive protein/albumin

Declarations

Acknowledgements

The authors are grateful to the staff of the medical record office of Xuanwu Hospital Capital Medical University who provided all patients' medical records for this study.

Funding

The current study received funding from Beijing Municipal Administration of Hospital Clinical Medicine Development of Special Funding Support (grant number: ZYLYX201801). The funding was used for the collection, analysis and interpretation of data and the writing of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed significantly to the work reported, including conception, study design, execution, data acquisition, analysis and interpretation. HB, CJ and TO contributed to the conception and study design, provided administrative and technical support and supervised the study. HB and ZS contributed to the drafting and writing of the manuscript. ZF and XN edited the draft along with contributing to the acquisition, analysis and interpretation of data. TO made critical revisions to the manuscript. The authors read and approved the final version of the manuscript. Moreover, they agree with the submission, and they are accountable for all aspects of this work.

Ethics approval and consent to participate

This retrospective cohort study was approved by the Ethics Committee of Xuanwu Hospital Capital Medical University, National Clinical Research Centre for Geriatric Diseases (2018-086). All participants provided a written informed consent for the retrieval and utilization of their records in our hospital database. In addition, the study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from all participants or their authorized family members.

Competing interests

The authors received grants from the Beijing Municipal People's Government during the implementation of this study and outside the submitted work. All authors declare that they have no other competing interests.

References

1. Rozanec JJ, Secin FP. Epidemiology, etiology and prevention of bladder cancer. *Arch Esp Urol.* 2020;73:872-8.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394-424.
3. Compérat E, Larré S, Roupert M, Neuzillet Y, Pignot G, Quintens H, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. *Virchows Arch.* 2015;466:589-94.
4. Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) – 2019 Update. *Eur Urol.* 2019;76:639-57.
5. Pane K, Mirabelli P, Coppola L, Illiano E, Salvatore M, Franzese M. New Roadmaps for Non-muscle-invasive Bladder Cancer With Unfavorable Prognosis. *Front Chem.* 2020;8:600.
6. Nicolazzo C, Busetto GM, Gradilone A, Sperduti I, Del Giudice F, Loreni F, et al. Circulating Tumor Cells Identify Patients with Super-High-Risk Non-Muscle-Invasive Bladder Cancer: Updated Outcome Analysis of a Prospective Single-Center Trial. *Oncologist.* 2019;24:612-6.
7. Piszczek R, Krajewski W, Małkiewicz B, Krajewski P, Tukiendorf A, Zdrojowy R, et al. Clinical outcomes and survival differences between primary, secondary and concomitants carcinoma *in situ* of urinary bladder treated with BCG immunotherapy. *Transl Androl Urol.* 2020;9:1338-44.
8. Galizia G, Auricchio A, de Vita F, Cardella F, Mabilia A, Basile N, et al. Inflammatory and nutritional status is a predictor of long-term outcome in patients undergoing surgery for gastric cancer. Validation of the Naples prognostic score. *Ann Ital Chir.* 2019;90:404-16.
9. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi.* 1984;85:1001-5.
10. Okada S, Shimada J, Teramukai S, Kato D, Tsunezuka H, Miyata N, et al. Risk Stratification According to the Prognostic Nutritional Index for Predicting Postoperative Complications After Lung Cancer Surgery. *Ann Surg Oncol.* 2018;25:1254-61.
11. Park SH, Lee S, Song JH, Choi S, Cho M, Kwon IG, et al. Prognostic significance of body mass index and prognostic nutritional index in stage II/III gastric cancer. *Eur J Surg Oncol.* 2020;46:620-5.
12. Donate-Moreno MJ, Lorenzo-Sánchez MV, Díaz de Mera-Sánchez Migallón I, Herraiz-Raya L, Esper-Rueda JA, Legido-Gómez O, et al. Inflammatory markers as prognostic factors in metastatic castration-resistant prostate cancer. *Actas Urol Esp.* 2020;44:692-700.
13. Barua SK, Singh Y, Baruah SJ, T P R, Bagchi PK, Sarma D, et al. Predictors of Progression-Free Survival and Overall Survival in Metastatic Non-Clear Cell Renal Cell Carcinoma: A Single-Center Experience. *World J Oncol.* 2019;10:101-11.
14. Mirili C, Yılmaz A, Demirkan S, Bilici M, Basol Tekin S. Clinical significance of prognostic nutritional index (PNI) in malignant melanoma. *Int J Clin Oncol.* 2019;24:1301-10.

15. Bartl T, Bekos C, Postl M, Alexander R, Polterauer S, Stefanie A, et al. The systemic immune-inflammation index (SII) is an independent prognostic parameter of survival in patients with invasive vulvar cancer. *J Gynecol Oncol.* 2021;32:e1.
16. Liu X, Jiang J, Yu C, Wang Y, Sun Y, Tang J, et al. Secular trends in incidence and mortality of bladder cancer in China, 1990-2017: A joinpoint and age-period-cohort analysis. *Cancer Epidemiol.* 2019;61:95-103.
17. Ottley EC, Pell R, Brazier B, Hollidge J, Kartsonaki C, Browning L, et al. Greater utility of molecular subtype rather than epithelial-to-mesenchymal transition (EMT) markers for prognosis in high-risk non-muscle-invasive (HGT1) bladder cancer. *J Pathol Clin Res.* 2020;6:238-51.
18. Peyton CC, Chipollini J, Azizi M, Kamat AM, Gilbert SM, Spiess PE. Updates on the use of intravesical therapies for non-muscle invasive bladder cancer: how, when and what. *World J Urol.* 2019;37:2017-29.
19. Barreira JV. The Role of Nutrition in Cancer Patients. *Nutr Cancer.* 2020;28:1-2.
20. Kano K, Yamada T, Yamamoto K, Komori K, Watanabe H, Takahashi K, et al. The Impact of Pretherapeutic Naples Prognostic Score on Survival in Patients with Locally Advanced Esophageal Cancer. *Ann Surg Oncol.* 2021; doi:10.1245/s10434-020-09549-5.
21. Ang JJ, Chia DKA, Chan DKH. Lymphocyte-White Cell Ratio Is a Novel Marker of Morbidity Following Colorectal Cancer Surgery. *J Surg Res.* 2021;259:71-8.
22. Elghiaty A, Kim J, Jang WS, Park JS, Heo JE, Rha KH, et al. Preoperative controlling nutritional status (CONUT) score as a novel immune-nutritional predictor of survival in non-metastatic clear cell renal cell carcinoma of ≤ 7 cm on preoperative imaging. *J Cancer Res Clin Oncol.* 2019;145:957-65.
23. Alagappan M, Pollom EL, von Eyben R, Kozak MM, Aggarwal S, Poultides GA, et al. Albumin and Neutrophil-Lymphocyte Ratio (NLR) Predict Survival in Patients With Pancreatic Adenocarcinoma Treated With SBRT. *Am J Clin Oncol.* 2018;41:242-7.
24. Crippa S, Pergolini I, Javed AA, Honselmann KC, Weiss MJ, Di Salvo F, et al. Implications of Perineural Invasion on Disease Recurrence and Survival After Pancreatectomy for Pancreatic Head Ductal Adenocarcinoma. *Ann Surg.* 2020; doi:10.1097/SLA.0000000000004464.
25. Caputo F, Dadduzio V, Tovoli F, Bertolini G, Cabibbo G, Cerma K, et al. The role of PNI to predict survival in advanced hepatocellular carcinoma treated with Sorafenib. *PLoS One.* 2020;15:e0232449.
26. Abe A, Hayashi H, Ishihama T, Furuta H. Prognostic impact of the prognostic nutritional index in cases of resected oral squamous cell carcinoma: a retrospective study. *BMC Oral Health.* 2021;21:40.
27. Suarez-Carmona M, Lesage J, Cataldo D, Gilles C. EMT and inflammation: inseparable actors of cancer progression. *Mol Oncol.* 2017;11:805-23.
28. Arda E, Yuksel I, Cakiroglu B, Akdeniz E, Cilesiz N. Valuation of Neutrophil/Lymphocyte Ratio in Renal Cell Carcinoma Grading and Progression. *Cureus.* 2018;10:e2051.
29. Yamada Y, Sakamoto S, Rii J, Yamamoto S, Kamada S, Imamura Y, et al. Prognostic value of an inflammatory index for patients with metastatic castration-resistant prostate cancer. *Prostate.* 2020;80:559-69.

30. Bittoni A, Pecci F, Mentrasti G, Crocetti S, Lupi A, Lanese A, et al. Systemic immune-inflammation index: a prognostic tiebreaker among all in advanced pancreatic cancer. *Ann Transl Med.* 2021;9:251.
31. Lee SF, Ng TY, Wong FCS. The Value of Prognostic Nutritional Index in Follicular Lymphoma. *Am J Clin Oncol.* 2019;42:202-7.
32. Ucar G, Ergun Y, Acikgoz Y, Uncu D. The prognostic value of the prognostic nutritional index in patients with metastatic colorectal cancer. *Asia Pac J Clin Oncol.* 2020;16:e179-84.
33. Tang X, Cao Y, Liu J, Wang S, Yang Y, Du P. Diagnostic and Predictive Values of Inflammatory Factors in Pathology and Survival of Patients Undergoing Total Cystectomy. *Mediators Inflamm.* 2020;2020:9234067.
34. Akan S, Ediz C, Sahin A, Tavukcu HH, Urkmez A, Horasan A, et al. Can the systemic immune inflammation index be a predictor of BCG response in patients with high-risk non-muscle invasive bladder cancer? *Int J Clin Pract.* 2021;75:e13813.
35. Solanki SL, Kaur J, Gupta AM, Patkar S, Joshi R, Ambulkar RP, et al. Cancer related nutritional and inflammatory markers as predictive parameters of immediate postoperative complications and long-term survival after hepatectomies. *Surg Oncol.* 2021;37:101526.
36. Karsiyakali N, Karabay E, Yucetas U. Predictive value of prognostic nutritional index on tumor stage in patients with primary bladder cancer. *Arch Esp Urol.* 2020;73:132-9.
37. Cui J, Chen S, Bo Q, Wang S, Zhang N, Yu M, et al. Preoperative prognostic nutritional index and nomogram predicting recurrence-free survival in patients with primary non-muscle-invasive bladder cancer without carcinoma in situ. *Onco Targets Ther.* 2017;10:5541-50.
38. Gorgel SN, Akin Y, Koc EM, Kose O, Ozcan S, Yilmaz Y. Retrospective study of systemic immune-inflammation index in muscle invasive bladder cancer: initial results of single centre. *Int Urol Nephrol.* 2020;52:469-73.
39. Abdel-Rahman O. Bladder cancer mortality after a diagnosis of nonmuscle-invasive bladder carcinoma. *Future Oncol.* 2019;15:2267-75.
40. Evers J, Grotenhuis AJ, Aben KK, Kiemeney LALM, Vrieling A. No clear associations of adult BMI and diabetes mellitus with non-muscle invasive bladder cancer recurrence and progression. *PloS One.* 2020;15:e0229384.
41. Dabi Y, Rouscoff Y, Anract J, Delongchamps NB, Sibony M, Saighi D, et al. Impact of body mass index on the oncological outcomes of patients treated with radical cystectomy for muscle-invasive bladder cancer. *World J Urol.* 2017;35:229-35.
42. Castillo-Martínez L, Castro-Eguiluz D, Copca-Mendoza ET, Pérez-Camargo DA, Reyes-Torres CA, Ávila EA, et al. Nutritional Assessment Tools for the Identification of Malnutrition and Nutritional Risk Associated with Cancer Treatment. *Rev Invest Clin.* 2018;70:121-5.
43. Gao Y, Zhou S, Jiang W, Huang M, Dai X. Effects of ganopoly (a Ganoderma lucidum polysaccharide extract) on the immune functions in advanced-stage cancer patients. *Immunol Invest.* 2003;32:201-15.

44. Gorelik L, Flavell RA. Transforming growth factor-beta in T-cell biology. *Nat Rev Immunol*. 2002;2:46-53.
45. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Mol Cancer Res*. 2006;4:221-33.
46. Shamamian P, Schwartz JD, Pocock BJ, Monea S, Whiting D, Marcus SG, et al. Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: a role for inflammatory cells in tumor invasion and angiogenesis. *J Cell Physiol*. 2001;189:197-206.
47. Müller I, Munder M, Kropf P, Hänsch GM. Polymorphonuclear neutrophils and T lymphocytes: strange bedfellows or brothers in arms? *Trends Immunol*. 2009;30:522-30.
48. Borsig L. The role of platelet activation in tumor metastasis. *Expert Rev Anticancer Ther*. 2008;8:1247-55.
49. Pu F, Li X, Wang S, Huang Y, Wang D. Platelet supernatant with longer storage inhibits tumor cell growth. *Transfus Apher Sci*. 2021;60:103042.

Tables

Table 1 Clinicopathological characteristics of patients with high-risk NMIBC (n=387)

Characteristics	Patients, n (%)
Gender	
Male	277 (71.58)
Female	110 (28.42)
Age	
Mean±SD	69.49±10.84
Median (range)	71 (34-89)
Smoking status	
Never smoker	229 (59.17)
Current or ex-smoker	158 (40.83)
BMI	
Mean±SD	24.07±3.35
Median (range)	23.58 (17.36–36.86)
Recurrence	
None	180 (46.51)
Yes	207 (53.49)
Tumour number	
1	173 (44.70)
2~7	143 (36.95)
≥8	71 (18.35)
Tumour size	
<3cm	303 (78.29)
≥3cm	84 (21.71)
Tumour grade	
LG	124 (32.04)
HG	263 (67.96)
T stage	
Ta	107 (27.65)
Tis	20 (5.17)

T1	260 (67.18)
LVI	
None	356 (91.99)
Yes	31 (8.01)
Concomitant CIS	
None	363 (93.80)
Yes	24 (6.20)
Blood cell counts, mean (SD)	
ALB(g/L)	41.93 (9.59)
LYMP($\times 10^9/L$)	1.94 (0.61)
NEUT($\times 10^9/L$)	3.89 (1.46)
PLT($\times 10^9/L$)	214.18 (46.81)
Nutrition-inflammation-based parameters, mean (SD)	
PNI	51.64 (11.67)
SII	447.46 (139.39)
Oncological outcomes	
Bladder recurrence	194 (50.12)
Upper urinary tract recurrence	13 (3.36)
Progression	82 (21.19)
Radical cystectomy	42 (10.85)
5-year recurrence rate	162/387 (41.86)
5-year recurrence rate of highest-risk NMIBC	59/90 (65.56)
5-year cancer specific mortality	43/365 (11.78)
5-year overall mortality	65/387 (16.80)
5-year cancer specific mortality of highest-risk NMIBC	35/83 (42.17)
5-year overall mortality of highest-risk NMIBC	42/90 (46.67)
Follow-up duration, months	
Median (range)	108 (5-191)

Abbreviations: NMIBC, non-muscle-invasive bladder cancer; SD, standard deviation; BMI, body mass Index; LG, low grade; HG, high grade; LVI, lymph vascular invasion; CIS, carcinoma in situ; ALB, albumin; LYMP, lymphocyte count; NEUT, neutrophil count; PLT, platelet count; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

Table 2 Correlations between PNI and SII as well as clinicopathological parameters in patients with high-risk NMIBC

Characteristics	PNI <50.17	PNI ≥50.17	p-value	SII <467.76	SII ≥467.76	p-value
	n=116	n=271		n=242	n=145	
Gender, n (%)			0.618			0.454
Male	81 (69.8)	196 (72.3)		170 (70.2)	107 (73.8)	
Female	35 (30.2)	75 (27.7)		72 (29.8)	38 (26.2)	
Age(years), n (%)			0.009			0.353
<63.5	29 (25.0)	105 (38.8)		88 (36.4)	46 (31.7)	
≥63.5	87 (75.0)	166 (61.2)		154 (63.5)	99 (68.3)	
Smoking status, n (%)			0.935			0.060
Never smoker	69 (59.5)	160 (59.0)		152 (62.8)	77 (53.1)	
Current or ex-smoker	47 (40.5)	111 (41.0)		90 (37.2)	68 (46.9)	
BMI n (%)			0.006			0.007
<22.31	62 (53.4)	104 (38.4)		91 (37.6)	75 (51.7)	
≥22.31	54 (46.6)	167 (61.6)		151 (62.4)	70 (49.6)	
Recurrence, n (%)			0.002			0.005
None	40 (34.5)	140 (51.7)		126 (52.1)	54 (37.2)	
Yes	76 (65.5)	141 (52.0)		116 (47.9)	91 (62.8)	
Tumour number, n (%)			0.048			0.007
Unifocal	43 (37.1)	130 (48.0)		121 (50.0)	52 (35.9)	
Multifocal	73 (62.9)	141 (52.0)		121 (50.0)	93 (64.1)	
Tumour size, n (%)			<0.001			<0.001
<3cm	75 (64.7)	228 (84.1)		208 (86.0)	95 (65.5)	
≥3cm	41 (35.3)	43 (15.9)		34 (14.0)	50 (34.5)	
Tumour grade, n (%)			0.001			0.033
LG	23 (19.8)	101 (37.3)		87 (36.0)	37 (25.5)	
HG	93 (80.2)	170 (62.7)		155 (64.0)	108 (74.5)	
T stage, n (%)			<0.001			0.005
T1	93 (80.2)	167 (61.6)		150 (62.0)	110 (75.9)	
≤Tis	23 (19.8)	104 (38.4)		92 (38.0)	35 (24.1)	

LVI, n (%)			0.006		0.004
None	100 (86.2)	256 (94.5)		230 (95.0)	126 (86.9)
Yes	16 (13.8)	15 (5.5)		12 (5.0)	19 (13.1)
Concomitant CIS, n (%)			0.002		0.009
None	102 (87.9)	261 (96.3)		233 (96.3)	130 (89.7)
Yes	14 (12.1)	10 (3.7)		9 (3.7)	15 (10.3)
ALB, n (%)			<0.001		<0.001
<42.19 g/L	105 (90.5)	120 (44.3)		119 (49.2)	106 (73.1)
≥42.19 g/L	11 (9.5)	151 (55.7)		123 (50.8)	39 (26.9)
LYMP, n (%)			<0.001		<0.001
<1.78×10 ⁹ /L	86 (74.1)	41 (15.1)		26 (10.7)	101 (69.7)
≥1.78×10 ⁹ /L	30 (25.9)	230 (84.9)		216 (89.3)	44 (30.3)
NEUT, n (%)			<0.001		<0.001
<4.36×10 ⁹ /L	82 (70.7)	252 (93.0)		237 (98.0)	97 (66.9)
≥4.36×10 ⁹ /L	34 (29.3)	19 (7.0)		5 (2.0)	48 (33.1)
PLT, n (%)			<0.001		<0.001
<235×10 ⁹ /L	97 (83.6)	259 (95.6)		233 (96.3)	121 (83.4)
≥235×10 ⁹ /L	19 (16.4)	12 (4.4)		7 (3.7)	24 (16.6)

Notes: Bold values indicate statistical significance.

Abbreviations: PNI, prognostic nutritional index; SII, systemic immune-inflammation index; NMIBC, non-muscle-invasive bladder cancer; BMI, body mass Index; LG, low grade; HG, high grade; LVI, lymph vascular invasion; CIS, carcinoma in situ; ALB, albumin; LYMP, lymphocyte count; NEUT, neutrophil count; PLT, platelet count.

Table 3 Univariate and multivariate Cox regression analyses of RFS in patients with high-risk NMIBC

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender		0.484		
Male	1 (reference)			
Female	0.896 (0.660-1.218)			
Age		0.025		0.195
<63.5	1 (reference)		1 (reference)	
≥63.5	1.409 (0.943-1.902)		1.230 (0.900-1.681)	
Smoking status		0.591		
Never smoker	1 (reference)			
Current or ex-smoker	1.079 (0.818-1.422)			
BMI		0.004		0.068
<22.31	1 (reference)		1 (reference)	
≥22.31	0.568 (0.309-0.837)		0.744 (0.374-1.007)	
Tumour number		<0.001		0.023
1	1 (reference)		1 (reference)	
2-7	2.298 (1.979-5.657)		1.297 (0.953-1.765)	
≥8	2.945 (2.034-6.963)		1.645 (1.143-2.369)	
Tumour size		<0.001		0.001
≤3cm	1 (reference)		1 (reference)	
>3cm	1.963 (1.320-3.167)		1.664 (1.222-2.266)	
Tumour grade		<0.001		0.027
LG	1 (reference)		1 (reference)	
HG	2.446 (1.939-5.906)		1.407 (1.039-1.906)	
T stage		0.002		0.039
Ta	1 (reference)		1 (reference)	
Tis	2.897 (1.839-6.411)		1.667 (0.864-3.216)	
T1	2.110 (1.718-5.285)		1.509 (1.087-2.095)	
LVI		<0.001		0.009

None	1 (reference)	1 (reference)
Yes	2.142 (1.339-4.531)	1.771 (1.166-3.746)
Concomitant CIS	0.004	0.024
None	1 (reference)	1 (reference)
Yes	1.871 (1.221-2.866)	1.511 (1.107-2.361)
PNI	0.001	0.017
<50.17	1 (reference)	1 (reference)
≥50.17	0.558 (0.421-0.740)	0.685 (0.499-0.910)
SII	0.005	0.014
<467.76	1 (reference)	1 (reference)
≥467.76	1.563 (1.170-2.088)	1.404 (1.119-1.917)

Notes: Bold values indicate statistical significance.

Abbreviations: RFS, recurrence-free survival; NMIBC, non-muscle-invasive bladder cancer; HR, hazard ratio; CI, confidence interval; BMI, body mass Index; LG, low grade; HG, high grade; LVI, lymph vascular invasion; CIS, carcinoma in situ; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

Figures

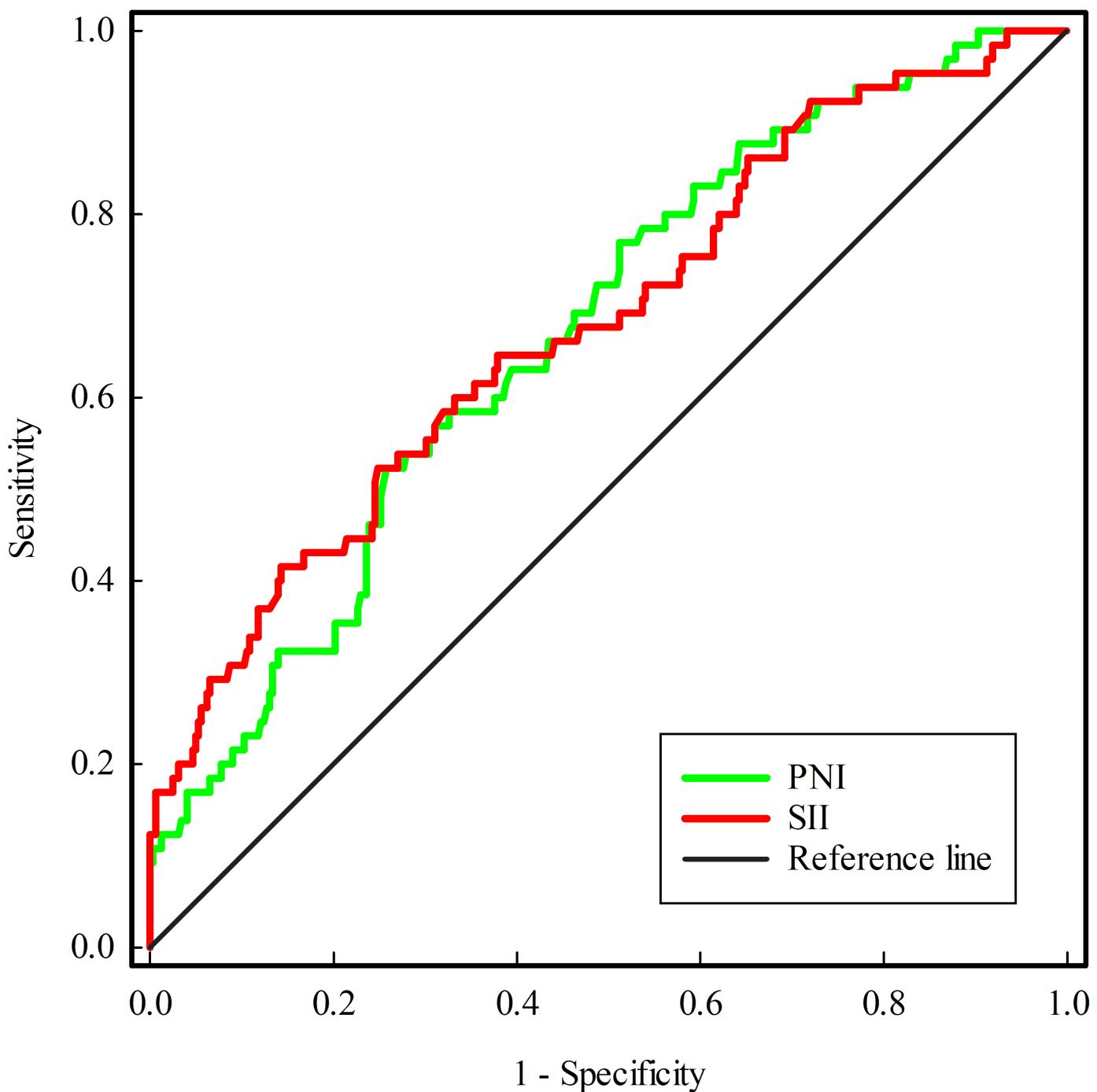


Figure 1

ROC curve analysis of the optimal cut-off values of PNI and SII. Abbreviations: ROC, receiver operating characteristic; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

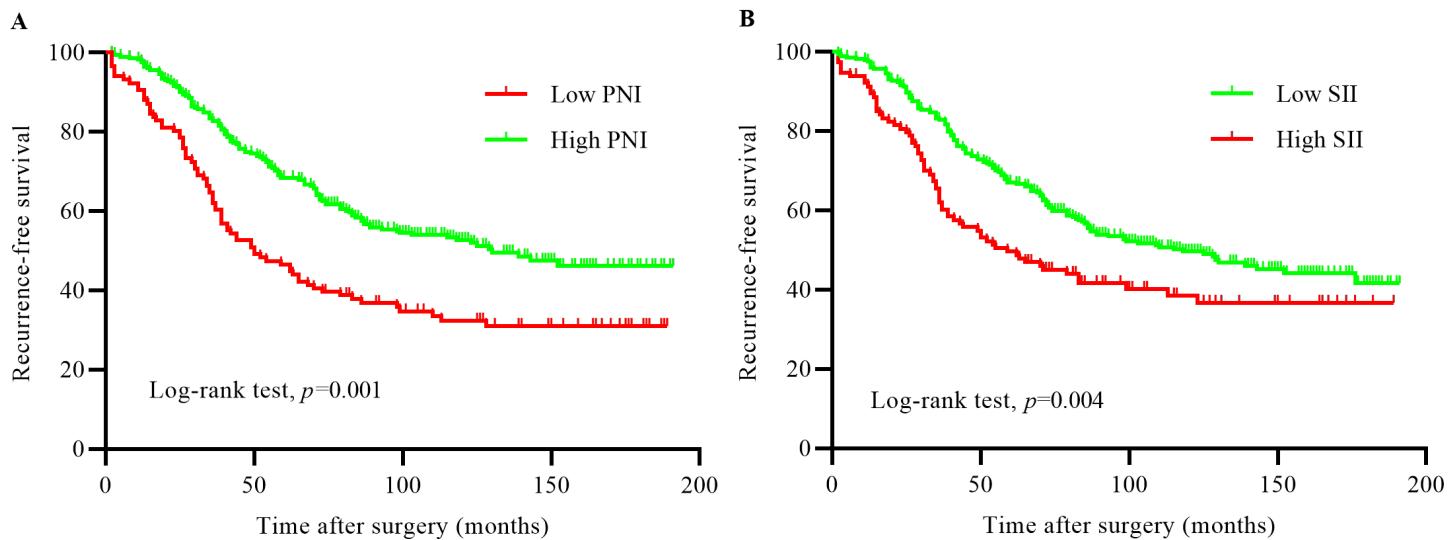


Figure 2

Kaplan-Meier analysis of RFS in high-risk NMIBC patients according to PNI (A) and SII (B).

Abbreviations: RFS, recurrence-free survival; NMIBC, non-muscle-invasive bladder cancer; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

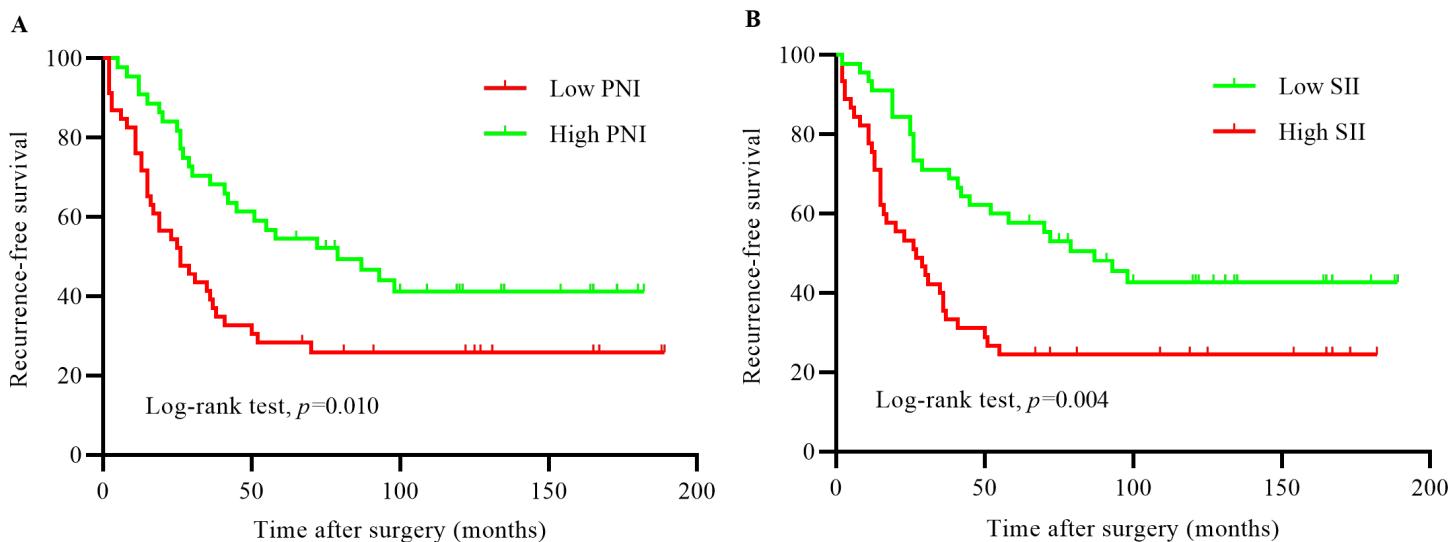


Figure 3

Kaplan-Meier analysis of RFS in highest-risk NMIBC patients according to PNI (A) and SII (B).

Abbreviations: RFS, recurrence-free survival; NMIBC, non-muscle-invasive bladder cancer; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.