Systemic Inflammatory Markers and Oncologic Outcomes in Patients with High-risk Non–muscle-invasive Urothelial Bladder Cancer

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Article info

Abstract

Background: Serum levels of neutrophils, platelets, and lymphocytes have been recognized as factors related to poor prognosis for many solid tumors, including bladder cancer (BC).
Objective: To evaluate the prognostic role of the combination of the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) in patients with high-risk non–muscle-invasive urothelial BC (NIMBC).
Design, setting, and participants: A total of 1151 NMIBC patients who underwent first transurethral resection of the bladder tumor (TURBT) at 13 academic institutions between January 1, 2002 and December 31, 2012 were included in this analysis. The median follow-up was 48 mo.
Intervention: TURBT with intravesical chemotherapy or immunotherapy.

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Outcome measurements and statistical analysis: Multivariable Cox regression analysis was performed to identify factors predictive of recurrence, progression, cancer-specific mortality, and overall mortality. A systemic inflammatory marker (SIM) score was calculated based on cutoffs for NLR, PLR, and LMR.

Results and limitations: The 48-mo recurrence-free survival was 80.8%, 47.35%, 20.67%, and 17.06% for patients with an SIM score of 0, 1, 2, and 3, respectively ($p < 0.01$, log-rank test) while the corresponding 48-mo progression free-survival was 92.0%, 75.67%, 72.85%, and 63.1% ($p < 0.01$, log-rank test). SIM scores of 1, 2, and 3 were associated with recurrence (hazard ratio [HR] 3.73, 7.06, and 7.88) and progression (HR 3.15, 4.41, and 5.83). Limitations include the lack of external validation and comparison to other clinical risk models.

Conclusions: Patients with high-grade T1 stage NMIBC with high SIM scores have worse oncologic outcomes in terms of recurrence and progression. Further studies should be conducted to stratify patients according to SIM scores to identify individuals who might benefit from early cystectomy.

Patient summary: In this study, we defined a risk score (the SIM score) based on the measurement of routine systemic inflammatory markers. This score can identify patients with high-grade bladder cancer not invading the muscular layer who are more likely to suffer from tumor recurrence and progression. Therefore, the score could be used to select patients who might benefit from early bladder removal.

1.   Introduction

Neutrophils act as short-lived effector cells of the innate immune system and play a primary role in resistance against extracellular pathogens and inflammation [1]. The tumor microenvironment is characterized by stimulation of the immune system, which leads to increases in various host components including stromal cells, growing blood vessels, and inflammatory infiltrates [1,2]. All these components have a pivotal role in the development and progression of many malignancies, including bladder cancer (BC) [3], through the release of cytokines by the tumor microenvironment [4].

Many biomarkers from routine blood tests have been evaluated in predicting BC outcomes in recent years, including hemoglobin levels, platelet counts, leukocyte counts, and C-reactive protein (CRP). In this regard, neutrophils and lymphocytes have been combined in the neutrophil/lymphocyte ratio (NLR). A high NLR has been recognized as a factor related to poor prognosis for many solid tumors, including BC [3]. A recent meta-analysis by Tang et al [5] proved that NLR had a predictive value for survival outcomes in BC patients, and that patients with a higher pretreatment NLR experienced worse survival.

Moreover, the systemic inflammatory response to tumors is associated with abnormalities of several blood components, including neutrophils, lymphocytes, and platelets [6]. However, the role of systemic inflammatory markers has been not fully investigated in the context of BC. In fact, current prognostic models for non–muscle-invasive bladder cancer (NMIBC) relying on pathological features such as T stage, grade, focality, tumor diameter, recurrence rate and concomitant carcinoma in situ (CIS) do not reach included these kinds of markers that could play a significant prognostic role [7].

The aim of this multicenter study was to evaluate the prognostic role of systemic markers of inflammation among patients with high-risk NMIBC.

2.   Patients and methods

2.1.   Patient population

A total of 1155 high-risk NMIBC patients treated at 13 academic institutions between January 1, 2002 and December 31, 2012 were included in this prospective observational study. Institutional review board approval was obtained at the leading center (IEO, Milan, Italy), and a data usage agreement was established with all participating centers.

Demographic, clinical and pathologic data for first and second transurethral resection of bladder tumor (TURBT) were collected for each patient and entered in a purpose-built database. Tumor histology was assessed at each institution and classified using the American Joint Committee on Cancer (AJCC) staging manual (6th and 7th editions).

Second TURBT (re-TURBT) was performed by the same urologist who performed the first TURBT within 6 wk [8]. The re-TURBT protocol included resection of the tumor scar and base, together with the bladder neck (for CIS) and red bladder patches. Each patient received adjuvant intravesical bacillus Calmette-Guérin (BCG) immunotherapy according to the European Association of Urology (EAU) recommendations [9]. The upper urinary tract was evaluated via radiological imaging in all subjects to exclude the presence of concomitant carcinoma.

Laboratory parameters were measured 30 d before surgery and data for calculating the NLR, platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) were collected. Patients with a urinary tract infection or inflammatory systemic diseases that could influence these parameters (chronic intestinal diseases, autoimmune diseases, leukaemia, lymphoma) were excluded from the study.

2.2. Follow-up

Only patients with >3 yr of follow-up were included. Follow-up was conducted according to EAU guidelines, with cystoscopy and urinary cytology every 3 mo [10]. The following oncologic outcomes were measured: time to first recurrence, time to first progression, cancer-specific mortality (CSM) and overall mortality (OM). Primary recurrence was defined as the reappearance of high-risk disease (high grade, T1, or CIS) after TURBT. Secondary progression was defined as development or a staging increase to lamina propria invasion (eg, increase from Ta to T1 or CIS to T1), muscle-invasive disease (stage $\geq$T2), lymph node (N+) or distant metastases (M1), or a grade increase from low to high (including CIS). CSM was defined as the time from random assignment to death resulting from bladder cancer, and OM as the time from random assignment to death resulting from any cause [9].

2.3. Statistical analysis

Continuous variables are presented as the median and interquartile range (IQR). Differences between groups were assessed using a Kruskall-Wallis or Mann-Whitney U test as appropriate. Categorical variables were tested using a χ^2 test or Fisher's exact test.

Multivariable Cox regression analysis was performed to identify factors predictive of recurrence, progression, CSM, and OM using the variables measured. For internal validation, the analysis was subjected to 500 bootstrap resamples.

NLR, PLR, and LMR were dichotomized according to cutoffs already used in the literature, namely 2.5, 150, and 3.41, respectively [11–13]. A systemic inflammatory marker (SIM) score was calculated on the basis of positivity according to these cutoffs, with 1 point assigned for each value exceeding the specified threshold and then summed, yielding a final score ranging from 0 to 3.

Kaplan-Meier curves were plotted to calculate the association between SIM and recurrence-free survival, progression-free survival, cancer-specific survival (CSS), and overall survival (OS). A log-rank test was used to verify statistical significance among the curves. Decision curve analysis (DCA) was performed to evaluate net benefit models included in the multivariable Cox regression analysis for predicting recurrence and progression. Subgroup analysis was performed according to smoking status.

All statistical analyses were carried out using Stata v.14 (StataCorp, College Station, TX, USA). For all comparisons, the significance level was set to $p < 0.05$ for differences between groups.

Table 1 – Baseline characteristics of the study cohort ($n = 1155$)

Variable	Result
Median age, yr (IQR)	71.0 (65.0–78.0)
Gender, n (%)	
Male	957 (82.86)
Female	198 (17.14)
Smoking status, n (%)	
Never	548 (47.45)
Current	327 (28.31)
Former	280 (24.24)
Median cigarettes per day, n (IQR)	10.0 (0.0–20.0)
Median smoking years, n (IQR)	20.0 (0.0–30.0)
Multifocal disease, n (%)	516 (44.68)
Tumor size $\geq$3 cm, n (%)	746 (64.64)
Carcinoma in situ, n (%)	156 (13.51)
Median erythrocyte sedimentation rate, mm/h (IQR)	13.0 (8.0–22.0)
Median C-reactive protein, mg/l (IQR)	2.1 (0.9–4.6)
Median neutrophils, $\times 10^3/\mu$l (IQR)	5.5 (3.8–9.8)
Median lymphocytes, $\times 10^3/\mu$l (IQR)	1.92 (1.5–2.6)
Median monocytes, $\times 10^3/\mu$l (IQR)	0.53 (0.40–0.76)
Median eosinophils, $\times 10^3/\mu$l (IQR)	0.17 (0.10–0.28)
Median basophils, $\times 10^3/\mu$l (IQR)	0.03 (0.01–0.05)
Median platelets, $\times 10^3/\mu$l (IQR)	233.0 (193.0–283.0)
Median neutrophil/lymphocyte ratio (IQR)	3.0 (1.95–4.58)
Median platelet/lymphocyte ratio (IQR)	119.7 (85.91–163.16)
Median lymphocyte/monocyte ratio (IQR)	3.5 (2.4–5.22)

IQR = interquartile range.

3. Results

3.1. Baseline characteristics in the overall study population

Table 1 lists the baseline characteristics of the study cohort. The median age was 71.0 yr (IQR 65.0–78.0), median NLR was 3.0 (IQR 1.96–4.6), median PLR was 119.7 (IQR 85.9–163.2), median LMR was 3.5 (IQR 2.4–5.2), and median SIM was 2 (IQR 1–2). Overall, 221 patients (19.1%) had previously received chemotherapy instillation: 53 (4.6%) received epirubicin and 168 (14.5%) mitomycin 40 mg. After re-TURBT, 288 patients (24.9%) had residual high-grade NMIBC, while 867 (75.1%) were negative. All patients received BCG immunotherapy and the median regimen duration was 12.0 mo (IQR 6.0–36.0). When patients were dichotomized according to the defined cutoffs, 778 (67.4%), 344 (29.8%), and 597 (51.7%) had NLR $\geq$2.5, PLR $\geq$150, and LMR $\geq$3.41, respectively.

3.2. Clinical and pathologic characteristics according to marker cutoffs

Table 2 shows the clinical and pathologic characteristics according to the previously defined marker cutoffs. Patients with NLR $\geq$2.5 had a significantly higher erythrocyte sedimentation rate (ESR; 15.0 vs 12.0 mm/h; $p < 0.01$) and CRP (2.3 vs 2.0 mg/l; $p = 0.02$). Similarly, for patients with LMR $\geq$3.41, both ESR (15.0 vs 12.0 mm/h; $p < 0.01$) and CRP (2.9 vs 2.0 mg/l; $p < 0.01$) were significantly higher. With regard to pathology, we found a higher rate of CIS only among patients with NLR $\geq$2.5 (15.3% vs 9.8%; $p = 0.011$) and a slower rate of tumor size $\geq$3 cm among patients with PLR $\geq$150 (58.1% vs 68.4%; $p = 0.003$).

Table 2 – Association of baseline clinicopathologic characteristics with NLR, PLR, and LMR cutoffs

Variable	NLR <2.5	NLR ≥2.5	p value	PLR <150	PLR ≥150	p value	LMR <3.41	LMR ≥3.41	p value
Patients (n)	377	778		811	344		558	597	
Median age, yr (IQR)	70.5 (64.0–77.0)	71.0 (65.0–78.0)	0.114	71.0 (65.0–78.0)	71.0 (65.0–78.0)	0.375	72.0 (65.0–78.0)	70.0 (64.0–77.5)	0.049
Gender, n (%)			0.009			0.061			0.134
Male	428 (87.0)	629 (80.25)		661 (81.50)	296 (86.05)		460 (82.44)	497 (83.25)	
Female	49 (13.0)	149 (19.15)		150 (18.50)	48 (13.95)		98 (17.56)	100 (16.75)	
Smoking status, n (%)			0.002			0.180			<0.001
Never	153 (40.58)	395 (50.77)		373 (45.99)	175 (50.87)		235 (42.11)	313 (52.43)	
Current	112 (29.71)	215 (27.63)		230 (28.36)	97 (28.20)		158 (28.32)	169 (28.31)	
Former	112 (29.71)	168 (21.59)		208 (25.65)	72 (20.93)		165 (29.57)	115 (19.26)	
Median cigarettes per day, n (IQR)	10.0 (0.0–20.0)	10.0 (0.0–20.0)	0.135	10.0 (0.0–20.0)	10.0 (0.0–20.0)	0.148	10.0 (0.0–15.0)	12.0 (0.0–20.0)	0.014
Median smoking years, n (IQR)	19.0 (0.0–30.0)	23.0 (0.0–35.0)	<0.01	20.0 (0.0–32.0)	20.0 (0.0–30.0)	0.714	20.0 (0.0–30.0)	20.0 (0.0–35.0)	0.054
Multifocal disease, n (%)	154 (40.85)	362 (46.53)	0.069	353 (45.53)	163 (47.38)	0.228	254 (45.52)	262 (43.89)	0.577
Tumor size ≥3 cm, n (%)	231 (61.44)	515 (66.20)	0.113	546 (67.41)	200 (58.14)	0.003	373 (66.85)	373 (62.58)	0.130
Carcinoma in situ, n (%)	37 (9.81)	119 (15.30)	0.011	103 (12.70)	53 (15.41)	0.218	79 (14.16)	77 (12.90)	0.391
Median ESR, mm/h (IQR)	12.0 (7.0–20.0)	15.0 (9.0–24.0)	<0.001	13.0 (8.0–22.0)	14.0 (8.5–22.0)	0.302	12.0 (7.0–20.0)	15.0 (9.0–25.0)	<0.01
Median CRP, mg/l (IQR)	2.0 (0.7–4.0)	2.3 (0.91–5.0)	0.02	2.27 (0.74–5.0)	2.0 (1.0–4.0)	0.918	2.0 (0.73–4.0)	2.9 (1.0–6.0)	<0.01

IQR = interquartile range; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; LMR = lymphocyte/monocyte ratio.

3.3. Clinical and pathologic characteristics according to SIM score

In total, 583 patients (50.5%) had a SIM score ≥2. Table 3 lists the clinical and pathologic variables according to SIM score. We found a significant increase in score with the number of cigarettes smoked and years of smoking. There was a lower rate of tumor size ≥3 cm among patients with high SIM score ($p = 0.016$), as well as a higher CIS rate ($p < 0.01$).

3.4. Oncologic outcomes according to SIM score

The median follow-up was 48 mo (IQR 40.0–66.0); in total, we observed 772 recurrences (66.8%), 315 progressions (27.3%), 81 cancer-specific deaths (7.0%), and 162 overall deaths (14.0%). The 48-mo recurrence-free survival was 80.8% (95% confidence interval [CI] 72.7–86.7%), 47.3% (95% CI 42.4–52.1%), 20.7% (95% CI 17.0–24.6%), and 17.1% (95% CI 9.9–25.9%) among patients with SIM scores of 0, 1, 2, and 3, respectively ($p < 0.01$, log-rank test). In multiple comparisons, between-group differences in recurrence-free survival were statistically significant (all $p < 0.01$) except for 2 versus 3 ($p = 0.24$). The 48-mo progression-free survival was 92.0% (95% CI 85.6–95.6%), 75.7% (95% CI 70.6–80.0%), 72.8% (95% CI 68.4–76.8%), and 63.1% (95% CI 51.9–72.4%) among patients with SIM scores of 0, 1, 2, and 3, respectively ($p < 0.01$, log-rank test). In multiple comparisons, the between-group differences in progression free-survival were statistically significant (all $p < 0.01$) except for 2 versus 3 ($p = 0.06$; Fig. 1).

For the 48-mo CSS, we observed significant differences between SIM 0 and 3 (97.1% vs 90.6%; $p < 0.01$), 1 and 3 (97.8% vs 90.6%; $p < 0.01$), and 2 and 3 (94.4% vs 90.6%; $p = 0.04$). We observed significant differences in 48-mo OS only for SIM 1 versus 2 (93.9% [95% CI 90.7–96.0%] and 89.6% [95% CI 85.9–92.4%]; $p = 0.02$; Fig. 2).

In bootstrap-adjusted multivariable Cox regression analyses, higher SIM score was associated with a significantly higher hazard ratio (HR) for recurrence (HR 3.7, 7.1, and 7.9) and progression (HR: 3.15, 4.4 and 5.8). Conversely, SIM was not associated with a higher probability of CSM or OM (Table 4).

Fig. 3 shows the DCA for models included in Table 4 and for individual factors. The model including SIM showed a greater clinical benefit of between 0.50 and 0.85 for predicting recurrence, and between 0.15 and 0.60 for progression when compared to all individual components.

### 3.5. Oncologic outcomes according to smoking status

We performed a subgroup analysis for current smokers and we found that the 48-mo recurrence-free survival was 65.0% (95% CI 48.2–77.6%), 39.9% (95% CI 30.3–49.3%), 19.6% (95% CI 13.1–27.1%), and 16.2% (95% CI 5.3–32.5%) for patients with SIM scores 0, 1, 2, and 3, respectively ($p < 0.01$). Multiple comparison revealed significant differences between SIM 0 and 1 ($p = 0.04$), 0 and 2 ($p < 0.01$), 0 and 3 ($p < 0.01$), 1 and 2 ($p < 0.01$), and 1 and 3 ($p < 0.01$; Supplementary Fig. 1).

Table 3 – Association between baseline clinicopathologic characteristics and cumulative marker score in the total cohort

Variable	Systemic inflammatory marker score				p value
	0	1	2	3	
Patients (n)	125	447	477	106	
Median age, yr (IQR)	73 (66.0–78.0)	70.0 (64.0)77.0)	71.0 (65.0–78.0)	70.0 (67.0–79.0)	0.13
Gender, n (%)					
Male	10 (86.40)	365 (81.66)	395 (82.81)	89 (83.69)	0.648
Female	17 (13.60)	82 (18.34)	82 (17.19)	17 (16.04)	
Smoking status, n (%)					<0.001
Never	38 (30.40)	195 (43.62)	257 (53.88)	58 (54.72)	
Current	40 (32.00)	125 (27.96)	130 (27.25)	32 (30.19)	
Former	47 (37.60)	127 (28.41)	90 (18.87)	16 (15.09)	
Median cigarettes per day, n (IQR)	10.0 (0.0–15.0)	10.0 (0.0–20.0)	10.0 (0.0–20.0)	14.5 (0.0–20.0)	0.018
Median smoking years, n (IQR)	15.0 (0.0–30.0)	20.0 (0.0–30.0)	25.0 (0.0–35.0)	20.0 (0.0–35.0)	<0.01
Multifocal disease, n (%)	55 (44.0)	186 (41.61)	224 (46.96)	51 (48.11)	0.357
Tumor size ≥3 cm, n (%)	96 (76.80)	274 (61.43)	314 (65.83)	62 (58.49)	0.007
Carcinoma in situ, n (%)	12 (9.60)	62 (14.09)	57 (11.95)	24 (22.64)	0.016
Median ESR, mm/h (IQR)	8.0 (5.8–14.0)	13.0 (8.0–20.0)	15.0 (10.0–25.0)	16.0 (8.0–25.0)	<0.01
Median CRP, mg/l (IQR)	2.0 (0.67–2.0)	2.0 (0.7–4.0)	2.53 (0.9–5.0)	3.0 (1.1–5.0)	<0.01

IQR = interquartile range; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
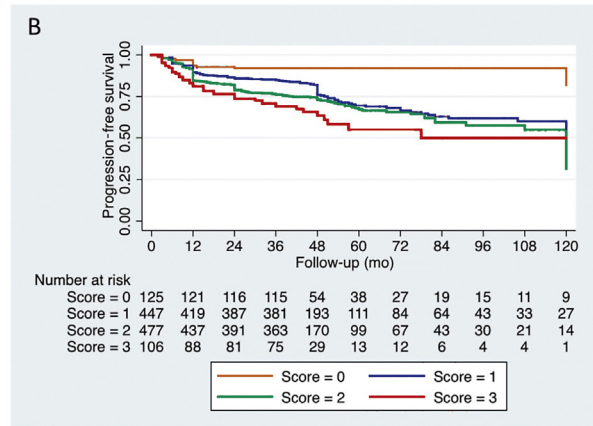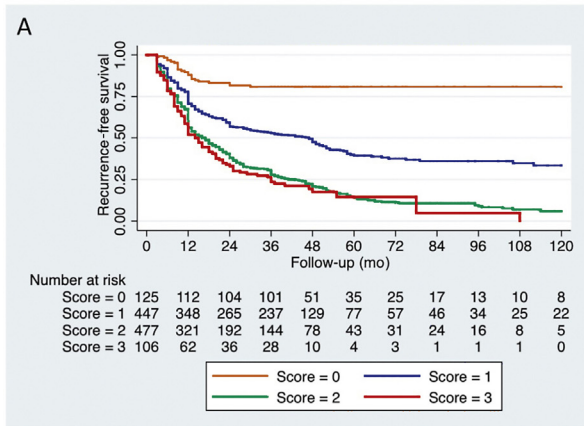
Fig. 1 – Kaplan-Meier estimates of (A) recurrence-free survival and (B) progression-free survival for high-grade T1 non–muscle-invasive bladder cancer stratified by systemic inflammatory marker score.
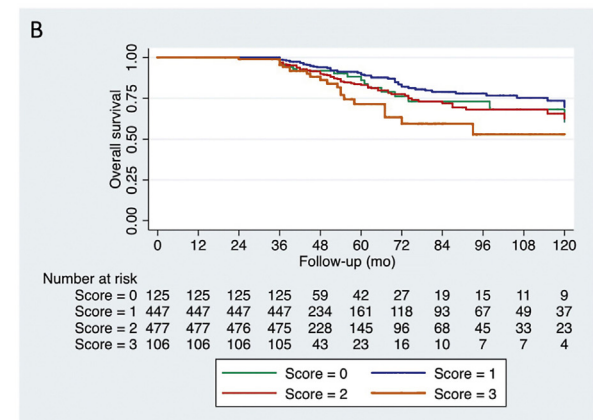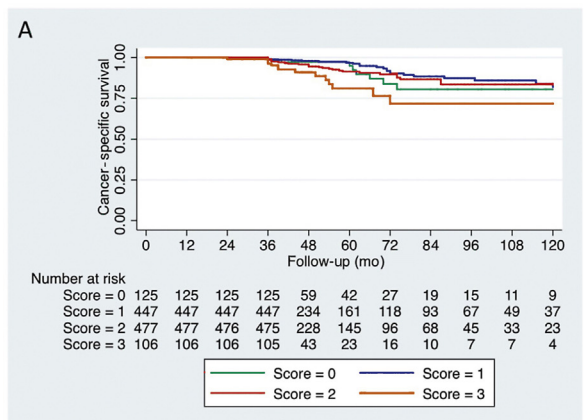

Fig. 2 – Kaplan-Meier estimates of (A) cancer-specific survival and (B) overall survival for high-grade T1 non–muscle-invasive bladder cancer stratified by systemic inflammatory marker score.

Table 4 – Multivariable Cox regression analysis for recurrence-free survival, progression-free survival, cancer-specific mortality, and overall mortality

Variable	Recurrence-free survival		Progression-free survival		Cancer-specific mortality		Overall mortality	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age in years	1.00 (0.99–1.01)	0.99	0.99 (0.98–1.00)	0.309	1.03 (1.01–1.06)	0.006	1.05 (1.02–1.06)	<0.001
Gender								
Male	Reference		Reference		Reference		Reference	
Female	1.15 (0.96–1.38)	0.130	1.20 (0.91–1.58)	0.194	0.88 (0.49–1.59)	0.686	1.02 (0.68–1.52)	0.923
Smoking status								
Never	Reference		Reference		Reference		Reference	
Current	1.01 (0.86–1.20)	0.86	0.84 (0.62–1.12)	0.24	0.92 (0.49–1.76)	0.803	1.06 (0.70–1.60)	0.428
Former	0.69 (0.57–0.84)	<0.001	1.32 (1.02–1.71)	0.036	1.25 (0.75–2.05)	0.383	0.85 (0.59–1.23)	0.382
Multifocal (yes vs no)	1.22 (1.05–1.40)	0.007	1.31 (1.05–1.64)	0.016	1.17 (0.75–1.82)	0.469	1.13 (0.83–1.55)	0.428
Tumor size (<3 vs ≥3 cm)	1.38 (1.19–1.62)	<0.001	1.72 (1.33–2.21)	<0.001	1.55 (0.94–2.55)	0.083	1.19 (0.85–1.67)	0.300
CIS (yes vs no)	1.06 (0.87–1.31)	0.53	1.92 (1.47–2.50)	<0.001	2.83 (1.75–4.57)	<0.001	2.25 (1.56–3.25)	<0.001
SIM score								
0	Reference		Reference		Reference		Reference	
1	3.73 (2.45–5.68)	<0.001	3.15 (1.69–5.86)	<0.001	0.68 (0.31–1.47)	0.328	0.36 (0.37–1.08)	0.099
2	7.06 (4.67–10.69)	<0.001	4.41 (2.38–8.18)	<0.001	1.00 (0.47–2.13)	0.981	0.97 (0.58–1.62)	0.909
3	7.88 (4.99–12.43)	<0.001	5.83 (2.97–11.45)	<0.001	1.96 (0.82–4.67)	0.128	1.28 (0.68–2.44)	0.438

HR = hazard ratio; CI = confidence interval; SIM = systemic inflammatory marker.
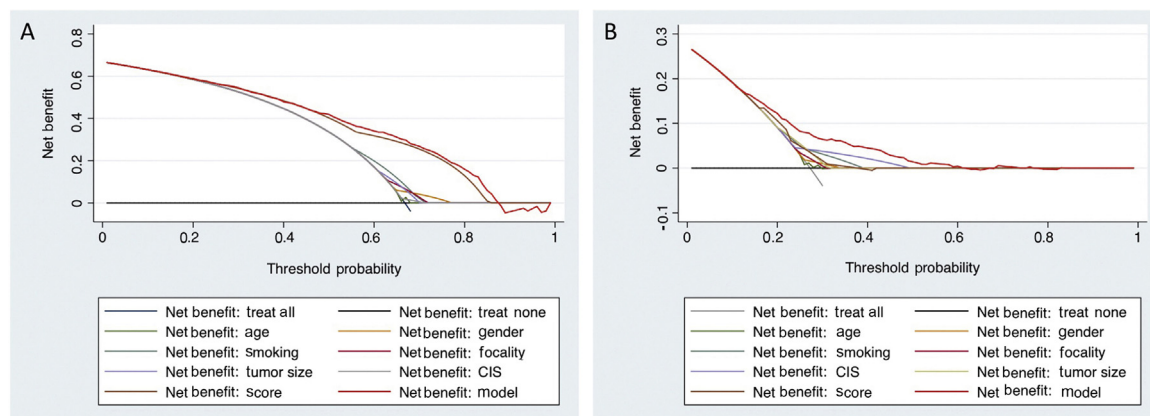
Fig. 3 – Decision curve analyses demonstrating the net benefit associated with (A) the recurrence and (B) the progression probabilities model. Decision curve analysis is a method for evaluating and comparing prediction models that incorporates clinical consequences.

Progression-free survival in this subgroup was 90.00% (95% CI 75.51–96.12%), 79.8% (95% CI 68.5–87.4%), 78.2% (95% CI 69.6–84.6%), and 63.9% (95% CI 40.3–80.2%) for patients with SIM scores of 0, 1, 2, and 3, respectively ($p = 0.09$). Multiple comparisons revealed significnat differences between SIM 0 and 3 ($p = 0.03$) and 1 and 3 ($p = 0.03$).

4. Discussion

Our study aim was to investigate the predictive role of SIMs among patients with high-risk NMIBC. Several findings from our analysis are worthy of note. We found that a single score based on NLR, PLR, and LMR cutoffs, denoted as SIM, can predict recurrence and progression in this patient population. A higher SIM score is related to worse outcomes, even after adjusting for pathological variables such as tumor size, CIS, and multifocality. Furthermore, inclusion of this score in DCA seems to be of clinical benefit over individual components in the predictive model.

A growing body of evidence supports the role of inflammatory markers in urothelial cancers. Tanaka et al [14] showed that a score defined by preoperative NLR, plasma fibrinogen, and serum CRP was an independent predictor of patient survival following radical nephroureterectomy. The role of NLR was evaluated in a recent meta-analysis of 17 studies involving 3159 urinary cancer cases; elevated NLR predicted worse clinical outcomes. Subgroup analyses revealed that elevated NLR was associated with a high recurrence rate and poor cancer-specific survival in bladder cancer and urothelial carcinoma. Elevated NLR was a significant prognostic marker for worse recurrence-free survival and CSS, regardless of ethnic background, and

predicted poor OS in the Caucasian population but not for Asian patients [15]. These results were confirmed by a study involving the Mayo Clinic Cystectomy Registry: patients with NLR = 2.7 had larger tumors (median 3.7 vs 2.6 cm; $p < 0.0001$) and were more likely at RC to have pathologic extravesical tumors (pT3/4; 44% vs 32%; $p < 0.0001$), advanced nodal stage ($p = 0.002$), lymph node tumor involvement (20% vs 13%; $p = 0.003$), a greater number of positive lymph nodes ($p = 0.001$), and lymph node density (7.4% vs 3.4%; $p = 0.0008$). Likewise, elevated NLR was associated with subsequent disease recurrence, and cancer-specific and all-cause mortality [16].

Moreover, despite the inverse association between SIM and tumor size, our results show a significantly higher CIS rate among patients with higher SIM, strengthening its link with potential progression of the disease. Thus, the SIM score could serve in this setting in selecting patients who might benefit from an early radical cystectomy strategy. The current prognostic model for NMIBC, which relies on pathologic features such as T stage, grade, focality, tumor diameter, recurrence rate, and concomitant CIS, does not have sufficient accuracy in identifying such cases to ensure better survival [7].

BC should be considered a heterogeneous disease in which genes and epigenetic mutations, together with immune system alterations, play different roles. These considerations have increased interest in personalized, molecular targeting, and immunotherapeutic approaches to improve survival and overall prognosis among patients with BC [21]. In this context, it has been demonstrated that NLR is a biomarker of early response to targeted therapy among patients with metastatic renal cell carcinoma [17].

Our study is not devoid of limitations. First, our cohort may involve heterogeneity owing to the multi-institutional study design and the lack of central pathology review of TURB specimens. Second, laboratory assays and pathology examinations were performed separately at each institution without central review and we did not perform SIM measurement in a follow-up setting after TURB. However, as previously demonstrated by Charlton et al [18], changes from the AJCC 6th to 7th editions caused no substantial movement between stages.

Third, we did not include other potential inflammation or immune system variables that might constitute promising biomarkers in the model. Finally, an external validation of our findings has still to be performed.

5. Conclusions

Patients with high-grade T1 stage NMIBC with high SIM scores have worse oncologic outcomes in terms of recurrence and progression. These results could be translated into clinical practice to stratify patients who might benefit from early cystectomy.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.euo.2018.06.006.

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