Prognostic significance of survivin, β-catenin and p53 expression in urothelial carcinoma

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ABSTRACT

Survivin, β-catenin, and p53 are well-known cell-cycle and apoptosis regulators. Urothelial carcinomas (UCs) are common, taking fourth place in men and ninth place in women. Compared to superficial tumors (Ta, CIS, or T1), invasive UCs are important with regard to recurrence, progression, and mortality. We tested the utility of the survivin, β-catenin, and p53 as biomarkers for early prediction of the invasiveness of UCs and the overall survival of the patients. We investigated high stage UC (n=147) and non-muscle invasive UC (NMI-UC) (n=113), using tissue microarray and immunohistochemistry. Spearman's correlation and multivariate Cox regression were used for statistical processing of the data. High expressions of β-catenin, survivin, and p53 were associated with high T stage, recurrence, progression, mortality, low recurrence-free survival, low progression-free survival and low overall survival ($p < 0.01$). Similar findings were achieved for recurrence and progression in the NMI-UC group, except for mortality. Moreover, a positive correlation was shown between p53 and β-catenin and between p53 and survivin (r=0.221, $p < 0.01$; r=0.236, $p < 0.01$, respectively). Survivin, p53, and β-catenin overexpression may have prognostic significance, indicating the aggressive behavior and poor prognosis of UCs. Dysregulation of those these cell-cycle and apoptosis regulators in bladder carcinoma could be used as a molecular marker to determine the best treatment strategy and could contribute to the development of targeted therapies.

KEYWORDS: Survivin; β-catenin; p53; bladder; urothelial carcinoma; clinicopathologic value
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INTRODUCTION

Bladder carcinomas are common, taking the fourth position on the list of the most frequent cancers in men and the ninth position in women [1]. The common feature of urothelial carcinoma (UC) is an increase in the frequency of recurrence and mortality along with the transition of the tumor to an invasive one [2]. The tumor is limited to a superficial area (stages Ta and CIS) or lamina propria (T1) in 70% of UC patients. Additionally, in more than 50% of those tumors, recurrence will be seen at least once, and in about 15% to 20% of cases, the histological grade or invasion depth will increase. Identification of the key regulatory molecules discovered in the signal transduction pathways has increased our understanding of the cellular events, including cell survival, apoptosis, proliferation, and even tumor-associated processes, such as invasion and metastasis [3]. Alterations in apoptosis, chiefly due to mutations, play an essential role in carcinogenesis, survival of neoplastic cells, and the increase in invasion capacity and metastasis of the disease [4]. Among those, survivin has a role in negative regulation of apoptosis or programmed cell death and functions as an apoptosis inhibitor. Induction of survivin results in cessation of apoptosis and increase in migration and metastasis [5]. Survivin has a role in cellular division and has also been expressed in the nucleus and in the cytosol of cells [6]. Although the molecular mechanisms of survivin have not been elucidated, the regulation of survivin is considered to be linked to the p53 protein. Moreover, survivin is upregulated by β-catenin in relation to the Wnt signaling pathway [5-9]. β-catenin functions as part of the E-cadherin/β-catenin complex and plays a role in cell-to-cell adhesion [10]. The Wnt/β-catenin pathways have been reported to regulate urothelial homeostasis and carcinogenesis [11] in addition to accumulating p53 in the case of activation [12]. Furthermore, p53 as a tumor suppressor gene

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is localized on human chromosome 17q23 and has an essential role in the cell cycle, apoptosis, and cellular growth [13]. Aberrations of p53 expression due to mutations are reported to play a central role in oncogenesis of the urinary bladder [14], particularly in 40% to 60% of invasive UCs [15, 16]. Additionally, p53 was reported to negatively regulate survivin expression. Together, they play a role in regulation of the cell cycle and apoptosis [17].

In this study, we investigated the immunohistochemical expression of survivin, β-catenin, and p53 in noninvasive and muscle-invasive UCs. We also examined the relationship of their expression with selected clinical parameters in order to estimate their potential to predict the progression of UCs.

MATERIALS AND METHODS

Clinicopathologic data

We included 147 patients in this study. All the patients had had transurethral resection or radical cystectomy and had received a diagnosis of bladder UC. All the pathological sections were reviewed to confirm the original diagnosis. The study groups were staged according to the 2010 American Joint Committee on Cancer guidelines [18] and graded according to the 2004 World Health Organization classification system for UC [19] by three expert pathologists (SS, AA, SO). According to the status of muscular layer invasion, patients were divided into two main subgroups: < pT2 (non-muscular invasion UC [NMI-UC]; n=113) and ≥ pT2 (muscular invasion [MI-UC]; n=34). Patients' data were obtained, including tumor recurrence, time to recurrence, progression, time to progression, and actual status on follow-up. Patients, whose data were missing, were excluded form the study.

Tissue microarray construction (TMA)

Cylindrical samples of 4 mm in diameter were taken from the most demonstrative areas of tumor tissue in paraffin blocks and compared to hematoxylin and eosin sections. This process was performed using manual tissue microarray (Quick Ray, Unitima Co. Ltd., Seoul, Korea). The resulting tumor tissue samples were relocked by paraffin and prepared for immunohistochemical evaluation.

Immunohistochemistry and scoring

Sections of 4 μm thickness were cut from 147 UC tissues. Dewaxed and rehydrated tissue sections were stained by using the streptavidin–biotin peroxidase complex method with specific primary antibodies. Immunohistochemical staining for survivin, β-catenin, and p53 was performed on step sections of TMA blocks. The slides were deparaffinized by two xylene rinses, followed by two rinses of 100% ethanol. Antigen retrieval was performed by heating the slides in a pressure cooker, filled with 7.5 mM sodium citrate (pH 6.0). After 5 min of casein blocking for nonspecific binding, the tissue sections were incubated for 25 min with primary antibodies for the detection of survivin (SP79, M3790, rabbit monoclonal, 1:100; Spring Bioscience, CA, USA), p53 (DO7, 453M-94, lot: 1320608D, 0.1 ml, mouse monoclonal, 1:200; Cell Marque, CA, USA), and β-catenin (224M-18, lot:1325508A, 7 ml, mouse monoclonal, ready to use; Cell Marque, CA, USA). This step was followed by detection using the Bond Polymer Refine kit for 25 min on the Bond Max Autostainer (Leica Biosystems, Newcastle upon Tyne, UK), visualization with diaminobenzidine chromogen, and counterstaining with hematoxylin. For survivin antibody, cases were scored positive when >10% of the cells reacted as previously described [20]. For β-catenin antibody, membranous and cytoplasmic staining was scored by percentage of tumor-cell positivity from 0 to 100 and staining intensity from 1 to 3 (1, weak; 2, moderate; 3, strong). The product of the percentage of positive cells and the staining intensity was then divided by 3, making the reactivity score range from 0 to 100. The results of immunostaining were designated as negative when the reactivity score was up to 10%, weakly positive when it was 10% to 50%, and strongly positive if it was 50% to 100%. Then the score was multiplied to get a total score: score 1 was recorded as negative, 2 to 4 weakly positive, 5 to 9 strongly positive [21]. Finally, for p53 antibody, nuclear staining was scored as p53-positive when there was moderate to strong nuclear immunoreactivity in more than 80% of the tumor cells [22].

Statistical analysis

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS, 2007). Pearson's chi-square test, Fisher Yates continuity correction, and Freeman and Halton (Monte Carlo) tests were used to compare the qualitative data. Spearman's correlation analysis was used in conformity assessment between immunohistochemical variables. Clinicopathologic data were evaluated using a log rank test and univariate and multivariate Cox regression analyses. $p < 0.05$ was considered statistically significant.

RESULTS

Patient demographics and clinicopathologic findings

The mean age of the 147 UC patients was 66.6 years (min 37 years, max 98 years). Of these, 72.1% were males (n=106), while 27.9% (n=41) were females. Tumor stage was defined patohistologically according to American Joint Committee on

Cancer (AJCC). UC with the superficial invasion (NMI-UC) was diagnosed in 76.9% (n=113) of patients, while UC with detrussor muscle invasion (MI-UC) was observed in 23.1 (n=34) cases. In addition, 45.6% (n=67) of cases were classified as low-grade carcinomas, while 54.4% (n=80) were denoted as high-grade carcinomas. During follow-up recurrence, progression and mortality were observed in 47.6% (n=70), 29.9% (n=44), and 24.5% (n=36) of patients, respectively.

IMMUNOHISTOCHEMICAL RESULTS

Nuclear survivin expression was observed in 44.2% (n=65) patients in the UC group and was positive in 37.2% (n=42) patients in the NMI-UC group (Figure 1a, 1b and 1c). In the UC group, a low expression of β-catenin was observed in 17.7% (n=26) of patients, whereas high β-catenin expression was observed in 29.3 (n=43) of patients. In the NMI-UC group, the low and high expressions of β-catenin were 17.7% (n=20) and 23.1% (n=26), respectively (Figure 1d, 1e and 1f). Nuclear p53 expression was observed in 40.8% (n=60) and 33.6% (n=38) patients in the UC and NMI-UC groups, respectively (Figure 1g, 1h and 1i).

Expression of biomarkers in relation to clinicopathologic parameters

High β-catenin expression and positive expression of survivin and p53 were significantly associated with a high T stage (≥ T2; p = 0.006, p = 0.003, and p = 0.002, respectively). High β-catenin expressions and positive expression of p53 were significantly associated with high tumor grade (p = 0.007 and p = 0.032, respectively). Univariate analyses of the NMI-UC group revealed a relationship between high nuclear survivin, p53, and β-catenin expression and recurrence and progression (p < 0.05, p < 0.01, and p < 0.01, respectively). Detailed results of survivin, p53, and β-catenin expressions along with all other clinicopathologic features analyzed in the study are presented in Table 1 and Table 2.

Prognostic value of the three biomarkers

During the follow-up period, tumor recurrence and progression were observed in 47.6% (n=70) and 29.9% (n=44) of patients, respectively. High nuclear survivin, p53, and cytoplasmic β-catenin expressions were significantly related to low recurrence free survival (RFS), progression free survival (PFS), and overall survival (OS) values in the log rank test of

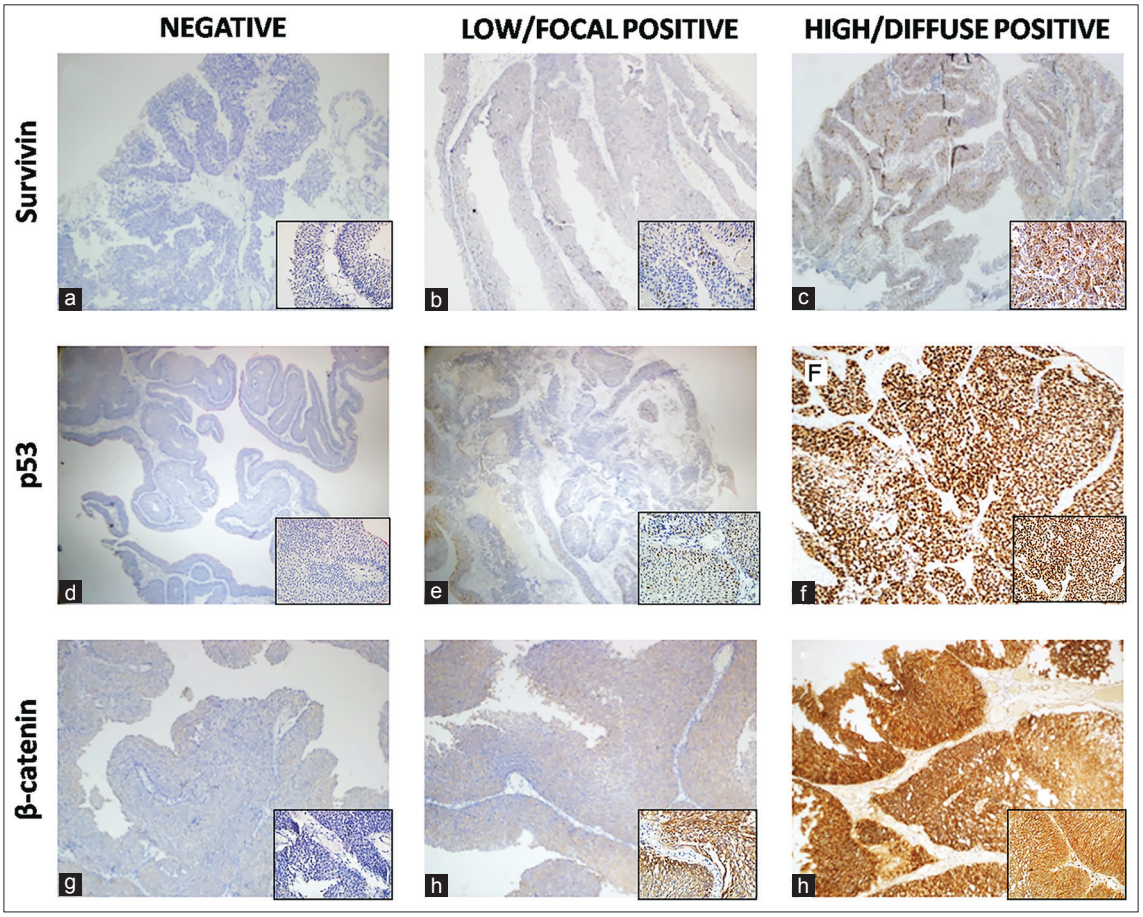

FIGURE 1. Immunohistochemical expressions of survivin (a, b, c), p53 (d, e, f), and β-catenin (g, h, i); negative expressions (a, d, g), low/focal positive expressions (b, e, h), and high/diffuse positive expressions (c, f, i). Insets at the bottom right represent higher magnification.

TABLE 1. Association between biomarker expression and clinicopathological characteristics

Characteristics	p53 (n (%))		*p* value	Survivin (n (%))		*p* value	β-catenin (n (%))			*p* value
	-	+		-	+		-	Low	High	
Age										
< 65 years (n=62)	38 (61.3)	24 (38.7)	[a]*0.657*	39 (62.9)	23 (37.1)	[a]*0.138*	37 (59.7)	6 (9.7)	19 (30.6)	[a]*0.089*
≥ 65 years (n=85)	49 (57.6)	36 (42.4)		43 (50.6)	42 (49.4)		41 (48.2)	20 (23.5)	24 (28.2)	
Gender										
Male (n=106)	65 (61.3)	41 (38.7)	[c]*0,509*	57 (53.8)	49 (46.2)	[c]*0,546*	55 (51.9)	20 (18.9)	31 (29.2)	[a]*0,819*
Female (n=41)	22 (53.7)	19 (46.3)		25 (61.0)	16 (39.0)		23 (56.1)	6 (14.6)	12 (29.3)	
First pT										
Ta-T1 (n=113)	75 (66.4)	38 (33.6)	[c]*0.002***	71 (62.8)	42 (37.2)	[c]*0.003***	67 (59.3)	20 (17.7)	26 (23.0)	[a]*0.006***
T2-T4 (n=34)	12 (35.3)	22 (64.7)		11 (32.4)	23 (67.6)		11 (32.4)	6 (17.6)	17 (50.0)	
First Grade										
Low (n=67)	46 (68.7)	21 (31.3)	[a]*0.032**	43 (64.2)	24 (35.8)	[a]*0.061*	42 (62.7)	14 (20.9)	11 (16.4)	[a]*0.007***
High (n=80)	41 (51.3)	39 (48.8)		39 (48.8)	41 (51.3)		36 (45.0)	12 (15.0)	32 (40.0)	
CIS										
Negative (n=128)	76 (59.4)	52 (40.6)	[c]*1.000*	75 (58.6)	53 (41.4)	[c]*0.125*	68 (53.1)	26 (20.3)	34 (26.6)	[a]*0.043**
Positive (n=19)	11 (57.9)	8 (42.1)		7 (36.8)	12 (63.2)		10 (52.6)	0 (0.0)	9 (47.4)	
Recurrence										
Absent (n=77)	59 (76.6)	18 (23.4)	[c]*0.001***	52 (67.5)	25 (32.5)	[a]*0.003***	59 (76.6)	11 (14.3)	7 (9.1)	[a]*0.001***
Present (n=70)	28 (40.0)	42 (60.0)		30 (42.9)	40 (57.1)		19 (27.1)	15 (21.4)	36 (51.4)	
Progression										
Absent (n=103)	74 (71.8)	29 (28.2)	[c]*0.001***	66 (64.1)	37 (35.9)	[c]*0.004***	69 (67.0)	17 (16.5)	17 (16.5)	[a]*0.001***
Present (n=44)	13 (29.5)	31 (70.5)		16 (36.4)	28 (63.6)		9 (20.5)	9 (20.5)	26 (59.1)	
Status										
Live (n=111)	75 (67.6)	36 (32.4)	[c]*0.001***	70 (63.1)	41 (36.9)	[c]*0.003***	69 (62.2)	18 (16.2)	24 (21.6)	[a]*0.001***
Exitus (n=36)	12 (33.3)	24 (66.7)		12 (33.3)	24 (66.7)		9 (25.0)	8 (22.2)	19 (52.8)	

[a]Pearson Ki-kare Test, [b]Fisher-Freeman-Halton Test, [c]Yates' Continuity Correction Test, **p*<0.05, ***p*<0.01

TABLE 2. Association between biomarker expression and clinicopathological characteristics in the NMI-UC subgroup

Characteristics	n	p53 (n (%))		*p* value	Survivin (n (%))		*p* value	β-catenin (n (%))			*p* value
		0	1+		0	1+	n (%)	0	1+	2+	0/1+vs 2+
Gender											
Male	85	56 (65.9)	29 (34.1)	1.000	51 (60.0)	34 (40.0)	0.390	49 (57.6)	16 (18.8)	20 (23.5)	1.000
Female	28	19 (67.9)	9 (32.1)		20 (71.4)	8 (28.6)	18 (64.3)	4 (14.3)	6 (21.4)		
First grade											
Low	64	46 (71.9)	18 (28.1)	0.225	43 (67.2)	21 (32.8)	0.274	40 (62.5)	14 (21.9)	10 (15.6)	0.057
High	49	29 (59.2)	20 (40.8)		28 (57.1)	21 (42.9)	27 (55.1)	6 (12.2)	16 (32.7)		
CIS											
Negative	100	66 (66.0)	34 (34.0)	1.000	65 (65.0)	35 (35.0)	0.227	61 (61.0)	20 (20.0)	19 (19.0)	0.010
Positive	13	9 (69.2)	4 (30.8)		6 (46.2)	7 (53.8)	6 (46.2)	0 (0.0)	7 (53.8)		
Recurrence											
Absent	63	51 (81.0)	12 (19.0)	0.001	47 (74.6)	16 (25.4)	0.007	49 (77.8)	10 (15.9)	4 (6.3)	0.001
Present	50	24 (48.0)	26 (52.0)		24 (48.0)	26 (52.0)	18 (36.0)	10 (20.0)	22 (44.0)		
Progression											
Absent	89	66 (74.2)	23 (25.8)	0.002	61 (68.5)	28 (31.5)	0.029	59 (66.3)	16 (18.0)	14 (15.7)	0.001
Present	24	9 (37.5)	15 (62.5)		10 (41.7)	14 (58.3)	8 (33.3)	4 (16.7)	12 (50.0)		
Status											
Live	98	68 (69.4)	30 (30.6)	0.150	65 (66.3)	33 (33.7)	0.093	61 (62.2)	18 (18.4)	19 (19.4)	0.042
Exitus	15	7 (46.7)	8 (53.3)		6 (40.0)	9 (60.0)	6 (40.0)	2 (13.3)	7 (46.7)		

[a]Pearson Ki-kare Test, [b]Fisher-Freeman-Halton Test, [c]Yates' Continuity Correction Test, **p*<0.05, ***p*<0.01

Kaplan–Meier survey analyses ($p < 0.01$). In the NMI-UC (n=113) group, Cox regression analyses revealed that high survivin and β-catenin expressions were correlated with tumor recurrence (Hazard ratio (HR) 3.876 and 5.851; 95% confidence interval [CI] 1.273–11.804 and 1.870–18.308; $p = 0.017$ and 0.002, respectively). Moreover, high β-catenin expression was found to be correlated to tumor progression (HR 3.104; 95% CI 1.092–8.823; $p = 0.034$). The only parameter found to be related to a poor survival in the NMI-UC group was a high grade of the tumor (HR 2.978; 95% CI 1.005–8.823; $p = 0.034$). The findings related to NMI-UC are summarized in Table 3.

Expression analysis of survivin, β-catenin, and p53 with respect to their prognostic utility showed that at least two of the markers were positive when poor prognostic factors, such

as a high grade, recurrence, progression, and mortality, were observed (Table 4).

Survival univariate analysis

Kaplan–Meier and log rank tests revealed that survivin-, β-catenin-, and p53-expressing patients had RFS ratios of 63.1%, 55.8%, and 60%, respectively. Mean overall survival was 27.01±2.73, 20.58±3.05, and 31.20±3.49 months, respectively. Progression-free survival ratios for survivin, β-catenin, and p53 expression in patients were 63.1%, 55.8%, and 60%, respectively. Overall survival was 40.85±3.68, 37.86±4.45, and 40.56±3.65 months. Overall survival rates were 63.1%, 55.8%, and 60%, respectively. Mean survival was 42.64±3.29, 42.98±3.57, and 43.88±3.12 months. The differences were statistically significant compared to expression-negative patients ($p < 0.01$) (Figure 2).

Correlation between expressions of survivin, p53, and β-catenin

β-catenin and p53 were positively correlated (r=0.221; $p < 0.01$), and p53 and survivin were also positively correlated (r=0.236; $p < 0.01$). We did not find any correlation between β-catenin and survivin (r=0.046; $p > 0.05$).

DISCUSSION

Identifying the markers to define whether to opt for medical or surgical treatment is still controversial for bladder carcinoma. The European Organization for Research and Treatment of Cancer scoring system comprises different factors, such as tumor size, tumor grade, tumor stage (pT), recurrence rate, and presence of carcinoma in situ, and cystectomy. Ongoing molecular, and immunohistochemical studies are aimed either to predict recurrence and progression or to invest in novel target therapy strategies, particularly for superficial/noninvasive bladder carcinoma. In this study, we investigated the relationship between expression of survivin, β-catenin and p53, known for their importance in cell-cycle and apoptosis, and prognostic parameters in UC and NMI-UC [23].

To our knowledge, survivin, β-catenin, and p53 expressions have not been extensively studied in bladder UC. In recent studies, nuclear survivin expression was found to be a negative prognostic factor for UCs [20,24], and promising results were reported for survivin-targeted therapies [23,25]. In our study, we observed a significant correlation between high nuclear expression of survivin and development of both recurrence and progression in UC and NMI-UC ($p < 0.01$).

TABLE 3. Multivariate Cox regression analysis in the NMI-UC subgroup

Markers and Parameters	Recurrence			Progression			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
β-catenin									
Gender	1.715	0.450-6.535	0.429	1.691	0.441-6.482	0.443	1.561	0.414-5.894	0.511
Grade	2.143	0.685-6.703	0.190	2.755	0.936-8.105	0.066	3.022	1.010-9.038	**0.048**
CIS	0.439	0.080-2.397	0.866	0.530	0.103-2.738	0.449	0.566	0.111-2.879	0.493
β-catenin (0/1+vs 2+)	5.851	1.870-18.308	**0.002**	3.104	1.092-8.823	**0.034**	2.107	0.730-6.080	0.168
p53									
Gender	1.565	0.424-5.777	0.501	1.788	0.491-6.514	0.378	1.698	0.468-6.158	0.421
Grade	2.370	0.769-7.307	0.133	2.707	0.921-7.960	0.070	3.046	1.025-9.052	**0.045**
CIS	0.893	0.184-4.324	0.888	0.876	0.180-4.275	0.870	0.766	0.161-3.647	0.737
p53	2.490	0.890-6.968	0.082	1.952	0.690-5.524	0.208	1.500	0.534-4.216	0.442
Survivin									
Gender	1.492	0.409-5.439	0.544	1.761	0.489-6.345	0.387	1.765	0.486-6.410	0.388
Grade	2.467	0.820-7.426	0.108	2.879	0.986-8.407	0.053	2.978	1.005-8.823	**0.049**
CIS	0.466	0.092-2.366	0.357	0.537	0.113-5.557	0.435	0.690	0.148-3.212	0.636
Survivin	3.876	1.273-11.804	**0.017**	2.802	0.977-8.035	0.055	2.568	0.906-7.280	0.076

TABLE 4. Comparison of survivin, p53 and β-catenin expression (+/-) with high grade, recurrence, progression and mortality

Markers	n	n (%)			
		High grade	Recurrence (+)	Progression (+)	Mortality (+)
β-catenin (-), p53 (-), survivin (-)	46	16 (34.8)	10 (21.7)	3 (6.5)	3 (6.5)
β-catenin (+)	11	8 (72.7)	6 (54.5)	3 (27.3)	1 (9.1)
p53 (+)	30	15 (50.0)	15 (50.0)	10 (33.3)	6 (20.0)
Survivin (+)	23	12 (52.2)	5 (21.7)	1 (4.3)	4 (17.4)
β-catenin (+), p53 (+)	10	8 (80.0)	9 (90.0)	6 (60.0)	5 (50.0)
β-catenin (+), survivin (+)	7	5 (71.4)	7 (100.0)	6 (85.7)	4 (57.1)
p53 (+), survivin (+)	5	5 (100.0)	4 (80.0)	4 (80.0)	4 (80.0)
β-catenin(+), p53 (+), survivin (+)	15	11 (73.3)	14 (93.3)	11 (73.3)	9 (60.0)

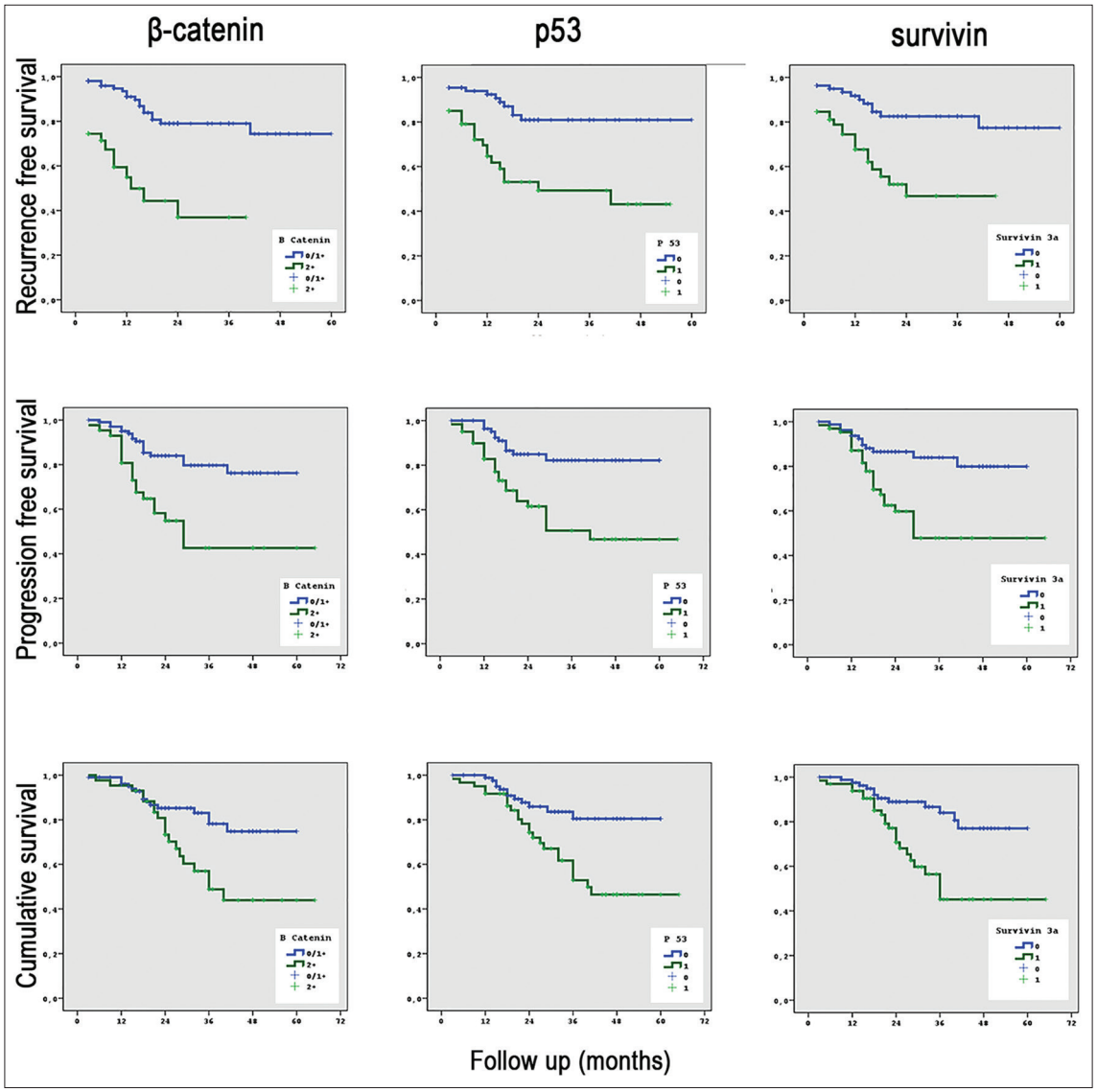

FIGURE 2. Kaplan–Meier univariate survival analyses of recurrence-free survival, progression-free survival, and overall survival curves related to survivin, β-catenin, and p53 expressions.

Nuclear survivin expression was also significantly associated with mortality ($p < 0.01$), and there was a significant relationship between nuclear survivin and the advanced stage of tumor ($p < 0.01$).

On the other hand, wild-type p53 transfection was found to be associated with repression of the survivin promoter [24]. Moreover, Mirza et al. reported that overexpression of p53 would posttranscriptionally control survivin expression [26]. Our study showed a positive correlation between the expression of p53 and nuclear survivin and a lack of cytoplasmic survivin expression. Furthermore, p53 overexpression is reported to be significantly related to recurrence, progression, and mortality in NMI-UC [27,28]. In contrast, Lianes et al. found no relationship with p53 overexpression between high-grade and staged bladder UC and prognostic parameters [29]. In our study, advanced stage (≥T2) and high-grade bladder carcinomas were found to be significantly correlated with p53 overexpression ($p < 0.01$). There were significant associations between p53 overexpression and development of recurrence, progression, and mortality in the UC group ($p < 0.01$). Interestingly, these findings were similar in the NMI-UC group except for mortality ($p > 0.05$) (Table 1). The latter finding suggests that p53 is not solely responsible for tumorigenesis of bladder cancer.

Molecular adhesion molecules are important components of signal transduction pathways related to tumor development [30]. Likewise, β-catenin as an adhesion molecule is also related to proliferation and invasion [31,32]. Chang et al. suggested that the induction of survivin-mediated resistance to apoptosis occurred through the loss of p53, rather than through the overexpression of β-catenin [33]. In our study, there was a significant relationship between β-catenin overexpression and advanced stage (≥T2) and high-grade bladder carcinoma ($p < 0.01$).

There were significant associations in both the UC and NMI-UC groups with β-catenin overexpression and the development of recurrence, progression, and mortality ($p < 0.01$). We observed a statistically significant positive correlation between β-catenin and p53 (r=0.221; $p < 0.01$). These findings suggest that β-catenin and p53 may work together in the development and progression of bladder carcinoma. Thus, our results suggest that alterations in survivin, β-catenin, and p53 behavior due to mutations could affect the cell cycle and apoptosis by interaction or collaborative pathway activation to promote bladder cancer recurrence, progression, and hence poor survival. These three could also take part in the decision-making process for cystectomy with transurethral resection material of UC that does not consist of the detrussor muscle. The findings also support the idea that inhibition of survivin, β-catenin, and p53 interaction in urothelial cells, through forthcoming targeted therapy strategies, could prevent the development of recurrent tumor and possibly invasion or metastasis.

CONCLUSIONS

Our results suggest that the immunohistochemical expressions of survivin, β-catenin, and p53 may be associated with clinical progression and may have predictive value for clinical outcomes in primary NMI-UC. Although further studies are needed to validate our findings, we suggest that these three biomarkers might be useful for the determination of treatment strategies in patients with primary NMI-UC. Patients with altered expression of these biomarkers may need closer surveillance and may be candidates for more aggressive treatment.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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