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Research Article

Immunohistochemical Expression of TRIP13 in Transitional and Squamous cell carcinoma of Urinary Bladder Carcinoma

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Abstract

Background: Urinary bladder carcinoma (UBC) is the 9th most common cancer globally. Thyroid receptor-interacting protein 13 (TRIP13) is a member of the AAA+ ATPase family. The upregulation of TRIP13 has been shown to be involved in the development and progression of different tumors, including UBC. **Method:** The current study included 50 formalin-fixed, paraffin-embedded tissue specimens of UBC. Tissue sections have been subjected to haematoxylin and eosin staining and immunohistochemical staining for TRIP13 expression. TRIP13 expression was estimated and its associations with clinicopathological factors were evaluated. The prognostic significance of TRIP13 was evaluated using univariate and multivariate COX regression analyses. **Results:** In the present study, 62% (n=31) of the cases showed 'negative/low' TRIP13 expression, whereas 38% (n=19) showed 'high' TRIP13 expression. A significant association was found between TRIP13 expression and tumor grade, stage, lymph node metastasis (LNM) and distant metastasis (P=0.012, 0.007, 0.045, <0.001, and 0.004 respectively). **Conclusion:** TRIP13 was remarkably correlated with poor prognosis.

Key words: Immunohistochemistry, TRIP13, Urinary bladder carcinoma.

Introduction

Urinary bladder carcinoma (UBC) is the most prevalent cancers of the urinary system [(1).] UBC is a global health problem, ranking as the 9th most common cancer and the 13th leading cause of cancer related deaths worldwide. It represents the 4th most common cancer in males and the 17th in females worldwide [(2)]. UBC is more predominant among men with 4:1 male: female ratio.[(3)]

The majority (90%) of UBC are urothelial carcinoma of the bladder (UCB) [(4)]. Whereas, other types include squamous cell carcinoma (SCC) (3 – 5 %), adenocarcinoma (0.5- 2 %), small cell carcinoma (< 0.5 %), sarcomatoid tumours, paraganglioma, melanoma and lymphoma [(5)]. In Egypt, UBC is ranked as the 2nd most commonly diagnosed malignancy between males [(6)]. The histopathological pattern of UBC had changed among Egyptians. Over the last decades, UCB had shown an increasement compared to SCC, after successful control of schistosomiasis.[(7)]

Regarding invasiveness of UBC, it's divided into 2 main categories, non-muscle invasive bladder cancer (NMIBC) and Muscle invasive bladder cancer (MIBC) based on the depth of bladder wall invasion of the primary tumour. Approximately half of the cases are NMIBC that tend to recur and may progress to a higher grade and higher pathologic stage with time .[(4)]

Recently, the treatment options for UBC are expanding rapidly. In advanced stage that show a poor response to the initial systemic therapy, drugs targeting checkpoints were shown to induce rapid response. Moreover, the combination of chemotherapy and immune

therapy could result in synergistic efficacy through multiple mechanisms. However, there is still no available targeted drug approved for the treatment of UBC [8]. Some research is targeted towards studying effective biomarkers and the identification of novel molecular markers. One of those biomarkers is Thyroid receptor-interacting protein 13 (TRIP13). TRIP13 is a member of the AAA+ ATPase family, which is known for mechanical forces derived from ATP hydrolase reactions. TRIP13 influences cell division and proliferation by playing a key role in chromosome recombination, spindle assembly checkpoint, chromosome synapsis, and chromosome structure development during meiosis .[9]

In the present study, we evaluated the immunoexpression pattern of TRIP13 in cases of UBC. Further, this was followed by assessment of its relationship with clinicopathological indicates, especially those related to prognosis .

Material and methods

This is a retrospective study, comprising of 50 randomly selected cases of primary UBC. Forty-two cases were obtained from radical cystectomy specimens, whereas 8 cases were obtained through transurethral resection on condition of containing muscularis propria. The selected cases were from the archives of histopathological laboratories of Minya Oncology Center, in the period between April 2014 and October 2016. Patients' data were obtained from the clinical and medical reports, including patients' age, gender, tumour type, gross pattern, tumour size, tumour grade, stage, lymph node metastasis, evidence of bilharzial cystitis, presence of insitu component, tumour necrosis, lymphovascular invasion, perineural invasion and TILs. Data for LNM, tumour size and distant metastasis were available for 42 cases.

Hematoxylin and eosin-stained sections were prepared and evaluated for the histological type of the tumor according to WHO histological classification of tumors of the urinary tract, 2022 (10), and for tumor stage based on AJCC/UICC TNM, 7th edition; 2010 [11]. TILs were assessed by percentage of intratumoral lymphocytes, and then cases were further stratified into two groups: intense infiltration (>10% of lymphocytic infiltration in direct contact with the tumor) and non-intense lymphocytic infiltration (<10%) [12]

Five μm sections were cut on positively charged slides, immersed in 3 changes of xylene, and rehydrated using graded series of alcohol. The endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 30 min at room temperature. For antigen retrieval, sections were treated in microwave by immersing in citrate buffer solution (pH 6) 4 times (5 minutes each) at 750 W. After that, slides were incubated with anti-polyclonal TRIP13 (1:100 dilution; Novus Biologicals, USA) for 1 hour in a humidity chamber followed by biotinylated secondary antibody for 30 min. The reaction was visualized with an avidin–biotin complex immunoperoxidase system using 3,3'diaminobenzidine as a chromogen (VENTANA detection kits, USA). The sections were counterstained with Meyer's hematoxylin, dehydrated, cleared and mounted then cover slipped. Negative control tissue sections were obtained by omitting the specific primary antibody from the staining procedure and replaced with PBS. As a positive control, the tissue section of testicular tissue was used.

TRIP13 immunoexpression was mainly detected in the nucleus of tumor cells. A scoring system was adapted using both percentage and intensity of the positively stained tumor cells. The percentage of positive tumor cells was assigned (0: negative; 1: <25%; 2: 25-50%; 3: >50%). The intensity of staining was graded using 0 – 3 scale (0: negative; 1: weak; 2: moderate; and 3: strong). The final score was the products of staining intensity multiplied by the score of positive cell percentage which ranged from 0 to 9. Then categorized into two groups according to the overall scores: negative/low expression: < 4 and high expression: ≥ 4.[8]

Statistical analysis

The analysis of the data was carried out using the IBM SPSS 20.0 statistical package software (IBM; Armonk, New York, USA). Data were expressed as mean±SD, minimum and maximum of range for quantitative parametric measures in addition to both number and percentage for categorized data. The Chi-square test or Fisher's exact test were used to compare categorical variables. In univariate survival

analysis, overall survival (OS) and disease-free survival (DFS) were estimated. Kaplan-Meier curves were used for plotting of patients' survival data. Differences between survival curves were tested using Log-Rank test. Cox multivariate regression analysis was used to analyze the hazard ratio and the prognostic value of clinical as well as other examined variables. P-values ≤ 0.05 were regarded as statistically significant.

Results:

Clinicopathological variables information was summarized in table (1). In the current study, TRIP13 expression was detected mainly in the nucleus of tumor cells. Negative/low expression was found in 62% (n=31) of cases whereas 38% (n=19) of the cases showed high TRIP13 expression Table (2) Fig (1a-1d) .

A significant positive association was found between TRIP13 expression and UBC grade (p=0.012) for UCB and (p=0.004) for SCC, stage, LNM and distant metastasis (p= 0.007, < 0.001 and 0.004 respectively). While no significant association was detected between TRIP13 expression and patients' age, sex, tumour size, gross pattern of tumour, type of tumour, state of muscle invasion, evidence of bilharziasis, insitu component, tumour necrosis, vascular invasion, perineural invasion or TILs (p = 0.607, 0.923, 0.065, 0.313, 0.656, 0.071, 0.665, 0.067, 0.392, 0.833, 0.661 and 0.216 respectively) Table.(2)

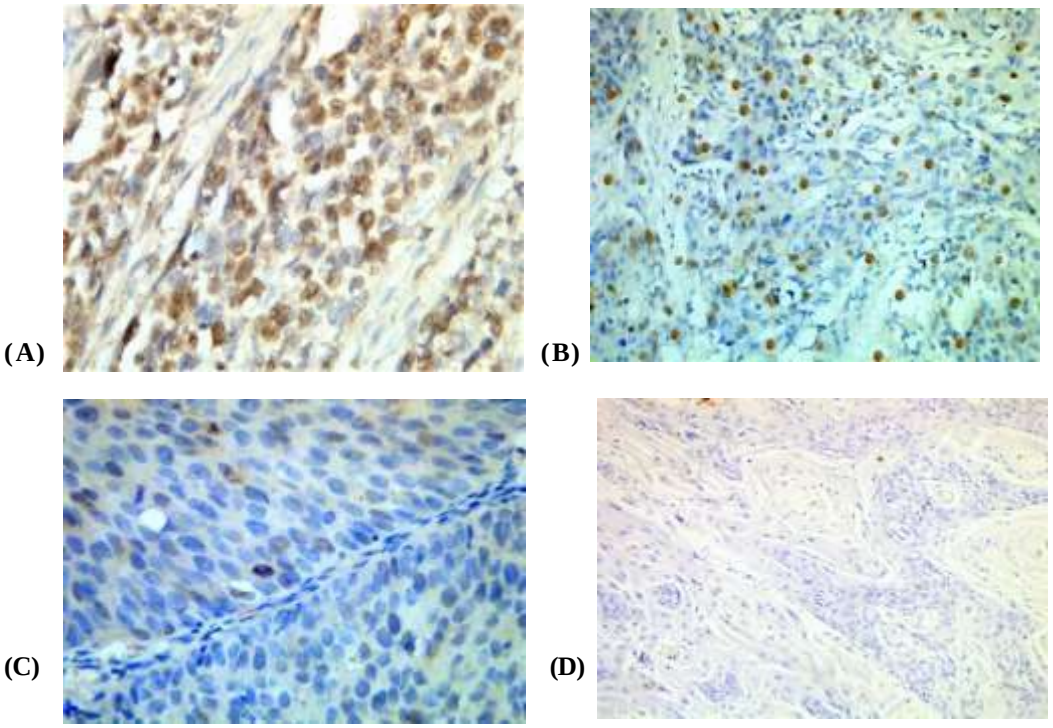
Among UCB cases, a significant positive association was detected between TRIP13 expression and tumour grade, stage, LNM and distant metastasis (p= 0.012, 0.019, <0.001 and 0.018 respectively). While among SCC cases a significant association was found with tumour grade only (p= 0.004).

The current study investigated OS and DFS of 50 cases of bladder cancer patients, variables analyzed included TRIP13 expression and clinicopathological data using univariate and multivariate Cox regression analysis. Regarding marker expression and OS, high TRIP13 expression had significantly shorter OS than those patients with negative/low TRIP13 expression (p=0.011) as shown in Fig. (2a). Cases with high TRIP13 expression had significantly shorter DFS than those patients with negative/low TRIP13 expression (p=0.010) as shown in Fig. (2b).

Regarding univariate survival analyses, there were significant associations between OS and tumour size (p=0.025), lymph node metastasis N2 (p=0.002), distant metastasis (p<0.001) and high TRIP13 expression (p= 0.038) as shown in table (3). Regarding DFS, significant associations were found between DFS and tumour size (p= 0.021), lymph node metastasis N2 (p<0.0001), vascular invasion (p= 0.031) and high TRIP13 expression (p= 0.025) as shown in table (4)

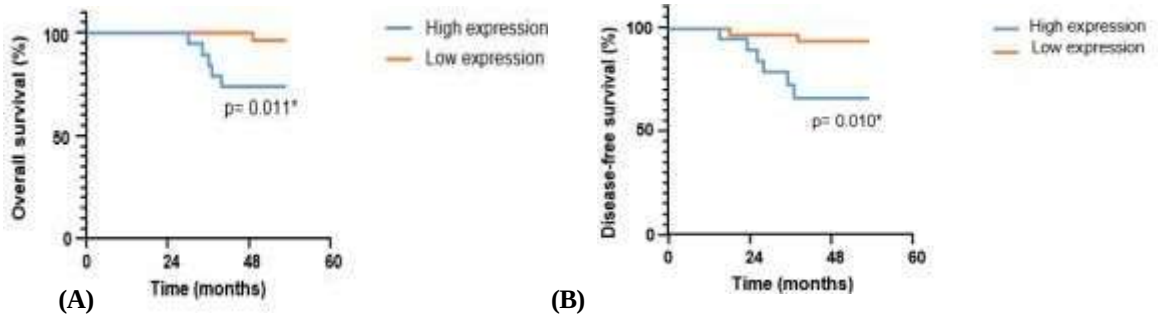
Cox multivariate regression analysis has been done to evaluate the prognostic significance of TRIP13 expression in UBC. In such analysis, the procedure has selected distant metastasis (p <0.001) as an independent prognostic indicator for OS, and selected vascular invasion (p= 0.019) and high TRIP13 expression (p= 0.013) as independent prognostic indicators for DFS. While the other variables included in the model did not reach significance level shown in table (3 and 4)

Fig (1):



TRIP13 immunoexpression in UCB and SCC cases: (A) High TRIP13 expression in high-grade UCB; (B) High TRIP13 expression in grade III SCC; (C) negative/low TRIP13 expression in low-grade UCB; (D) negative/low TRIP13 expression in low grade SCC.

Fig (2):



Representative significance of TRIP13 expression level for the OS and DFS: (A) The prognostic significance of TRIP13 expression level for the OS of bladder cancer; (B) The prognostic significance of TRIP13 expression level for the DFS of bladder cancer.

Table (1): Clinicopathological features of patients with Urinary bladder carcinoma.

Clinicopathological Features	No. (%)
Age at surgery	
≤ 62 yrs	26 (52%)
> 62 yrs	24 (48%)
Sex	
Male	45 (90%)
Female	5 (10%)

Size (n=42)	
≤ 5	27 (64.29%)
> 5	15 (35.71%)
Gross pattern of tumour	
Ulcerative	27 (54%)
Fungating mass	15 (30%)
Infiltrative mass	8 (16%)
Tumour Type	
Urothelial carcinoma	35 (70%)
Squamous cell carcinoma	15 (30%)
Tumour Grade	
Low Grade UCB	8 (16%)
High Grade UCB	27 (54%)
SCC grade I	2 (4%)
SCC grade II	9 (18%)
SCC grade III	4 (8%)
Stage of tumour	
T1 (lamina propria)	6 (12%)
T2a (Superficial muscle)	5 (10%)
T2b (deep muscle)	16 (32%)
T3 (Perivesical fat)	19 (38%)
T4 (adjacent organs)	4 (8%)
State of muscle invasion	
NMIBC	6 (12%)
MIBC	44 (88%)
Lymph Node metastasis (n=42)	
N0	21 (50%)
N1	14 (33.33%)
N2	7 (16.67%)
Evidence of bilharziasis	
Positive	27 (54%)
Negative	23 (46%)
Insitu Component	
Positive	10 (20%)
Negative	40 (80%)
Tumour Necrosis	
Positive	36 (72%)
Negative	14 (28%)
Vascular Invasion	
Positive	22 (44%)
Negative	28 (56%)
Perineural Invasion	
Positive	6 (12%)
Negative	44 (88%)
TILs	
Intense	26 (52%)
Non intense	24 (48%)
Distant metastasis (n=42)	
M0	37 (88.10%)
M1	5 (11.90%)

Table (2): Association between TRIP13 expression and different clinicopathological variables

Clinicopathological Features	No. (%)	TRIP13 Expression		P value
		negative/ low Expression (N=31)	High Expression (N=19)	
Age at surgery				
≤ 62 yrs	26 (52%)	17 (65.38%)	9 (34.62%)	**0.607**
> 62 yrs	24 (48%)	14 (58.33%)	10 (41.67%)	
Sex				
Male	45 (90%)	28 (62.22%)	17 (37.78%)	**0.923**
Female	5 (10%)	3 (60%)	2 (40%)	
Size (n=42)				
≤ 5	27 (64.29%)	19 (70.37%)	8 (29.63%)	**0.065**
> 5	15 (35.71%)	6 (40%)	9 (60%)	
Gross pattern of tumour				
Ulcerative	27 (54%)	18 (66.67%)	9 (33.33%)	**0.313**
Fungating mass	15 (30%)	7 (46.67%)	8 (53.33%)	
Infiltrative mass	8 (16%)	6 (75%)	2 (25%)	
Tumour Type				
Urothelial carcinoma	35 (70%)	21 (60%)	14 (40%)	**0.656**
Squamous cell carcinoma	15 (30%)	10 (66.67%)	5 (33.33%)	
Tumour Grade	8 (16%)	8 (100%)	0 (0%)	
Low Grade UCB	27 (54%)	13 (48.15%)	14 (51.85%)	**0.012***
High Grade UCB				
SCC grade I	2 (4%)	2 (100%)	0 (0%)	**0.004***
SCC grade II	9 (18%)	8 (88.89%)	1 (11.11%)	
SCC grade III	4 (8%)	0 (0%)	4 (100%)	
Stage of tumor	6 (12%)	6 (100%)	0 (0%)	**0.007***
T1 (lamina propria)	5 (10%)	5 (100%)	0 (0%)	
T2a (Superficial Muscle)	16 (32%)	10 (62.50%)	6 (37.50%)	
T2b (deep muscle)	19 (38%)	10 (52.63%)	9 (47.37%)	
T3 (Perivesical fat)	4 (8%)	0 (0%)	4 (100%)	
T4 (adjacent organs)				
State of muscle invasion	6 (22%)	6 (100%)	0 (0%)	**0.071**
NMIBC	44 (78%)	25 (56.82%)	19 (43.18%)	
MIBC				
Lymph Node metastasis (n=42)				
N0	21 (50%)	18 (85.71%)	3 (14.29%)	
N1	14 (33.33%)	7 (50%)	7 (50%)	**0.001***
N2	7 (16.67%)	0 (0%)	7 (100%)	
Evidence of bilharziasis				
Positive	27 (54%)	16 (59.26%)	11 (40.74%)	**0.665**
Negative	23 (46%)	15 (65.22%)	8 (34.78%)	
Insitu Component				
Positive	10 (20%)	9 (90%)	1 (10%)	**0.067**
Negative	40 (80%)	22 (55%)	18 (45%)	
Tumour Necrosis				
Positive	36 (72%)	21 (58.33%)	15 (41.67%)	**0.392**
Negative	14 (28%)	10 (71.43%)	4 (28.57%)	
Vascular Invasion	22 (44%)	14 (63.64%)	8 (36.36%)	**0.833**
Positive	28 (56%)	17 (60.71%)	11 (39.29%)	
Negative				

Perineural Invasion				
Positive	6 (12%)	3 (50%)	3 (50%)	**0.661**
Negative	44 (88%)	28 (63.64%)	16 (36.36%)	
TILs				
Intense	26 (52%)	14 (53.85%)	12 (46.15%)	**0.216**
Non intense	4 (52%)2	17 (70.83%)	7 (29.17%)	
Distant metastasis (n=42)				
M0	37(88.10%)	25 (67.57%)	12 (32.43%)	**0.004***
M1	5 (11.90%)	0 (0%)	5 (100%)	

Test of significance by Chi-square and Fischer exact tests p-value considered significant at <0.05*

Table (3): Univariate and multivariate Cox regression analyses of OS in UBC patients

Death	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p. value**	**HR (95% CI)**	**p. value**
Age (y)	1.02 (0.94-1.12)	0.604	1.63 (0.003-1011.351)	0.882
Sex (female)	0.59 (0.07-5.08)	0.634	152816965.4 (0-8.981E+118)	0.885
Type of tumor				
UC	1		1	
SCC	0.43 (0.05-3.67)	0.428	0 (0-1.189E+068)	0.854
Gross pattern				
Ulcerative	1		1	
Fungating	1.29 (0.22-7.78)	0.776	1.406E+18 (0-2.644E+06)	0.4
Infiltrative	1.07 (0.11-10.26)	0.955	6.722E+20 (0-3.349E+062)	0.328
Size >5	11.74 (1.36-101.54)	**0.025***	34038.527 (0-1.425E+065)	0.884
Grade (UC): Low	1	0.44	NE	NE
High	31.08 (0.005-189013.63)			
Grade (SCC)				
Grade I	1		NE	NE
Grade II	1 (0-5.421E+26)	>0.99		
Grade III	701.09 (0-2.86 E+25)	0.805		
Stage				
T1	1		1	
T2	1 (0.09-11.61)	>0.99	NE	
T3	1 (0.08 -12.14)	>0.99	NE	
T4	1 (0.01-92.64)	>0.99	1032.644 (0-3.368E+17)	0.684
NMIBC/MIBC	26.02 (0.001-570572.77)	0.523	NE	NE
LN	5.77 (0.67-49.44)	0.11	9.848E+31 (0-1.522E+08)	0.193
N0	0.17 (0.02-1.49)	0.11	NE	NE
N1	0.39 (0.05-3.37)	0.395	0 (0-2.139E+058)	0.5
N2	14.86 (2.61-84.66)	**0.002***	NE	NE
Bilharziasis	0.75 (0.15-3.74)	0.726	0.14 (0-6.763E+044)	0.97
Insitu component	0.033 (0-121.99)	0.416	0 (0-2.204E+054)	0.707
Necrosis	0.43 (0.09-2.13)	0.298	0 (0-1.989E+067)	0.733
Vascular invasion	0.64 (0.12-3.49)	0.604	251.38 (0-4.027E+051)	0.839
Perineural invasion	4.79 (0.86-26.83)	0.074	6.370E+15 (0-1.763E+051)	0.382
Lymphocytic infiltration	5.49 (0.6-44.78)	0.134	0 (0-7.833E+26)	0.808

Type of operation: RC	1			
TUR	5.29 (0.06-462.16)	0.465	NE	NE
Distant metastasis	63.1 (7.26-548.2)	**<0.001***	63.1 (7.26-548.2)	**<0.001***
Expression: Negative	1		1	
Low	1.05 (0-75.12)	0.996	NE	
High	9.76 (1.14-83.87)	**0.038***	0 (0-1.733E+038)	0.869

Table (4): Univariate and multivariate Cox regression analyses of DFS in UBC patients

Recurrence	**Univariate analysis**		**Multivariate analysis**	
	HR (95% CI)	**p. value**	**HR (95% CI)**	**p. value**
Age (y)	1.005 (0.93-1.09)	0.889	0.86 (0.08-8.97)	0.897
Sex (female)	0.74 (0.09-6.01)	0.777	0.06 (0-6.958E+13)	0.061
Type of tumor				
UC	1		1	
SCC	0.31 (0.04-2.49)	0.268	0.25 (0-1.847E+16)	0.944
Gross pattern				
Ulcerative	1		1	
Fungating	2.19 (0.44-10.86)	0.339	1.077E+20 (0-6.701E+043)	0.099
Infiltrative	2.14 (0.36-12.81)	0.405	2.417E+23 (0-2.818E+05)	0.090
Size >5	5.41 (1.29-22.72)	**0.021***	2.63 (0-2.102E+15)	0.956
Grade (UC): Low	1	0.408	NE	NE
High	2.45 (0.29-20.33)			
Grade (SCC)				
Grade I	1		NE	NE
Grade II	1 (0-3.682E+28)	>0.99		
Grade III	597.34 (0-2.192 E+28)	0.831		
Stage				
T1	1		1	
T2	16708.93 (0-5.370E+143)	0.953	NE	
T3	71875.628 (0-2.306E+144)	0.946	NE	
T4	NE	NE	NE	NE
NMIBC/MIBC	26.07 (0.006 – 108700.463)	0.443	NE	NE
LN	4.06 (0.82-20.16)	0.086	3.244E+32 (0-7.670E+072)	0.115
N0	0.25 (0.05-1.22)	0.086	NE	NE
N1	0.96 (0.23-4.03)	0.957	0 (0-184548.404)	0.108
N2	18.21 (3.58-92.61)	**<0.0001***	NE	NE
Bilharziasis	0.24 (0.05-1.2)	0.083	0.012 (0-6.350E+14)	0.821
Insitu component	0.41 (0.05-3.36)	0.407	0 (0-7.093E+0.053)	0.736
Necrosis	2.77 (0.34-22.54)	0.342	0 (0-7.185E+05)	0.624
Vascular invasion	10.13 (1.25-82.40)	**0.031***	12.44 (1.52-102.06)	**0.019***
Perineural invasion	2.14 (0.26-17.56)	0.479	1.820E+20 (0-2.374E+044)	>0.99
Lymphocytic infiltration	0.65 (0.16-2.71)	0.552	0 (0-13184.972)	0.175
Type of operation: RC	1			
TUR	5.34 (0.13-218.9)	0.376	NE	NE
Distant Metastasis	NE	NE	NE	NE

Expression: Negative	1		1		
Low	9.09 (0-29.09)	0.945	0.899 (0-75.50)	0.995
High	6.28 (1.25-31.40)	**0.025***	7.91 (1.55-40.37)	**0.013***

Discussion

The current study found that TRIP13 immunostaining was localized mainly in the nucleus. High expression was seen in 38% of cases. No significant differance in TRIP13 expression score was detected between UCB cases and SCC cases .

Concerning tumour grade, we noticed a significant positive association between TRIP13 expression and tumour grade. Among high grade UCB cases (51.85%) showed high TRIP13 expression, however all the grade III SCC showed high TRIP13 expression. Thus, indicating a relation between TRIP13 expression and lack of differentation. Notabley our findings were in agreement with the findings of Lu et al. who found that expression of TRIP13 was positively associated with tumour grade in breast invasive ductal carcinoma [13]. Unlike Niu et al. and Gao et al. who didn't find a significant relation between TRIP13 expression and tumour grade in UBC .[8,14]

In the present study, we found an evident significant association between TRIP13 expression and tumour stage. Also, a significant association found between TRIP13 expression and distant metastasis, as only 32.43% of cases of M0 stage showed high expression while all of M1 cases showed high expression. This result came in line with Gao et al. and Niu et al. who reported significant association between TRIP13 expression and both of tumour stage and distant metastasis in UCB (8,14). While Lu et al. found no significant association between TRIP13 expression and tumour stage in melanoma.[15]

Also, a significant association between TRIP13 expression and presence of LN metastasis was observed as olny 14.29% of cases of N0 stage showed high expression while 66.67% of LN positive tumours showed high expression score. This finding was in agreement with the finding of Gao et al. who reported significant association between TRIP13 expression and LN metastasis .[14]

The oncogenic effect of TRIP13 was confirmed in vivo and in vitro studies. TRIP13 knockdown inhibits cell proliferation, colony formation, invasion and cell motility. The role of TRIP13 in EMT process could explain the role of TRIP13 in promotion of tumour invasion and metastasis [16]. Our findings together with these finding suggest the role of TRIP13 in urinary bladder progression, invasion and spread.

This study noticed no significant association between TRIP13 expression and patients' age, sex and tumour size. Our findings were consistent with the findings of Gao et al. and Niu et al. who also found no significant association between TRIP13 expression with age, sex of patients and tumour size in UBC [8,14]. Meanwhile a significant relation with the large tumour size was found in UBC [17]. Also, a significant association between TRIP13 expression with tumour size in hapatocellular carcinoma was found.[18]

Finally, our study also found no statistically significant associations between TRIP13 expression and tumour gross pattern, tumour type, muscle invasion, evidence of bilharziasis, tumour necrosis, insitu component, vascular invasion, perineural invasion or lymphocytic infiltrate .

The analysis of TRIP13 expression and clinicopathological features of UBC in relation to OS and DFS demonstrated that cases with high TRIP13 expression had significantly shorter OS than those patients with negative/low TRIP13 expression. Also, cases expressed high TRIP13 expression had significantly shorter DFS than those patients with negative/low TRIP13 expression. Consistant with our finding Gao et al. found that TRIP13 expression was correlated with reduced OS and DFS.[14]

Dai et al. reported that the OS survival curve showed that patients with positive expression of TRIP13 had an unfavorable OS time when compared with patients who did not express TRIP13, and concluded that aberrant expression of TRIP13 should participate in the process of invasion and metastasis of UCB [19]. So, TRIP13 can be considered as a valuable

indicator for prediction of bladder cancer patients' prognosis.

Recently, more studies had focused on the effects of TRIP13 in cancer progression, prognosis, and drug resistance. Low expression of TRIP13 can inhibit tumor cells proliferation, migration, and invasion, and promote apoptosis and EMT (14). Banerjee et al. have shown that overexpression of TRIP13 was associated with reduced sensitivity to anticancer drugs in SCC of the head and neck.[20]

Lastly, it might be assumed that TRIP13 drives the malignant progression UBC. In this context, the current study demonstrated the presence of a significant association between TRIP13 expression and many poor prognostic factors of UBC specially increased tumor grade, advanced stage, and lymph node metastasis. In addition to its prognostic role as a poor indicator for both of OS and DFS.

Conclusion

TRIP13 plays a key role in UBC progression and spread. Our finding also suggests TRIP13 as a novel and prognostic marker in UBC.

Conflict of interest: Nil .

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References

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. (CA) a cancer journal for clinicians, 68(6), 394-424.

2. Fang, W., Yang, Z. Y., Chen, T. Y., Shen, X. F., & Zhang, C. (2020). Ethnicity and survival in bladder cancer: a population-based study based on the SEER database. Journal of translational medicine, 18, 1-11.

3. Saginala, K., Barsouk, A., Aluru, J. S., Rawla, P., Padala, S. A., & Barsouk, A. (2020). Epidemiology of bladder cancer. Medical Sciences, 8(1), 15.

4. Jalanko, T., de Jong, J. J., Gibb, E. A., Seiler, R., & Black, P. C. (2020). Genomic subtyping in bladder cancer. Current urology reports, 21(2), 1-10.

5. Miyazaki, J., & Nishiyama, H. (2017). Epidemiology of urothelial carcinoma .

International Journal of Urology, 24(10), 730-734.

6. Antoni, S., Ferlay, J., Soerjomataram, I., Znaor, A., Jemal, A., & Bray, F. (2017). Bladder cancer incidence and mortality: a global overview and recent trends. European urology, 71(1), 96-108.

7. Moussa, S., & El-Sheshtawy, W. (2017). Pathological Pattern of Urinary Bladder Cancer: Data from a Single Egyptian Institute. Research in Oncology, 13(1), 14-17.

8. Niu, L., Gao, Z., Cui, Y., Yang, X., & Li, H. (2019). Thyroid receptor-interacting protein 13 is correlated with progression and poor prognosis in bladder cancer. Medical science monitor: international medical journal of experimental and clinical research, 25(9), 6660-6668.

9. Yost, S., De Wolf, B., Hanks, S., Zachariou, A., Marcozzi, C., Clarke, M. & Rahman, N. (2017). Biallelic TRIP13 mutations predispose to Wilms tumor and chromosome missegregation. Nature genetics, 49(7), 1148-1151.

10. Netto, G. J., Amin, M. B., Berney, D. M., Compérat, E. M., Gill, A. J., Hartmann, A. & Moch, H. (2022). The 2022 World Health Organization classification of tumors of the urinary system and male genital organs—part B: prostate and urinary tract tumors. European urology.

11. Magers, M. J., Lopez-Beltran, A., Montironi, R., Williamson, S. R., Kaimakliotis, H. Z., & Cheng, L. (2019). Staging of bladder cancer. Histopathology, 74(1), 112-134.

12. Rouanne, M., Betari, R., Radulescu, C., Goubar, A., Signolle, N., Neuzillet, Y. & Lebret, T. (2019). Stromal lymphocyte

infiltration is associated with tumour invasion depth but is not prognostic in high-grade T1 bladder cancer. European Journal of Cancer, 108, 111-119.

13. Lu, S., Qian, J., Guo, M., Gu, C., & Yang, Y. (2019). Insights into a crucial role of TRIP13 in human cancer. Computational and structural biotechnology journal, 17, 854-861.

14. Gao, Y., Liu, S., Guo, Q., Zhang, S., Zhao, Y., Wang, H. & Wang, Z. (2019). Increased expression of TRIP13 drives the tumorigenesis of bladder cancer in association with the EGFR signaling pathway. International journal of biological Sciences, 15(7), 1488.

15. Lu, W., Mengxuan, Z., Ming, R., Zixu, G., Yong, Z., Simin, Z., ... & Jianying, G. (2022). TRIP13/FLNA Complex Promotes Tumor Progression and Is Associated with Unfavorable Outcomes in Melanoma. Journal of Oncology, 2022.

16. Chen, Y., Chen, D., Qin, Y., Qiu, C., Zhou, Y., Dai, M. & Jiang, Y. (2022). TRIP13, identified as a hub gene of tumor progression, is the target of microRNA-4693-5p and a potential therapeutic target for colorectal cancer. Cell death discovery, 8(1), 1-10.

17. Loloi, J., Allen, J. L., Schilling, A., Hollenbeak, C., Merrill, S. B., Kaag, M. G., & Raman, J. D. (2020). In the World of Bladder Tumors: Size Does Matter. Bladder Cancer, 6(2), 195-200.

18. Ju, L., Li, X., Shao, J., Lu, R., Wang, Y., & Bian, Z. (2018). Upregulation of thyroid hormone receptor interactor 13 is associated with human hepatocellular carcinoma. Oncology reports, 40(6), 3794-3802.

19. Dai, C., Zhang, Y., & Zhou, L. (2021). Expression of TRIP13, ZEB1, and E-cad in Infiltrating Urothelial Carcinoma of Bladder and Their Clinical Significance.

20. Banerjee, R., Liu, M., Bellile, E., Schmitd, L. B., Goto, M., Hutchinson, M. K. N. & D'Silva, N. J. (2022). Phosphorylation of TRIP13 at Y56 induces radiation resistance but sensitizes head and neck cancer to cetuximab. Molecular Therapy, 30(1), 468-484.