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Value of Immunological Biomarkers in Early Prediction of Bacillus Calmette-Guerin Failure in High-Risk Non-muscle-invasive Bladder Cancer

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Abstract

Objectives To investigate the predictive value of different immunological markers on treatment outcomes after bacillus Calmette-Guerin (BCG) induction in high-risk non-muscle-invasive bladder cancer (NMIBC).

Patients and Methods Patients who underwent transurethral resection of bladder tumors for NMIBC were assessed for study eligibility. Urine and blood samples were taken from patients at baseline (immediately before the first dose of induction). Urine samples were evaluated for interleukin (IL)-6, IL-8, IL-10, IL-11, and interferon- γ by solid-phase enzyme-linked immunosorbent assay (ELISA). Blood samples were evaluated for epidermal growth factor receptor (*EGFR*) and human epidermal growth factor receptor-2 (*HER2*) using quantitative reverse transcriptase-polymerase chain reaction analysis. Each marker was assessed in relation to tumor recurrence.

Results Between June 2016 and December 2019, 160 patients were included. Tumor recurrence occurred in 47 (29.38%) patients over a median (IQR) follow-up of 24 (12: 49) months. Using univariate analysis, the following urinary cytokines were associated with higher recurrence: urinary IL-6, 8, 10, 11, and interferon-γ. Also, serum *EGFR* and *HER2* were associated with higher recurrence. On multivariate Cox regression analysis, significant variables include *HER2* [HR (95%CI): 2.675 (1.367-5.233), p= 0.004], and IL-11 [HR (95%CI): 0.889 (0.825-0.957), p= 0.002].

Conclusions Serum *HER2* and urinary IL-11 could be applied in clinical practice to predict BCG failure in patients with high-risk NMIBC, so those patients could be offered other modalities (radical cystectomy) early with better survival. Further studies are recommended to establish their exact role.

Key words BCG failure, biomarkers, high risk, non muscle invasive

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Introduction

Non-muscle-invasive bladder cancer (NMIBC) that is, stage Ta, T1, and carcinoma in situ (CIS) constitutes approximately 75% of all newly diagnosed cases of bladder cancer [1]. NMIBCs are rarely lethal, however, 50-70% of patients experience disease recurrence, and 10-30% progress to life-threatening muscle-invasive bladder cancer (MIBC) [2].

For patients with intermediate-risk and high-risk tumors, intravesical Bacillus Calmette-Guerin (BCG) instillation is recommended as the first choice of treatment [3]. Nevertheless, BCG response is inconstant with recurrence and progression rates seemingly ranging from 32% to 43% and 9.5% to 14%, respectively [4]. In addition, the need for frequent cystoscopies, biopsies, and long-term surveillance of NMIBC imposes high costs on the patient and society and is associated with significant patient anxiety. Furthermore, early radical cystectomy in patients with BCG failure gives better survival [5]. Therefore, the identification of prognostic factors that could predict BCG failure is of the highest importance to offer patients another line of treatment with better outcomes.

Prior attempts to predict BCG response focused on clinicopathological characteristics, such as stage, grade, and concomitant CIS. However, tumors with similar histopathological appearance can show large differences in disease aggressiveness and outcome. It is now believed that the most important determinant of BCG response is the patient's capability to generate an adequate immune response [6].

Intravesical BCG instillation induces the activation of urothelial cells and antigen-presenting cells (APCs), which produce cytokines and chemokines that attract granulocytes and mononuclear cells to the bladder. These events are characterized by the typical epithelioid and giant cell granulomas found in the bladder wall after BCG instillation, which contain macrophages, dendritic cells, lymphocytes, neutrophils, and fibroblasts. Several cytokines have been implicated in this cell-mediated response, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor-α, and interferon (IFN) [7].

Over the last decade, several studies evaluated the prognostic values of different immunological markers after BCG instillation and their impact on treatment outcomes [8-10]. However, these studies were limited by either a small sample size, short follow-up, or retrospective nature. These limitations triggered us to assess the predictive value of different immunological markers on treatment outcomes after BCG induction in high-risk NMIBC in a larger number of patients with adequate follow-up in a prospective fashion.

Patients and Methods

Study population

This is a prospective observational study that included patients with high-risk NMIBC who were treated by transurethral resection (TURBT). The study protocol was approved by the institutional review board. The experimental procedures were carried out in accordance with the ethical standards of the Helsinki Declaration and informed consent was obtained from all participants.

Exclusion Criteria

Patients with previous BCG instillation, benign pathology, variant histology, non-urothelial carcinoma, upper tract urothelial tumors, detrusor muscle invasion, and low- or intermediate-risk NMIBC were all excluded.

Primary TURBT procedures, postoperative care, and repeat biopsy

TURBT procedures were done using a resectoscope by an expert urologist Histopathological assessment of resected tumor specimens was evaluated by expert uro-pathologists. Repeat biopsy was taken in all patients at 4-6 weeks after the initial primary procedures. Then, 2 weeks later, all patients included in the study received 80 mg intravesical BCG for 6 consecutive weeks as an induction regimen of intravesical BCG. At 4 weeks after the induction phase, a 'check' cystoscopy was done, and patients with no tumor were scheduled for a maintenance regimen of intravesical BCG for 3 consecutive weeks at 3 and 6 months, and 6 monthly thereafter for a period of 3 years.

Specimen handling, processing, and assay details

Urine and blood samples were collected at baseline (immediately before the first instillation of the induction regimen). These samples were collected according to standard operating procedures at our center for similar studies.

Cytokines measurements

Urinary IL-6, IL-8, IL-10, IL-11, and IFN-γ levels were measured in the supernatants. Cytokines concentrations were determined in the urine of all patients by solid phase ELISA Immunoassay (R&D Systems, Minneapolis, MN, USA). All samples were measured in duplicate in accordance with the manufacturer's recommendations.

Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) analysis

RNA was extracted from blood samples using QIAamp RNA Blood Mini kit (Qiagen, Hilden, Germany). In all, 1 microgram of total RNA was reverse transcribed with random primers, using the High-Capacity cDNA Archive Kit (Applied Biosystems, Foster City, CA, USA). The RT-qPCR analysis was carried out with SYBER Green PCR Master Mix (Applied Biosystems). Primers for EGFR and HER2 with glycerldehyde-3-phosphate dehydrogenase were used as the PCR control.

Follow-up and outcomes

During the maintenance regimen, all patients underwent cystoscopy/cytology at 3-month intervals for 2 years and at 6-month intervals thereafter. Upper tract imaging was done whenever indicated. An initial complete response (ICR) was defined as tumor-free cystoscopy at 3 months after biopsy. Recurrence was defined as the development of new tumor in patients with an ICR. Progression was defined as upstaging to muscle invasion.

Statistical analysis

Data were described by the median (IQR) and category frequencies for scale and nominal variables, respectively. P-values were calculated using the Mann-Whitney U and the Chi-square tests, respectively. Spearman rho was used to estimate the strength and direction of the correlation between the markers. Survival curves were drawn using the Kaplan Meier method with the log-rank test used to provide statistical significance. Cut-off values of scale variables were selected based on the maximally selected rank statistic method in survminer and maxstat R packages. Predictors of recurrence-free survival were estimated using the univariate and multivariate Cox regression models. Because of the significant

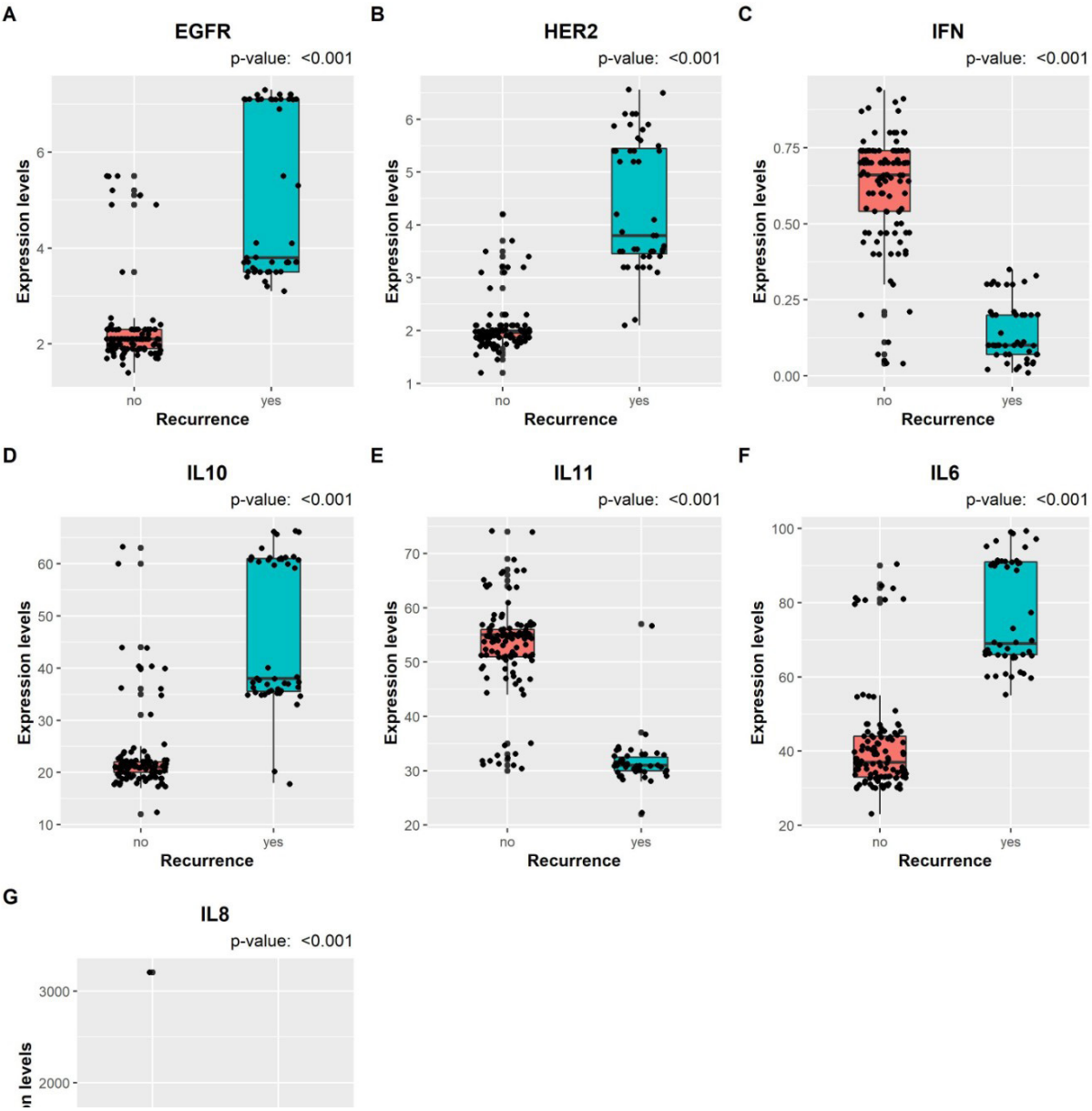

Figure 1. The levels of each tumor markers (EGFR, HER2, IFN-γ, IL-10, IL-11, IL-6, IL-8) stratified according to the recurrence status.

correlation between the independent variables, the variation inflation factor (VIF) and tolerance were used to exclude multiple collinearities in the multivariate analysis. Statistical analyses were used using the R programming language (4.1.2) with a p-value < 0.05 is considered statistically significant.

Results

Demographics

Between June 2014 and December 2019, A total of 160 patients with a mean (SD) age of 67.01 (7.92) years were included in this study. The main study population was males [139 (86.88%)]. Tumor recurrence occurred in 47 (29.38%) patients over a median (IQR) follow-up of 24 (12: 49) months. The median (IQR) follow-up was 30 (14: 54) months. **Table 1a-b** shows the characteristics of the study population.

Factors associated with recurrence

Significant variables include *EGFR* median (IQR) [2.1 (1.9: 2.3) versus 3.8 (3.5: 7.1), p< 0.001 MW], *HER2* median (IQR) [1.967 (1.87: 2.01) versus 3.8 (3.455: 5.45), p< 0.001 MW], IFN-γ median (IQR) [0.66 (0.54: 0.74) versus 0.1 (0.07: 0.2), p< 0.001 MW], IL-10 median (IQR) [21 (20: 22) versus 38 (35.5: 61), p< 0.001 MW], IL-11 median (IQR) [55 (51: 56) versus 31 (30: 32.5), p< 0.001 MW], IL-6 median (IQR) [37 (33: 44) versus 69 (66:91), p< 0.001 MW], IL-8 median (IQR) [203 (163: 277) versus 501 (452.5: 699), p< 0.001 MW], prior recurrence [primary: 105 (92.92%) versus 12 (25.53%), recurrent: 8 (7.08%) versus 35 (74.47%), p< 0.001 X2] for Recurrence no versus yes, respectively. **Table 2** shows the characteristics of patients with recurrence. **Figure 1** shows the levels of the tumor markers stratified according to the recurrence status.

Correlation between tumor markers

Table 1a. Patients characteristics.

Items	Variable	Cases (160 in total, 100%)
Recurrence	no	113 (70.62%)
	yes	47 (29.38%)
	Time to recurrence, months	24 (12:49)
CIS	age	67.01 (7.92)
	no	156 (97.5%)
	yes	4 (2.5%)
Number	single	85 (53.12%)
	2-7	68 (42.5%)
	8 or more	7 (4.38%)
Prior recurrence	primary	117 (73.12%)
	recurrent	43 (26.88%)
Site: lateral	No	74 (46.25%)
	Yes	86 (53.75%)
Site: posterior and trigone	No	59 (36.88%)
	Yes	101 (63.12%)
Size	<3 cm	61 (38.12%)
	3 or more cm	99 (61.88%)
Sex	Male	139 (86.88%)
	Female	21 (13.12%)
Cystectomy	no	149 (93.12%)
	yes	11 (6.88%)

Table 1b. Patients characteristics in each tumor markes.

Patients	Samples	Tumor markers	Median (IQR)
Recurrence	Blood	*EGFR*	2.15 (1.98: 3.61)
	Blood	*HER2*	2.01 (1.87: 3.4)
	Urinary	IFN-γ	0.54 (0.2: 0.7)
	Urinary	IL-10	22 (20: 36)
	Urinary	IL-11	51 (32: 55)
	Urinary	IL-6	43 (35: 66)
	Urinary	IL-8	232 (187.75: 451.75)

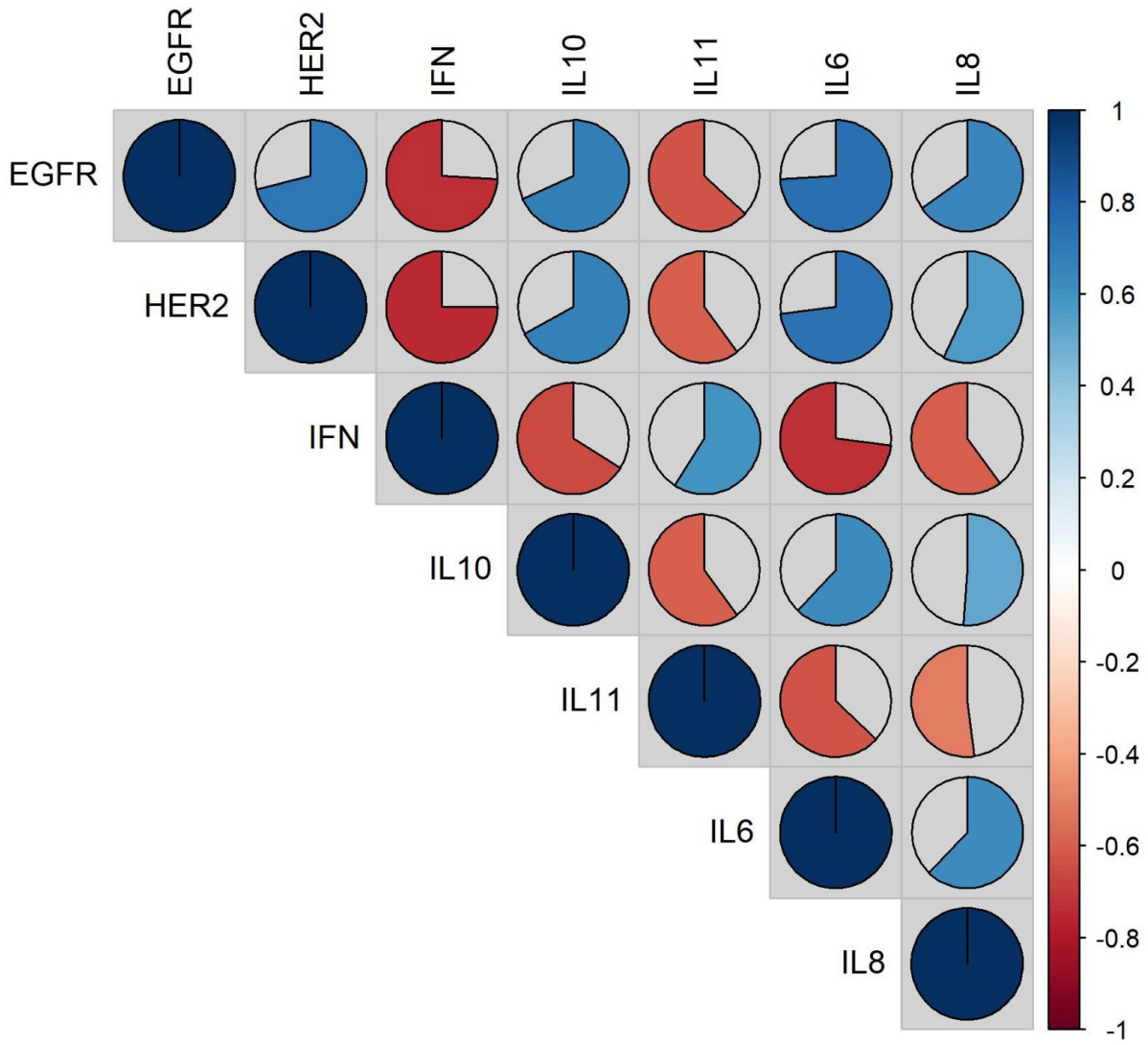

Figure 2. Correlation between each tumor markers (EGFR, HER2, IFN-γ, IL-10, IL-11, IL-6, IL-8).

EGFR has positive correlations with *HER2* [strong], IL-10 [moderate], IL-6 [strong], IL-8 [moderate] and has negative correlation with IFN-γ [strong], IL-11 [moderate]. *HER2* has positive correlations with IL-10 [moderate], IL-6 [strong], IL-8 [moderate] and has negative correlation with IFN-γ [strong], IL-11 [moderate]. IFN-γ has positive correlations with IL-11 [moderate] and has negative correlation with IL-10 [moderate], IL-6 [strong], IL-8 [moderate]. IL-10 has positive correlations with IL-6 [moderate], IL-8 [moderate] and has negative correlation with IL-11 [moderate]. IL-11 and has negative correlation with IL-6 [moderate], IL-8 [moderate]. IL-6 has positive correlations with IL-8 [moderate]. Results are shown in **Figure 2**.

Survival curves for recurrence-free survival

Kaplan Meier survival curves are shown in **Figure 3**. Significant variables comparing low versus high levels (survival at 12 months and 60 months, p-value) were *EGFR* (100% vs 73%, 100% vs 22%, p< 0.001), *HER2* (100% vs 71%, 98% vs 18%, p< 0.001), IFN-γ (73% vs 100%, 22% vs 100%, p< 0.001), IL-10 (99% vs 75%, 97% vs 23%, p< 0.001), IL-11 (72% vs 100%, 22% vs 96%, p<0.001), IL-6 (100% vs 73%, 98% vs 22%, p< 0.001), IL-8 (98% vs 73%, 98% vs 15%, p< 0.001), and type: primary vs recurrent (96% vs 74%, 85% vs 20%, p< 0.001), respectively. Cut-off values used for stratifying scale variables were, 2.54 for *EGFR*, 3.1 for *HER2*, 0.35 for IFN-γ, 31 for IL-10, 34 for IL-11, 55 for IL-6, and 398 for IL-8.

Univariate and multivariate COX regression analysis

Significant variables include *EGFR* [HR (95%CI): 1.69 (1.47-1.944), p< 0.001], *HER2* [HR (95%CI): 2.238 (1.857-2.698), p< 0.001], IFN-γ [HR (95%CI): 0.003 (0-0.016), p< 0.001], IL-10 [HR (95%CI): 1.063 (1.046-1.081), p< 0.001], IL-11 [HR (95%CI): 0.848 (0.804-0.895), p< 0.001], IL-6 [HR (95%CI): 1.054 (1.038-1.069), p< 0.001], IL-8 [HR (95%CI): 1.001 (1-1.001), p= 0.002], prior recurrence: recurrent [HR (95%CI): 8.836 (4.583-17.038), p< 0.001]. Multicollinearity exists in 4 variables: *EGFR* (VIF:

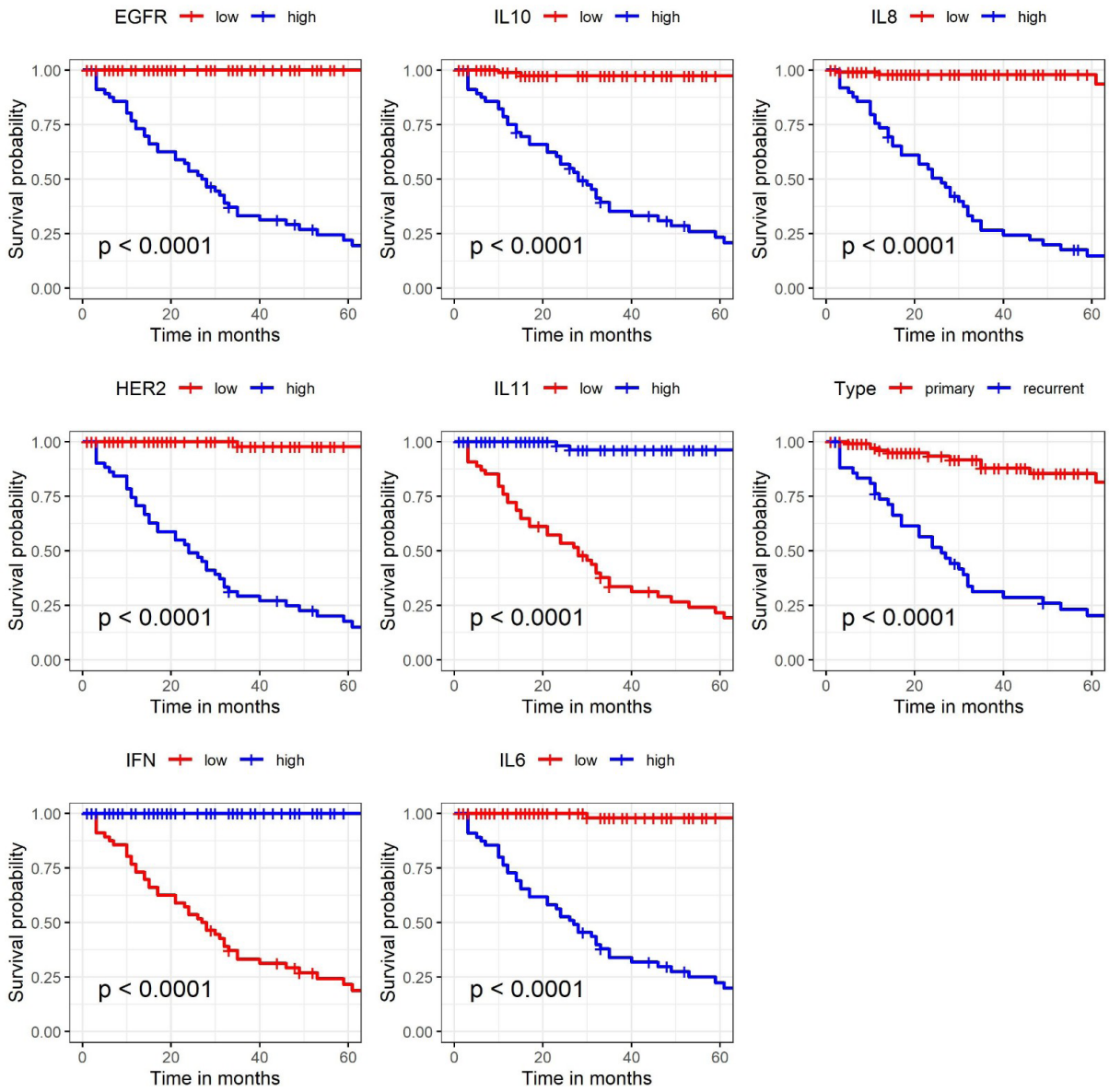

Figure 3. Kaplan Meier survival curves for recurrence-free survival in each tumor markers (EGFR, HER2, IFN-γ, IL-10, IL-11, IL-6, IL-8).

19.2, Tolerance: 0.052), *HER2* (VIF: 16.2, Tolerance: 0.062), IL-10 (VIF: 10.7, Tolerance: 0.093), IL-6 (VIF: 10.8, Tolerance: 0.093), after the exclusion of *EGFR* from the multivariate analysis, multicollinearity between the predictors disappeared. On multivariate Cox regression analysis, significant variables include *HER2* [HR (95%CI): 2.675 (1.367-5.233), p= 0.004], and IL-11 [HR (95%CI): 0.889 (0.825-0.957), p= 0.002]. Univariate and multivariate analyses are shown in **Table 3**.

Discussion

A full course of BCG is by far the most useful regimen to lessen the recurrence and progression of high-risk NMIBC. Based on the European association of urology (EAU) guidelines, the BCG outcome can be classified as unresponsive if high-grade recurrence occurred within the instillation period (refractory) or within 6 months after completing the course, or if the CIS recurred within one year [1]. BCG-unresponsive patients might have poor survival because of the delay in curative management and the disease's aggressive nature [5]. Identifying those with unfavorable responses is of ultimate importance to minimize the costs and the stresses of BCG shortage. Several variables have been studied including clinicopathological criteria [11], fluorescent in situ hybridization (FISH) of tumor cells [12], molecular biomarkers [13], and urine cytology [14]. While the exact mechanism of BCG is unknown, the immune response has been suggested as playing an important role. Hence, urinary cytokines might be a surrogate for the BCG effect [15]. This study examined the effect of the expression level of different urinary cytokines on the response of BCG.

Our study found that lower levels of IL-11 and higher levels of HER2 were significant predictors of RFS on multivariate analysis. IL-11 is a secreted cytokine with an anti-inflammatory nature probably achieved by reducing the number of macrophages at the inflammation site [16]. The potential link between inflammation

Table 2. The difference in characteristics between patients who developed recurrence versus no recurrence.

Recurrence		no	yes	p-value
Age mean (SD)		67.381 (8.226)	66.106 (7.118)	0.3[ST]
EGFR median (IQR)		2.1 (1.9: 2.3)	3.8 (3.5: 7.1)	< 0.001[MW]
HER2 median (IQR)		1.967 (1.87: 2.01)	3.8 (3.455: 5.45)	< 0.001[MW]
IFN-γ median (IQR)		0.66 (0.54: 0.74)	0.1 (0.07: 0.2)	< 0.001[MW]
IL-10 median (IQR)		21 (20: 22)	38 (35.5: 61)	< 0.001[MW]
IL-11 median (IQR)		55 (51: 56)	31 (30: 32.5)	< 0.001[MW]
IL-6 median (IQR)		37 (33: 44)	69 (66: 91)	< 0.001[MW]
IL-8 median (IQR)		203 (163: 277)	501 (452.5: 699)	< 0.001[MW]
CIS	no	109 (96.46%)	47 (100%)	0.3[F]
	yes	4 (3.54%)	0 (0%)	
Number	single	61 (53.98%)	24 (51.06%)	0.3[F]
	2-7	49 (43.36%)	19 (40.43%)	
	8 or more	3 (2.65%)	4 (8.51%)	
Prior recurrence	primary	105 (92.92%)	12 (25.53%)	< 0.001[X2]
	recurrent	8 (7.08%)	35 (74.47%)	
Site: lateral	No	52 (46.02%)	22 (46.81%)	1[X2]
	Yes	61 (53.98%)	25 (53.19%)	
Site: posterior and trigone	No	39 (34.51%)	20 (42.55%)	0.4[X2]
	Yes	74 (65.49%)	27 (57.45%)	
Size	<3 cm	43 (38.05%)	18 (38.3%)	1[X2]
	3 or more cm	70 (61.95%)	29 (61.7%)	

MW: Mann Whitney U test; X2: Chi-square test; F: Fischer's exact test; ST: Student t test.

and the pathogenesis of cancer might explain the IL-11 role in cancer development [17]. In one report, IL-11 was downregulated in human bladder cancer cell lines and was associated with tumor grade and stage [18]. The authors proposed that lower levels might be a mechanism of bladder tumor carcinogenesis and progression and more active treatment should be administered because of the more aggressive biology of these tumors [18].

HER2, a type I trans-membrane 185 kDa tyrosine kinase receptor, is normally responsible for regulating cell proliferation, increasing angiogenesis, inhibiting apoptosis, and decreasing cellular adhesion by the activation of various signaling pathways [19]. In addition to bladder cancer, *HER2* overexpression has been identified in several tumor types, including breast and ovarian cancers. The 5-year disease-free survival was significantly reduced (9.7% vs 48.5%) in patients with positive *HER2* and the expression of *HER2* was linked to decreased disease-specific survival [20] which is in concordance with the current findings.

In our study, all other studied markers were significantly associated with RFS on survival and univariate analyses. These findings, together with others, imply their significance in the pathogenesis of bladder cancer. IL-8 is an angiogenic factor that is expressed in inflammation and carcinogenesis with elevated urinary protein levels have been shown in patients with urothelial carcinoma [21-23]. Elevated urinary levels were linked to higher disease stages [21], increased probability of recurrence [22], and reduced efficacy of intravesical therapies such as mitomycin C and BCG [24]. Likewise, IL-6, a 26 kDa glycoprotein, plays an important role in the pathogenesis of several malignancies by inducing angiogenesis and inhibiting apoptosis of cancer cells [25]. In bladder cancer patients, it was reported elevated serum levels of IL-6 when compared to non-cancer patients suggesting a possible role in urothelial carcinoma [26].

IL-10 is a cytokine synthesis inhibitory factor (CSIF) that has been shown to inhibit cellular immune responses via several mechanisms. IL-10 can block the macrophage accumulation at the tumor site, and down-regulate the expression of MHC-II on

Table 3. Univariate and multivariate Cox regression analysis for the predictors of recurrence-free survival.

Cox regression analysis	Variables	Hazards ratio	95%CI	p-value
Univariate	Age	0.982	(0.947-1.018)	0.3
	EGFR	1.69	(1.47-1.944)	< 0.001
	HER2	2.238	(1.857-2.698)	< 0.001
	IFN-γ	0.003	(0-0.016)	< 0.001
	IL-10	1.063	(1.046-1.081)	< 0.001
	IL-11	0.848	(0.804-0.895)	< 0.001
	IL-6	1.054	(1.038-1.069)	< 0.001
	IL-8	1.001	(1-1.001)	0.002
	Number 2-7	1.169	(0.636-2.15)	0.6
	Number 8 or more	2.038	(0.705-5.893)	0.2
	Prior recurrence (recurrent vs primary)	8.836	(4.583-17.038)	< 0.001
	Site: lateral (Yes vs no)	0.989	(0.557-1.755)	1
	Site: posterior and trigone (Yes vs no)	0.863	(0.484-1.541)	0.6
	Size 3 or more cm	0.869	(0.482-1.568)	0.6
Multivariate	*HER2*	2.675	(1.367-5.233)	0.004
	IFN-γ	0.441	(0.015-12.687)	0.6
	IL-10	0.943	(0.889-1.001)	0.05
	IL-11	0.889	(0.825-0.957)	0.002
	IL-6	0.992	(0.942-1.045)	0.8
	IL-8	1.001	(0.999-1.002)	0.2
	Prior recurrence (recurrent vs primary)	1.83	(0.834-4.017)	0.1

these cells, thus suppressing the induction of immune responses [27]. Consequently, blocking IL-10 activity could enhance BCG induction of Th1 immunity and improve the outcome. Previous evidence suggested that IL-10 was upregulated in high-grade and advanced tumor stages [28] which confirms the findings of the current report. On the contrary, it has been shown that higher levels of IFN-γ might predict an enhanced T-cell mediated antitumor immune response and a better prognosis. In one study evaluating a group of patients with metastatic, muscle-invasive, and non-muscle-invasive bladder cancer, IFN-γ was associated with a decreased risk of mortality with improved survival rates though the significance was only delineated in the muscle-invasive group only [29].

The last biomarker evaluated in the current study is the *EGFR* which is a transmembrane protein that upregulation produced uncontrolled cell division and has been linked to several cancers including lung, anal, and head and neck cancers [30]. In our study, the effect of *EGFR* was not evaluated in the multivariate analysis because of the multicollinearity between its level and other evaluated biomarkers. This significant correlation would ruin the statistical analysis and hence it was omitted from the final analysis. While the current study shed the light on some potential prognostic factors for BCG response and elected the most significant factors, it has some limitations that deserve mention. First, it is a single-center study reflecting certain patients' demographics and cancer characteristics with might not be identical to the results from patients of different geographical distribution. In addition, the lack of exclusion of concurrent urinary tract infections during or after BCG induction may alter urinary cytokines levels by its local inflammatory response. For the survival analysis, we have identified the cut-off value based on a single statistical method among many while there is no known optimal method to determine the cut-off values. However, the Cox analysis is included as it does not depend on stratifying factors based on cut-offs. Several potential prognostic factors were not evaluated with might enhance the findings of the current study. The results of the current study need to be validated on a larger scale and in a multi-institutional setting.

Conclusions

Serum *HER2* and urinary IL-11 during BCG therapy in high-risk NMIBC may serve to identify patients at risk for superficial bladder cancer recurrence and may be predictive of the long-term clinical response and survival. Well-powered, multicenter prospective studies are needed to ascertain our results and to identify the most relevant cutoff values for these biomarkers for tailoring treatment to individuals.

Acknowledgements

None.

Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

MGE, HA and AA: Conception, design of study and manuscript preparation; MSE, LAB, AF and AMH: Data collection and analysis; AE: Approval for the final version of the manuscript and funding supports.

Competing interests

The authors have no competing interest.

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