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Mean platelet volume to lymphocyte ratio as an inflammatory marker associated with high-grade recurrence and progression of non-muscle-invasive bladder cancer treated with Bacillus Calmette-Guérin

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Introduction To assess the value of a novel inflammatory marker involving the ratio between mean platelet volume and lymphocyte counts (MPVL) in the prediction of high-grade recurrence-free survival (HG RFS) and progression-free survival (PFS) in patients with non-muscle-invasive bladder cancer (NMIBC) treated with adjuvant Bacillus Calmette-Guérin (BCG) therapy.

Material and methods In this retrospective, single tertiary centre study the medical records of 216 consecutive patients with NMIBC, who received BCG between 2010 and 2019, were reviewed. Kaplan-Meier curves and Cox proportional hazard regression were used for survival analysis.

Results We included 194 patients who underwent transurethral resection of a bladder tumour and received at least an induction course of BCG. The majority of patients presented with high-grade T1 tumours (n = 114, 59%). Within a median follow-up of 65 months (IQR: 27–93), 35 patients (18%) experienced progression, and 69 (34.5%) had a high-grade recurrence. Kaplan-Meier analyses revealed a significant association between higher MPVL and worse PFS and HG RFS (both p <0.05). Specifically, patients with higher MPVL demonstrated decreased 5-year PFS (75% vs 90%) and HG RFS (54.5% vs 75%) compared to lower MPVL counterparts. Multivariate analyses confirmed the independent prognostic value of MPVL for HG RFS (HR = 1.7, p = 0.047) and PFS (HR = 2.37, p = 0.026).

Conclusions In patients with NMIBC treated with adjuvant BCG, an elevated inflammatory marker comprising mean platelet volume and lymphocyte count ratio may serve as a prognostic factor associated with worse PFS and HG RFS. The role of MPVL in clinical decision-making must be validated in further multicentre prospective studies.

Key Words: non-muscle-invasive bladder cancer ‹› mean platelet volume to lymphocyte ratio ‹› recurrence ‹› progression ‹› BCG ‹› inflammatory marker

INTRODUCTION

Bladder cancer (BC) is the most common malignancy of the urinary tract and ranks as the 10th most frequently diagnosed cancer worldwide [1]. BC is a heterogeneous disease that includes non-muscle-invasive bladder carcinoma (NMIBC) and muscle-invasive bladder carcinoma (MIBC) with different management and clinical outcomes [2–4]. Urologists should always use a risk-based therapeutic approach to recommend the most effective management for each patient considering the variety of therapeutic options available [3, 5]. For patients with NMIBC, viable options include transurethral resection of the bladder tumour (TURBT), postoperative single instillations, adjuvant therapies with intravesical

chemo- or immunotherapeutic agents, such as Bacillus Calmette-Guerin (BCG), and early cystectomy in selected cases [1, 5, 6]. The current gold standard adjuvant therapy for NMIBC with a high risk of progression is intravesical BCG [1, 7]. Since Morales et al.'s initial report of the efficacy of BCG in treating bladder cancer in 1976, more than 40 years of development have proven to BCG's status as a critically significant treatment for NMIBC [7, 8]. However, up to 30% of patients fail to respond to BCG therapy, which is associated with high progression risk and a clinical dilemma regarding treatment choices for BCG-unresponsive NMIBC due to the shortage of available bladder-sparing treatments [9, 10]. Development of high-grade recurrence or progression is inevitable, to meet the BCG unresponsive criteria prompting BCG cessation and indication for radical cystectomy [10, 11]. Low-grade recurrences, although clinically relevant, do not preclude further BCG treatment and are not considered as BCG-unresponsive disease [10, 12]. Unfortunately, currently recommended risk models were not designed to specifically predict high-grade recurrences, but recurrences in general [13–15]. Therefore, the search for reliable prognostic markers of response to BCG has been widely conducted in recent years [5, 9, 13].

Inflammation associated with bladder tumour is widely recognised as a prognostic factor and plays a significant role in both tumour development and patient outcomes [16, 17]. Platelets, as essential blood cells involved not only in clot formation but also in inflammation, have been shown to affect prognosis in different cancers [18, 19]. Platelet-based biomarkers, such as mean platelet volume (MPV), are cost-effective and readily accessible indicators of inflammatory states in various pathological conditions [18, 20]. Elevated MPV is often associated with increased platelet turnover, indicating the presence of larger, metabolically active platelets that are more prone to aggregation and chemical mediator release [21]. These characteristics are particularly relevant in the context of inflammation and cancer, where platelet activation can promote disease progression through mechanisms like angiogenesis and the secretion of bioactive molecules [19]. MPV is regarded as an inflammatory measure of rheumatic, digestive, and cardiovascular diseases [20, 22]. However, studies on the MPV to lymphocyte ratio (MPVL) for the prognosis of bladder tumours are scarce [23, 24].

We aimed to evaluate the value of a novel inflammatory marker involving the ratio between mean platelet volume and lymphocyte counts in the prediction of high-grade recurrence and progression of NMIBC in patients treated with BCG.

MATERIAL AND METHODS

Study design and inclusion criteria

This is a retrospective, single tertiary centre study. Medical records of 216 consecutive patients with intermediate-, high-, and very high-risk NMIBC, who underwent TURBT between 2011 and 2019 and were further treated with BCG instillations were reviewed. We excluded patients who did not receive at least an induction course of BCG (n = 11), patients who received delayed BCG therapy >4 months after TURBT (n = 7), and those with missing laboratory data (n = 4). None of the patients had active inflammatory disease or infection. Only patients with complete medical records regarding clinical data, histopathological data, and blood parameters were included.

Treatment

Patients were qualified for TURBT after the exclusion of urinary tract infection. All patients who underwent incomplete initial TURBT received repeat TURBT (reTUR; also called second or restaging transurethral resection). ReTUR was performed whenever indicated by clinical guidelines or upon the treating physician's decision. Surgical specimens were reviewed by a genitourinary pathologist, graded according to 1973 and 2004 WHO grading systems and staged according to the 2009 TNM classification. Patients eligible for BCG therapy in the standard schedule included those with high-grade tumours, T1 stage, carcinoma *in situ* (CIS), or multiple and recurrent low-grade Ta tumours. After a minimum of 2 weeks of post-surgery recovery, all patients received an induction course consisting of at least 5 out of 6 weekly instillations. The maintenance schedule included 3 instillations of intravesical BCG each week at 3, 6, 12, 18, 24, 30, and 36 months.

Follow-up and outcomes

Follow-up included cystoscopy and urine cytology performed regularly (every 3 months in the first 2 years and every 6 months from the second to the fifth year). Suspicion of recurrence or progression was verified each time with TURBT or transurethral bladder biopsy.

Progression and high-grade recurrence survival were primary outcomes. Progression was defined as the development of MIBC or distant metastasis. High-grade recurrence was defined as a grade 3 or high-grade tumour presence during or after BCG treatment. Recurrence was defined as the occurrence

of any bladder malignancy irrespective of tumour grade.
Survival was calculated from the date of index TURBT to the occurrence of the event of interest. Patients were censored at the date of last follow-up, death due to any cause, or the date of salvage radical cystectomy.

Assessment of clinicopathologic and laboratory data

Descriptive variables included clinical, histopathological, and laboratory data. Histopathological data included primary staging and grading. Clinical data included previous patterns of recurrence, tumour size, multifocality, age, gender, and comorbidities. Laboratory data included preoperative blood parameters assessed prior to TURBT.
Blood samples were collected for complete blood count assessment using EDTA as the anticoagulant, and stasis was consistently applied during venipuncture. Blood samples were assessed in the hospital laboratory with an automatic analyser. The mean platelet volume was calculated by haematological analysers, based on volume distribution during routine preoperative complete blood count tests. The normal reference values for MPV, as providedby our laboratory guideline, range between 7.0 and 12.0 fl.
The ratio of mean platelet volume to lymphocyte count was calculated to derive the novel inflammatory marker. Other inflammatory indices such neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), systemic inflammatory response index (SIRI – neutrophil × monocyte/lymphocyte), and pan-immune-inflammation value (PIV – neutrophil × monocyte × platelets/lymphocyte) were calculated as previously [9, 25, 26]. The optimal cutoff value for the inflammatory marker was determined by the receiver operating characteristic curve with J statistic.

Statistical analysis

Kaplan-Meier curves and Cox proportional hazard regression were used for survival analysis. Median follow-up was computed using reverse Kaplan-Meier method. Univariate and multivariate Cox proportional hazard analyses were performed to identify the predictors of high-grade recurrence-free survival (HG RFS) and progression-free survival (PFS). Multivariate analyses included only selected variables based on the univariate analyses. Stepwise selection of variables was applied. Hazard ratios (HR) along with 95% confidence intervals (95% CI) were derived from Cox proportional hazard regression.
The log-rank test was used for the comparison of Kaplan-Meier curves. Continuous variables are presented as median values accompanied by ranges between quartiles (IQR), and categorical variables are presented as numbers and percentages. Differences between groups were evaluated with the U-Mann-Whitney test for continuous variables and with Fischer's exact test or the χ^2 test for categorical variables. For all statistical analyses, a two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed with the SAS System, version 9.4 (SAS Institute, Cary, NC, USA).

Bioethical standards

Due to the study's character, the Institutional Review Board waived the need for study approval. The study was performed in accordance with the Declaration of Helsinki and its later amendments.

RESULTS

We included 194 patients who underwent TURBT and received at least an induction BCG course. The cohort included 123 T1 tumours (63.5%), 45 Ta tumours (23.2%), and 26 isolated carcinomas in situ (13.4%). High-grade histology was found in 169 (87.1%) and low-grade in 25 patients (12.9%). Median survival follow-up was 65 months (IQR 27–93 months). During the study period, progression occurred in 35 patients (18%), high-grade recurrence in 69 patients (34.5%), and any tumour recurrence in 86 patients (44%). Novel EAU2021 risk stratification classified 129 (66.5%) and 34 (17.5%) patients as high and very high risk, and only 31 (16%) as intermediate risk [27]. Baseline characteristics are presented in Table 1.

Mean platelet volume to lymphocyte ratio

The median lymphocyte count and mean platelet volume were 1.87 G/l and 10.9 fl, respectively. We categorised MPV and MPVL into high and low values as described above. A total of 119 patients (61.3%) presented with a preoperative MPV above 10.6 fl, chosen as the cutoff. Additionally, 111 patients (57.2%) had a high preoperative MPV to lymphocyte ratio (MPVL), defined as a ratio above 5.6.
There were 26 progressions in patients with high MPV and high MPVL values, constituting 21.9% and 23.4% of respective groups. The remaining 9 progressions were found in patients with low MPV and low MPVL values, accounting for 12% and 10.8% ($p = 0.08$ and $p < 0.05$, respectively). Similarly, high-grade

recurrences were more frequent in high-MPV (41% vs 24% p < 0.05) and MPVL (40.5% vs 26.5%, p < 0.05) groups compared to low-MPV and MPVL groups (Table 2).

Comparison of groups with high and low mean platelet volume and lymphocyte counts

We evaluated the differences between groups with higher and lower MPVL to identify confounders and potential associations with other prognostic factors in NMIBC (Table 2). No significant differences were observed in the medians of EORTC or CUETO risk scores, nor in tumour staging between the high- and low-MPVL groups. However, patients with higher MPVL were older (median age 74 vs 67 years) and included a larger proportion of EAU2021 intermediate-risk patients (24.1% vs 9.9%) compared to the low-MPVL group. As expected, lymphocyte and platelet counts were lower, whereas median MPV was higher in the high-MPVL compared to the low-MPVL cohort.

Survival analysis

Estimates of one-year and 5-year PFS were 91% and 81.5%, respectively. Estimates of one-year and 5-year HG RFS were 80% and 63%, respectively. Kaplan-Meier analyses demonstrated decreased PFS and HG RFS in patients with high MPVL (both p <0.05) compared to low MPVL counterparts (5-year PFS 75% vs 90%; 5-year HG RFS 54.5% vs 75%) (Figure 1). High MPV was associated with worse HG RFS (p <0.05), but the conventional level of statistical significance for PFS was not met (p = 0.12). Additional sensitivity analysis performed in the cohort of patients > 65 years of age confirmed the prognostic value of MPVL for PFS, HG RFS, and RFS (Figure 2).

Univariate and multivariate analysis for high-grade recurrence-free survival

Univariate analyses with Cox proportional hazards identified clinicopathological and laboratory factors associated with HG RFS and PFS (Table 3A and B). The following factors were selected in the univariate analyses for HG RFS: high-grade tumour (HR = 3.43, 95% CI: 1.07–10.9, p = 0.037), tumour multiplicity (HR = 2.2, 95% CI: 1.31–3.7, p = 0.002), pathology at ReTUR (T1HG vs T0; HR = 3.12, 95% CI: 1.51–6.44, p = 0.002; CIS vs T0; HR = 2.29, 95% CI: 1.06–4.9, p = 0.033; no reTUR vs T0; HR = 2.03, 95% CI: 1.09–3.78, p = 0.026), EORTC 2006 recurrence risk score (HR = 1.17, 95% CI: 1.06–1.29, p = 0.002),

Table 1. *Baseline characteristics of included patients with NMIBC treated with BCG*

Variables		Whole cohort	
		No. of pts/ median	% of patients/ IQR
Stage	Ta	45	23.20
	T1	123	63.40
	CIS	26	13.40
Tumor grade	High-grade	169	87.11
	Low-grade	25	12.89
Concomitant CIS	No	172	88.66
	Yes	22	11.34
Multiplicity	No	90	46.39
	Yes	104	53.61
Large tumor >3 cm	No	133	68.56
	Yes	61	31.44
Previous history of recurrence	High-grade tumour	24	12.37
	Low-grade tumour	47	24.23
	Primary	123	63.40
ReTURBT status	T0	68	35.05
	T1HG	26	13.40
	TaHG	4	2.06
	TaLG	5	2.58
	CIS	27	13.92
	None	64	32.99
EAU risk groups	IR	31	15.98
	HR	129	66.49
	VHR	34	17.53
Age	Years	71	64–78
Charlson comorbidity score		6	4–7
EORTC 2006 recurrence risk	Median	6	5–8
EORTC 2006 progression risk score	Median	12	9–14
CUETO recurrence risk score	Median	9	7–11
CUETO progression risk score	Median	9	8–10
Neutrophil counts	G/l	4.6	3.7–5.8
Lymphocyte counts	G/l	1.87	1.4–2.4
Platelet counts	G/l	221.5	188–265
Mean platelet volume	Median (fl)	10.9	10.2–11.5
NLR	Median	2.5	1.9–3.4
MPV/ lymphocyte	Median	6.0	4.7–7.5

CIS – carcinoma *in situ*; IR – intermediate-risk; HR – high-risk; MPV – mean platelet volume; NLR – neutrophil to lymphocyte ratio; No. of pts – number of patients; IQR – interquartile range; ReTURBT – repeat transurethral resection of the bladder tumour; VHR – very-high-risk

CUETO recurrence risk score (HR = 1.11, 95% CI: 1.02–1.20, p = 0.01), high MPV-to-lymphocyte ratio (HR = 1.72, 95% CI: 1.03–2.86, p = 0.038), and high MPV (HR = 1.87, 95% CI: 1.08–3.2, p = 0.024).

In the multivariate analyses, high MPVL (HR = 1.7, 95% CI: 1.01–2.85, p = 0.047), EORTC 2006 recurrence risk score (HR = 1.22, 95% CI: 1.09–1.36, p <0.001), tumour grade (HR = 3.5, 95% CI: 1.06–11.5, p <0.039), and the pathological results of reTUR (T1HG vs T0, HR = 3.63, 95% CI: 1.75–7.52, p <0.001; CIS vs T0, HR = 2.61, 95% CI: 1.2–5.59, p = 0.015) were independent predictors of high-grade recurrence-free survival (Table 4A).

Univariate and multivariate analysis for progression-free survival

The following factors were selected in the univariate analyses for PFS: T stage (T1 vs Ta, HR = 2.77, 95% CI: 0.83–9.23, p = 0.096; CIS vs Ta, HR = 4.32, 95% CI: 1.14–16.3, p = 0.031), tumor multiplicity (HR = 2.82, 95% CI: 1.31–6.01, p = 0.008), pathology at ReTUR (T1HG vs T0; HR = 2.92, 95% CI: 1.1–7.71, p = 0.03; ReTUR not performed vs T0; HR = 2.0, 95% CI: 0.88–4.51, p = 0.10), EORTC 2006 progression risk score (HR = 1.12, 95% CI: 1.02–1.21, p = 0.016), CUETO progression risk score (HR = 1.16 95% CI: 0.98–1.34, p = 0.07)

Table 2. *Comparison of clinicopathologic features between patients with high and low mean platelet volume to lymphocyte ratio (MPVL)*

Variables		High MPVL > 5.6		Low MPVL ≤ 5.6		P-value
		No. of pts/median	% of patients/IQR	No. of pts/median	% of patients/IQR	
Stage	Ta	23	27.71	22	19.82	0.44
	T1	49	59.04	74	66.67	
	CIS	11	13.25	15	13.51	
Tumour grade	Grade 1	5	6.02	3	2.70	0.40
	Grade 2	13	15.66	14	12.61	
	Grade 3	65	78.31	94	84.68	
Concomitant CIS	No	74	89.16	98	88.29	1.0
	Yes	9	10.84	13	11.71	
Multiplicity	No	36	43.37	54	48.65	0.47
	Yes	47	56.63	57	51.35	
Large tumour >3 cm	No	59	71.08	74	66.67	0.54
	Yes	24	28.92	37	33.33	
Previous history of recurrence	High-grade tumour	10	12.05	13	11.71	0.62
	Low-grade tumor	23	27.71	24	21.62	
	Primary	50	60.24	74	66.67	
EAU 2021 risk groups	IR	20	24.10	11	9.91	0.022
	HR	48	57.83	81	72.97	
	VHR	15	18.07	19	17.12	
Age	Years	74	66–79	67	62–77	0.003
Charlson comorbidity score	Median	6	4–7	5	4–7	0.23
EORTC 2006 recurrence risk	Median	6	5–8	6	4–9	0.64
EORTC 2006 progression risk score	Median	12	9–14	12	8–15	0.41
CUETO recurrence risk score	Median	7	5–7	7	4–10	0.95
CUETO progression risk score	Median	9	8–10	8	7–10	0.034
Neutrophil counts	G/l	4.36	3.60–5.68	5.06	3.73–5.96	0.17
Lymphocyte counts	G/l	1.46	1.18–1.73	2.45	2.10–2.97	<0.001
Platelet counts	G/l	206	174–243	244	209–285	<0.001
Mean platelet volume	Median (fl)	11.0	10.3–11.7	10.6	10.0–11.2	0.011

CIS – carcinoma *in situ*; IR – intermediate-risk; IQR – interquartile range; IR – intermediate-risk; MPVL – mean platelet volume to lymphocyte ratio; No. of pts – number of patients; IR – intermediate-risk

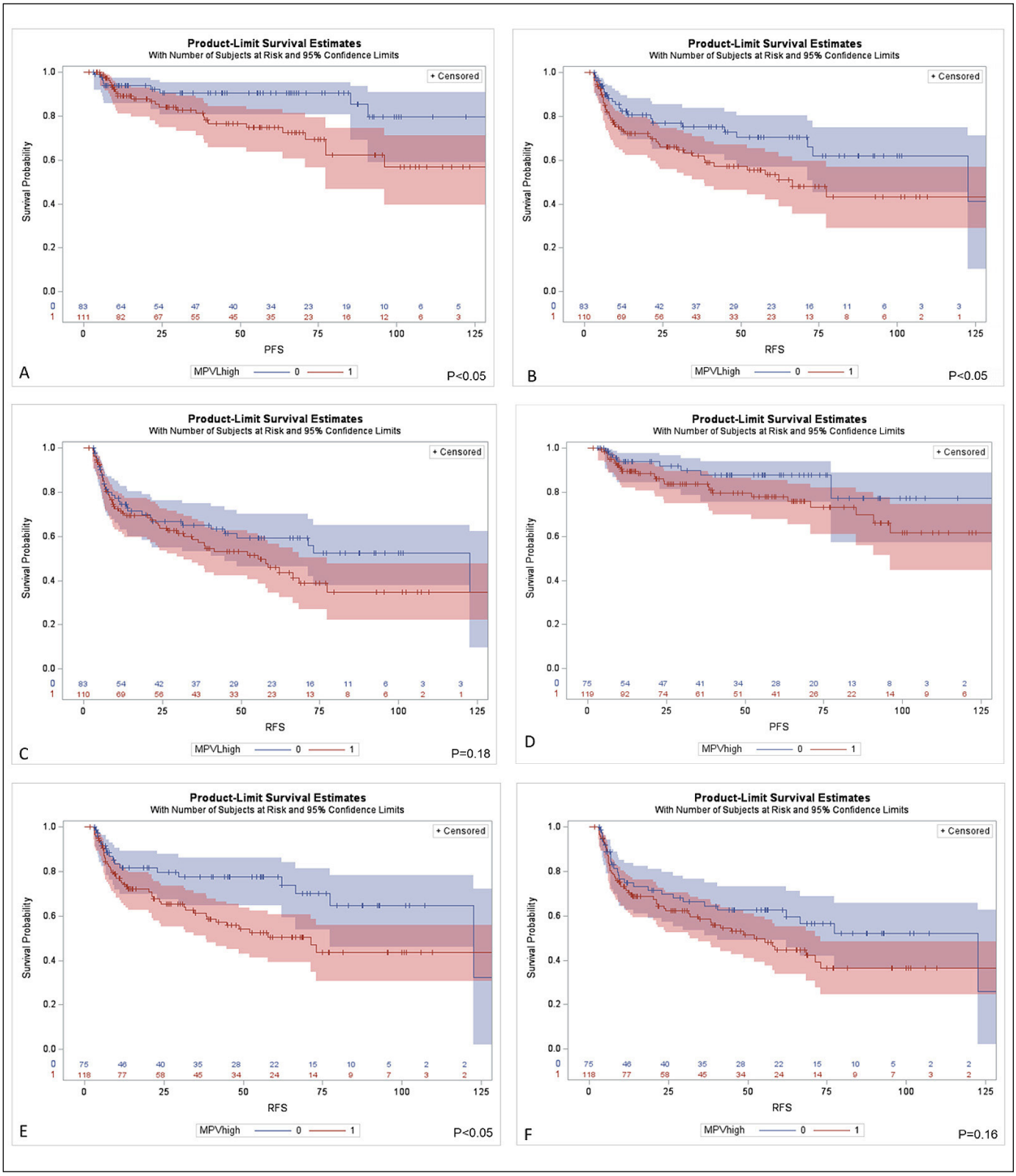

Figure 1. *Kaplan-Meier curves illustrating progression-free survival, high-grade recurrence-free survival, and recurrence-free survival in patients with higher and lower mean platelet volume-to-lymphocyte ratio (A, B, and C, respectively) and higher and lower mean platelet volume (D, E, and F, respectively).*

HG RFS – high-grade recurrence-free survival; MPVhigh – high mean platelet volume; MPVLhigh – high mean platelet volume to lymphocyte ratio; PFS – progression-free survival; RFS – recurrence-free survival

Table 3. *Univariate analyses with Cox proportional hazards for predicting high-grade high-grade recurrence-free survival* **(A)** *and progression-free survival* **(B)**

A

	High-grade recurrence			
Variable		HR	95% CI	P-value
Stage	Ta	ref	–	
	T1	1.725	0.87–3.41	0.12
	CIS	1.992	0.84–4.69	0.12
Tumour grade	Low-grade	ref	–	
	High-grade	3.428	1.07–10.9	**0.037**
Previous history of recurrence	Low–grade tumour	ref	–	
	High–grade tumour	1.886	0.88–4.03	**0.10**
	Primary tumour	0.964	0.53–1.74	0.90
Concomitant CIS	No	ref	–	
	Yes	1.615	0.84–3.09	0.15
Multiplicity	No	ref	–	
	Yes	2.205	1.31–3.70	**0.002**
Large tumour >3 cm	No	ref	–	
	Yes	0.771	0.44–1.33	0.36
Detrusor muscle in index TURBT	Yes	ref	–	
	No	1.030	0.58–1.82	0.92
ReTURBT status	T0	ref	–	
	T1HG	3.120	1.51–6.44	**0.002**
	TaLG	1.028	0.13–7.73	0.98
	CIS	2.287	1.06–4.90	**0.033**
	ReTURBT not performed	2.033	1.09–3.78	**0.026**
Age	Years	1.018	0.99–1.04	0.18
Charlson comorbidity index	Points	1.147	1.00–1.30	**0.04**
Gender	Female	ref	–	
	Male	0.902	0.52–1.54	0.71
EORTC 2006 recurrence risk	Points	1.170	1.06–1.29	**0.002**
EORTC 2006 progression risk score	Points	1.135	1.06–1.21	**<0.001**
CUETO recurrence risk score	Points	1.110	1.02–1.20	**0.011**
CUETO progression risk score	Points	1.231	1.09–1.38	**<0.001**
MPV to lymphocyte ratio	Continuous	1.067	0.99–1.14	**0.084**
MPV	Continuous	1.193	0.92–1.53	0.17
MPV to lymphocyte ratio	≤5.6	ref	–	
	>5.6	1.719	1.03–2.86	**0.038**
MPV	≤10.6	ref	–	
	>10.6	1.866	1.08–3.20	**0.024**
Neutrophil to lymphocyte ratio	≤2.4	ref	–	
	>2.4	1.628	0.99–2.67	**0.055**
Lymphocyte to monocyte ratio	≤2.55	ref	–	
	>2.55	1.711	1.05–2.77	**0.029**
Systemic immune inflammation index	≤500	ref	–	
	>500	1.311	0.79–2.16	0.28
Systemic inflammation response index	≤1.5	ref	–	
	>1.5	1.691	1.03–2.77	**0.037**
Pan–immune inflammation value	≤470	ref	–	
	>470	1.676	1.02–2.73	**0.039**

95% CI – 95% confidence interval; CIS – carcinoma *in situ*; HR – hazard ratio; MPV – mean platelet volume; ReTURBT– repeat transurethral resection of the bladder tumour

B

Variable		Progression HR	95% CI	P-value
Stage	Ta	ref	–	
	T1	2.774	0.83–9.23	**0.096**
	CIS	4.324	1.14–16.3	**0.031**
Tumour grade	Low-grade	ref	–	
	High-grade	4.900	0.66–35.8	0.12
Previous history of recurrence	Low-grade tumour	ref	–	
	High-grade tumour	2.178	0.66–7.19	0.20
	None	1.786	0.68–4.68	0.24
Concomitant CIS	No	ref	–	
	Yes	0.246	0.03–1.80	0.17
Multiplicity	No	ref	–	
	Yes	2.816	1.31–6.01	**0.008**
Large tumour >3 cm	No	ref	–	
	Yes	1.168	0.58–2.34	0.66
Detrusor muscle in index TURBT	Yes	ref	–	
	No	0.565	0.21–1.46	0.24
ReTURBT status	T0	ref	–	
	T1HG	2.923	1.10–7.71	**0.03**
	TaLG	0.000	0.00–.	0.99
	CIS	1.719	0.53–5.57	0.37
	ReTURBT not performed	1.997	0.88–4.51	**0.095**
Age	Years	1.021	0.98–1.05	0.25
Charlson comorbidity index	Points	1.152	0.96–1.38	0.13
Gender	Female	ref	–	
	Male	1.685	0.69–4.06	0.25
EORTC 2006 recurrence risk	Points	1.177	1.02–1.34	**0.018**
EORTC 2006 progression risk score	Points	1.115	1.02–1.21	**0.016**
CUETO recurrence risk score	Points	0.993	0.88–1.11	0.91
CUETO progression risk score	Points	1.155	0.98–1.34	**0.069**
MPV to lymphocyte ratio	Continuous	1.121	1.02–1.22	**0.011**
MPV	Continuous	1.245	0.87–1.77	0.23
MPV to lymphocyte ratio	≤5.6	ref	–	
	>5.6	2.389	1.11–5.10	**0.025**
MPV	≤10.6	ref	–	
	>10.6	1.803	0.84–3.84	0.13
Neutrophil to lymphocyte ratio	≤2.4	ref	–	
	>2.4	1.625	0.81–3.23	0.17
Lymphocyte to monocyte ratio	≤2.55	ref	–	
	>2.55	1.630	0.83–3.17	0.15
Systemic immune inflammation index	≤500	ref	–	
	>500	1.274	0.64–2.53	0.49
Systemic inflammation response index	≤1.5	ref	–	
	>1.5	1.273	0.65–2.48	0.47
Pan-immune inflammation value	≤470	ref	–	
	>470	1.444	0.72–2.86	0.29

95% CI – 95% confidence interval; CIS – carcinoma *in situ*; HR – hazard ratio; MPV – mean platelet volume; ReTURBT– repeat transurethral resection of the bladder tumour

Table 4. *Multivariate analysis with Cox proportional hazards for predicting high-grade recurrence-free survival* **(A)** *and progression-free survival* **(B)**

A

High-grade recurrence				
Variable		HR	95% CI	P-value
EORTC 2006 recurrence risk score	Points	1.223	1.09–1.36	<0.001
ReTURBT status	T0	ref	–	
	T1HG	3.631	1.75–7.52	<0.001
	TaLG	0.825	0.10–6.30	0.85
	CIS	2.616	1.20–5.69	0.015
	ReTURBT not performed	1.955	1.03–3.71	0.041
Tumour grade	Low-grade	ref	–	
	High-grade	3.508	1.06–11.5	0.039
MPV to lymphocyte ratio	≤5.6	ref	–	
	>5.6	1.696	1.01–2.85	0.047

95% CI – 95% confidence interval; CIS – carcinoma *in situ*; HR – hazard ratio; MPV – mean platelet volume; ReTURBT– repeat transurethral resection of the bladder tumour

B

Progression				
Variable		HR	95% CI	P-value
Stage	Ta	ref	–	
	T1	3.103	0.93–10.3	0.066
	CIS	4.425	1.16–16.7	0.028
Multiplicity	No	ref	–	
	Yes	3.059	1.42–6.55	0.004
MPV to lymphocyte ratio	≤5.6	ref	–	
	>5.6	2.376	1.10–5.09	0.026

95% CI – 95% confidence interval; CIS – carcinoma *in situ*; HR – hazard ratio; MPV – mean platelet volume

and high MPVL (HR = 2.39, 95% CI: 1.11–5.1, p = 0.025).

In the multivariate analysis, tumour T stage (T1 vs Ta, HR = 3.1, 95% CI: 0.93–10.3, p = 0.066; CIS vs Ta; HR = 4.43, 95% CI: 1.16–16.7, p = 0.028), multiplicity (HR = 3.06, 95% CI: 1.42–6.55, p = 0.004), and high MPVL (HR = 2.38, 95% CI: 1.1–5.09, p = 0.026) were independent predictors of progression-free survival (Table 4B).

DISCUSSION

In this retrospective study, we evaluated the role of a novel inflammatory marker involving the ratio between mean platelet volume and lymphocyte counts in the prediction of high-grade recurrence and progression of NMIBC in patients treated with BCG. We found that high preoperative MPVL was associated with an increased risk for progression, and both high MPV and high MPVL were associated with an increased risk of high-grade recurrence. Worse high-grade recurrence- and progression-free survival were observed in patients with higher MPVL. Multivariate analyses confirmed the independent prognostic value of MPVL for both HG RFS and PFS.

The combination of MPV and lymphocyte into one marker encapsulates the measures of inflammatory state, immune capability, and platelet activation. To the best of our knowledge, we are the first to demonstrate the prognostic role of the ratio between MPV and lymphocyte count in the cohort of predominantly high-risk NMIBC treated with BCG. Our previous study showed that another inflammatory platelet-based marker – PLR – predicts the occurrence of BCG-unresponsive NMIBC [9]. Some studies presented contradictory results of the prognostic value of MPV in NMIBC [18, 28]. We identified only 2 studies on MPVL in NMIBC, showcasing its prognostic significance in selected cohorts [23, 24]. One study highlighted its association with

disease-free survival among patients predominantly with Ta tumours without reported adjuvant intravesical therapy [23]. The other study demonstrated the association of MPVL with recurrence-free survival, specifically among patients with predominantly low-grade Ta tumours, who underwent intravesical chemotherapy [24]. Furthermore, we demonstrate the potential utility of MPVL in the prognostication of high-grade recurrence and progression in the setting of BCG-treated high-risk NMIBC.

The designed endpoints of our study ensure better applicability of our results in the setting of BCG-treated individuals, in whom high-grade recurrence and progression are the main outcomes of interest [10, 11]. Low-grade recurrences do not preclude further BCG instillations and do not meet the criteria for being classified as BCG-unresponsive [11]. Hence, the prediction of high-grade recurrence is crucial for identifying patients who would benefit from BCG. Therefore, we have found that patients with higher MPVL have higher risk of not responding to BCG.

Increased interest in inflammatory markers has been observed in recent years, with various indices reported as predictive of survival outcomes in multiple cancers [16, 29]. Greater implementation of immunotherapies and reliance on the role of the immune system have increased interest in validating such markers in the clinical setting [5]. Treatment of high-risk NMIBC is unique because

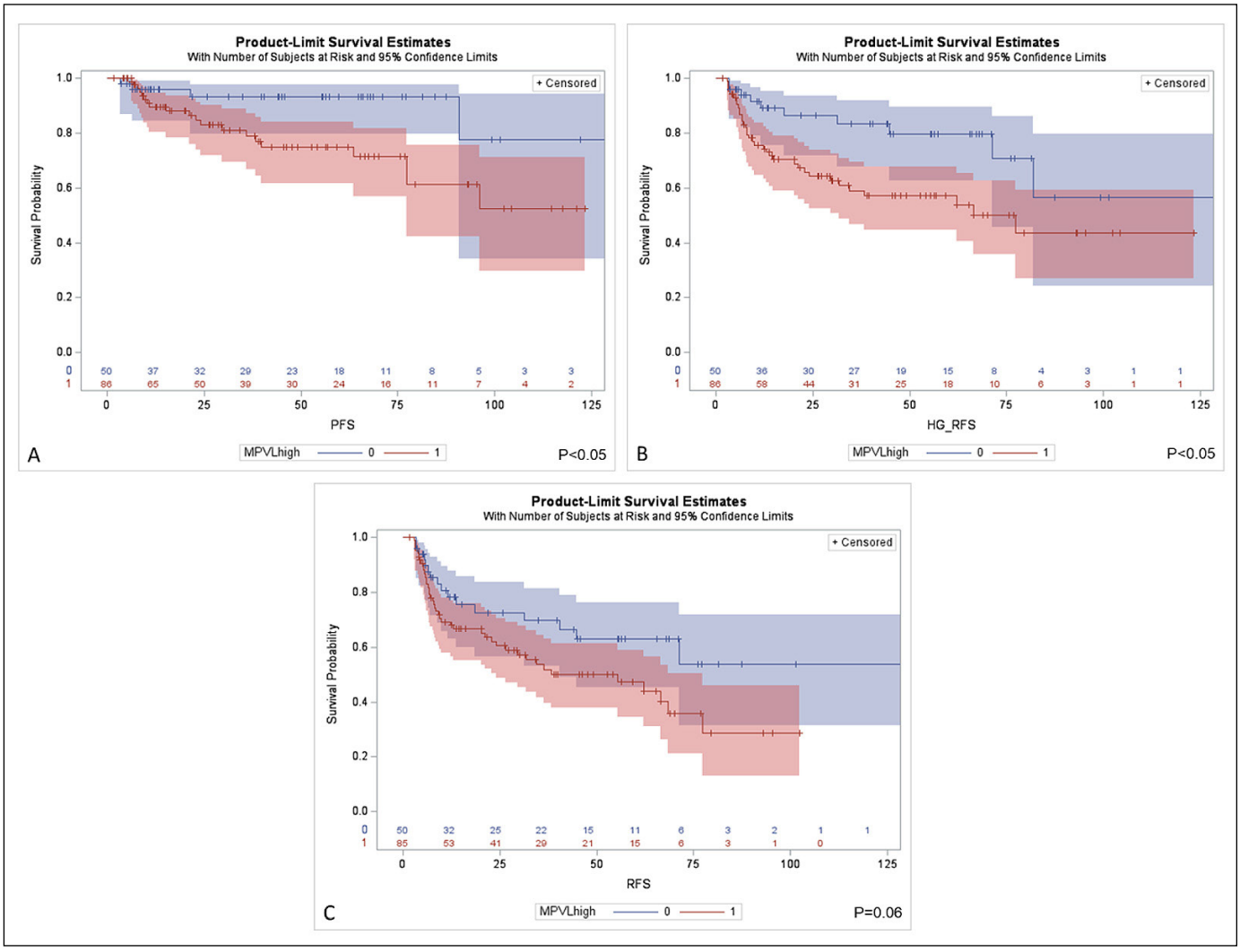

Figure 2. *Subgroup analysis in patients with NMIBC who are older than 65 years. Kaplan-Meier curves illustrate progression-free survival, high-grade recurrence-free survival, and recurrence-free survival in patients with higher and lower mean platelet volume-to-lymphocyte ratio (A, B, and C, respectively).*

HG RFS – high-grade recurrence-free survival; MPVhigh – high mean platelet volume; MPVLhigh – high mean platelet volume to lymphocyte ratio; PFS – progression-free survival; RFS – recurrence-free survival

it consists of state-of-the-art immunotherapy with live attenuated BCG strains, which has been the standard of adjuvant therapy following TURBT for over 40 years [30]. Urothelial BC is usually considered an immunogenic malignancy, and the presence of multiple immune cells upon BCG instillation including neutrophils, CD8+ T cells, NK cells, and macrophages, is well-recognised [17, 31].

Elevated MPV is often found in patients with increased platelet turnover, as newly produced platelets are usually bigger [21]. Intensive thrombopoiesis can result from a higher demand for platelets, which may occur after increased platelet use in clot formation or due to increased decomposition. Other pathologies such as cancer, autoimmune inflammatory diseases, or other systemic diseases have also been identified as causes of higher MPV [21, 22]. Moreover, the larger size of platelets usually suggests that they are younger, implying that these larger platelets exhibit higher metabolic and enzymatic activity and have a greater propensity for aggregation and release of chemical mediators [21]. Platelets, through the expression of cell surface molecules and the secretion of diverse proteins, nucleotides, and bioactive lipids, may contribute to inflammation and cancer progression [19]. Specifically, cancer cell-induced platelet activation leads to the release of proteases and bioactive phospholipids, fostering angiogenesis [19].

Lymphocyte counts have previously been reported as prognostic for NMIBC outcomes when incorporated in one of the well-known markers such as NLR, LMR, or PLR [9, 28, 29, 32]. Apparently, lymphocyte counts are the component of each of the above markers. During BCG therapy, lymphocytes are necessary for adaptive immunity, and the blood level of lymphocytes might reflect the organism's ability to mount an anti-cancer response. Particularly, cytotoxic T CD8+ lymphocytes were reported to be increased in post-BCG bladder tissues from responders [33].

As mentioned earlier, MPVL is not the only inflammatory marker associated with RFS and PFS in NMIBC. Of note, our study highlighted the prognostic role of high systemic inflammation response index and high pan-immune inflammation value for HG RFS. SIRI was previously demonstrated as a predictor of RFS and PFS among BCG-treated NMIBC patients, but PIV has been never validated in the NMIBC setting [25, 34]. However, one study reported its association with survival following radical cystectomy [25]. These inflammatory markers appear to reflect similar immune properties, warranting a thorough comparison in large validation cohorts.

MPVL may therefore serve as adjunct to current risk models to determine the risk of high-grade recurrence and progression. In our study, the multivariate model for PFS prediction included also tumour T stage and multiplicity, which are well-established risk factors incorporated in the EAU 2021, EORTC 2006, and CUETO stratification tools [14, 15, 27].

The multivariate model for high-grade RFS prediction included the EORTC 2006 recurrence risk score, pathology at reTUR, tumour grade, and high MPVL as independent risk factors. The EORTC 2006 recurrence risk score was previously validated for the prediction of recurrence with relatively low accuracy, when used as standalone factor [35, 36]. We express apprehension regarding the non-inclusion of reTUR status for prognostic considerations in available risk models [13, 14, 27]. In the investigation that established the innovative EAU 2021 risk model (encompassing 22% of patients at T1 stage), reTUR was performed in 16% of individuals [27]. Conversely, within the EORTC 2006, EORTC 2016, and CUETO cohorts, reTUR was not systematically carried out [13–15].

Of interest, in the univariate analysis, Charlson comorbidity score was identified as a risk factor for high-grade RFS. Patients with BC are often affected by a high burden of co-existing cardiovascular and pulmonary diseases [37]. Both age and smoking exposure are strongly associated with the development of comorbidities and are both risk factors for NMIBC recurrence [15, 38, 39]. Our previous study showed that the Charlson comorbidity score constituted a prognostic factor for progression and cancer-specific mortality among elderly patients with T1HG who were treated with BCG [37]. Comorbid conditions and life expectancy influence treatment decisions in NMIBC and must also be evaluated in the context of outcomes. A larger cohort of patients is required for re-evaluation of the association between comorbidity burden and oncological outcomes of NMIBC.

Limitations of our study stem from its inherent retrospective single-centre character and small sample size. The potential influence of measurement techniques and analysers, along with their impact on blood test results, should be considered when extrapolating the findings of our study.

CONCLUSIONS

The novel inflammatory marker comprised of mean platelet volume and lymphocyte counts ratio might be considered a prognostic factor associated with unfavourable progression-free survival and high-grade recurrence-free survival in patients with NMIBC treated with adjuvant BCG. Because we are the first to highlight the role of MPVL in the prognosis of BCG-treated NMIBC, further multicentre prospective validations are warranted to confirm the value of MPVL in clinical decision-making.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FUNDING
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ETHICS APPROVAL STATEMENT
The study was conducted in accordance with the Declaration of Helsinki and its later amendments. Ethical review and approval were waived for this study by the Ethics Committee of the Medical University of Warsaw due to its character.

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