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Original Research Article

Role of serum CA 19-9 as a tumor marker in TCC bladder

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ABSTRACT

Background: There is a dearth of reliable blood and urine markers for transitional cell carcinoma of urinary bladder. CA 19-9 is a well-known marker for gastrointestinal malignancies and is being investigated for other malignancies including carcinoma bladder. In this prospective study, we evaluated the role of serum CA 19-9 as a tumor marker and correlated its level with tumor grade and stage.
Methods: One hundred and fifteen patients with transitional cell carcinoma of urinary bladder and 69 healthy volunteers, as controls were included in the study. Preoperative blood sample was analysed for level of CA 19-9 using ELISA kit (normal - 0 U/ml to 37U/ml) and were correlated with grade and TNM stage of tumor.
Results: The range of the control group is 2-38U/ml (mean: 17.67±9.68U/ml); TCC group is 1-94U/ml (mean: 37.12±31.52U/ml) (p=0.304). When CA 19-9 level >37IU/ml was taken as cut-off for a positive test, sensitivity of detecting T3 disease, T4 disease, MIBC, presence of node and high grade tumour were 80%, 75%, 70.3%, 78% and 57.8% respectively. However, there was a statistically significant increase in levels of CA19-9 in relation to higher grade (<0.001), presence of muscle invasion (<0.001), T stage (<0.001) and N stage (<0.001).
Conclusions: Serum CA19-9 is almost invariably raised in patients with high grade and invasive disease. Thus, it has a place as a prognostic marker rather than as a diagnostic tool due to its low sensitivity for TCC bladder.

Keywords: High grade bladder cancer, Muscle invasive bladder cancer, Prognostic tumour marker, Transitional cell carcinoma, Serum tumor marker, Serum CA 19-9

INTRODUCTION

Urinary bladder cancer has increased in incidence and it has been ranked the 9th most common malignancy worldwide. There is a strong male predilection and the male to female ratio is greater than 3:1.[1] It is the 7th most common malignancy in men, however it only the 17th most common in women.[2] In the US and Europe, approximately 145,000 patients succumb to urinary bladder cancer every year.[2] As recorded in the National Cancer Registry Programme, the incidence of bladder cancer in India stands at 2.25% (per 100,000 people annually). There is an increased incidence among men (3.67%) and less incidence in women at (0.83%).[3] The north-eastern part of this country is a well known hub of various cancers and transitional cell carcinoma of bladder is no exception. Of late, there is a considerable increase in patients with TCC in northeast India.

Non muscle invasive cancer (NMIBC) constitute 70% of patients with bladder cancer at presentation. Among these patients with NMIBC, 70% of them present in stage Ta, 20% in T1, and the remaining 10% as CIS.[4] The natural history of bladder cancer is best determined by the disease stage and histological grade. NMIBC patients usually fare better in the long run and half of them do not have recurrence at 5 years.[5] Among the remaining half, 20% of patients seems to have 1 recurrence and the rest of the 30% usually have multiple recurrences.[6] Fifty to seventy percent of tumours with recurrences have similar

histological grade and stage as that of primary tumour, while progression to muscle-invasive cancer (MIBC) occurs in 20%-40%.[7,8]

The monitoring measures include periodic cystoscopic examination and urine based diagnostic studies.[9,10] Urine cytology is still the gold standard for screening of bladder cancer since decades. Urine cytology for malignant cells is a subjective test and it needs adequate number of exfoliated cells for a higher sensitivity. Cellular alterations occur from improper collection and storage which can affect the diagnostic accuracy.[11,12]

There are many tumour markers that have been approved for clinical use like bladder tumour antigen (BTA), nuclear matrix proteins (NMP22), and fibrinogen degradation products. However, the sensitivity and specificity of these markers are limited.[13,14]

CA 19-9 (carbohydrate antigen 19-9) is known as sialylated Lewis (a) antigen or cancer antigen. It is a tumour maker that has been mainly approved in the treatment of pancreatic cancer. Binding of monoclonal antibody to CA 19-9, the tumor surface marker Sialyl-Lewis A is the basis of CA 19-9 test.[15,16] The role of CA19-9 in pancreatic cancer management is well proven with therapeutic and prognostic value.[17,18] A few studies have reported an association of CA 19-9 with TCC bladder.[19-22] Some studies have also found an increased association of extravesical disease and lymph node metastates with increased CA 19-9 expression.[23,24]

However, literature regarding the role of CA 19-9 as a tumour marker for TCC bladder cancer is sparse. Our aim was to evaluate the serum level of CA19-9 in patients with TCC bladder and controls; and correlate CA19-9 level to various tumor stages, nodal status, metastasis, histological grade and muscle invasion.

METHODS

This is a prospective study constituting 115 patients with TCC of bladder (83 males and 32 females) treated in our institute from June 2016 to May 2018. Institutional ethical committee approval was taken for the study. Age ranged from 29 years to 70 years. We investigated 126 patients with suspected TCC bladder. After TURBT, 5 patients had squamous cell carcinoma of UB and 6 patients had benign lesions of urinary bladder. These 11 patients had been excluded from the study. All patients with suspected bladder tumour or upper tract transitional cell carcinoma had been evaluated clinically and imaging studies like ultrasound were performed. Patients had been evaluated for urine cytology for malignant cells with urine samples of three consecutive morning. Those with multiple tumours or having size greater than 3cm or broad based or with hydroureteronephrosis or features suggestive of muscle invasion underwent CECT/galodinium enhanced MRI of whole abdomen. Patients underwent TURBT and in those who had muscle invasion in biopsy later underwent radical cystectomy with ileal conduit. Those with MIBC who were unfit or preferred bladder preservation protocol were offered trimodality therapy. All patients whose histopathological examination came out to be TCC bladder were included in the study. While patients with non urothelial histology like squamous cell carcinoma, adenocarcinoma and those patients with any history of other malignancy were excluded from the study. A group of 69 patients with renal calculi, UTI, or BEP who were admitted in our department were taken as the control group.

Serum levels of CA 19-9 were determined preoperatively or prior to starting neoadjuvant chemotherapy. Blood sample were collected from peripheral vein in a clotted vial. Serum separation was done by centrifugation at 4000 rpm for 10 minutes and then refrigerated till the analysis. Analysis of CA19-9 was done by ELISA (enzyme linked immunosorbent assay) kit available in our institute. The normal range of CA19-9 was taken as 0U/ml to 37U/ml.

Serum levels of CA 19-9 of TCC group were compared with the control group. The TCC group was further categorised into NMIBC and MIBC, high grade and low grade according to histology, and according to TNM staging (AJCC 7th, 2010). Comparison of CA 19-9 levels of these subgroups were done to find the statistical significance.

RESULTS

We evaluated 126 patients (123 patients with suspected TCC bladder and 3 patients with suspected upper tract TCC). After TURBT, 5 patients had SCC of UB and 6 patients had benign lesion of UB. These patients were excluded from the study. Hundred fifteen patients with TCC bladder were included in the study. There were 83 males and 32 females. The median age was 60 years and median CA 19-9 level was 15 IU/ml (Table 1) (Figure 1) (Figure 2). One hundred patients underwent TURBT and 15 patients had radical cystectomy with ileal conduit.

Table 1: Distribution of age and CA19-9 in the TCC patients (n=115).

	Median (IQR)	Range
Age (years)	60 (56-66)	29-70
CA 19-9 (IU/ml)	15 (6-31)	1-94

Among the patients, 42 patients had Ta tumours, 36 patients had T1 tumours, 20 patients had T2 disease, 13 patients had T3 disease and 4 patients had T4 disease. Fourteen patients had positive regional nodes. Distant metastasis was present in 5 patients (2 hepatic metastases and 3 skeletal metastases). On categorisation 78 patients had NMIBC and 37 MIBC. On histopathological examination, 70 patients had low grade tumor and 45 patients had high grade tumor.

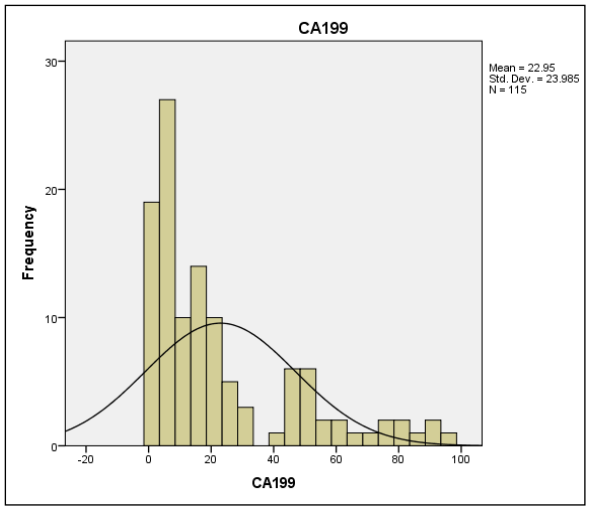

Figure 1: Histogram showing distribution of CA 19-9 in the patients with TCC (n=115).

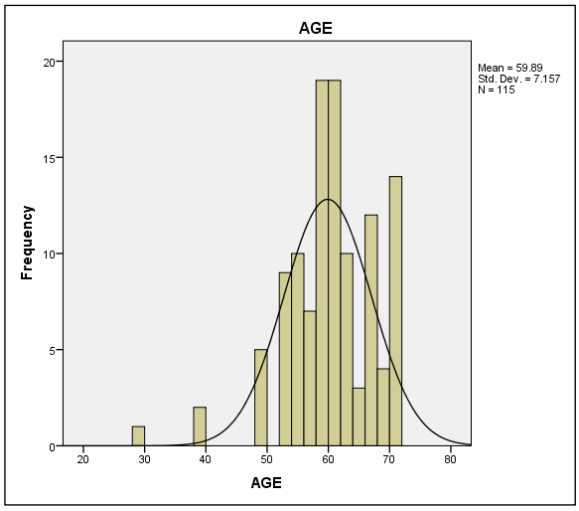

Figure 2: Histogram showing distribution of age in the patients with TCC (n=115).

Table 2: Comparison of CA 19-9 distribution in patients with TCC and controls.

Disease group	Patients (n)	%	Mean (±SD)	Range	p value
Control	69		17.67±9.68	2-38	0.304
TCC	115		37.12±31.52	1-94	

Table 3: CA 19-9 distribution in various groups of patients of TCC.

Disease Group	Patients (n)	Median CA 19-9	IQR (CA-19-9)	Range (CA 19-9)	p value
Muscle invasiveness					
NMIBC	78	9	4-18.25	1-50	<0.001
MIBC	37	49	8-67	1-94	
TNM group					
Ta	42	11	4-18	1-31	<0.001
T1	36	9	6-18.5	2-50	
T2	20	45	7.25-51.25	2-55	
T3	13	63	34.25-84.5	3-94	
T4	4	74	18.5-85.5	1-88	
N0	101	11	6-23	1-64	<0.001
N1	14	76.5	34.25-88.25	1-94	
M0	110	15	6-27.25	1-94	0.246
M1	5	75	4.5-81.5	1-83	
Histological grade					
Low Grade	70	10	4-19	1-50	<0.001
High Grade	45	45	7-61	1-94	

The distribution of CA 19-9 level among patients with TCC and controls in shown below in Table 2. There is no statistically significant difference between the 2 groups (p = 0.304). The comparison of CA 19-9 levels in the various disease groups have been shown together with their statistical significance in Table 3. Kruskal Willis test has been used for comparison of means among the T groups (tumor group). Mann Whitney U test has been used for comparison of means between the other groups.

Tumor stage (T stage), nodal status (N stage), muscle invasion (≥T2) and grade of tumor showed statistically significant relation with CA 19-9 levels. However, presence of metastasis (M status) failed to show any significant relation with CA 19-9 levels. The box plots showing comparison of distribution of CA 19-9 among various disease groups have been shown in Figure 3, Figure 4, Figure 5, Figure 6 and Figure 7.

The ROC curve analysis with the Area under Curve (AUC) of CA 19-9 level for predicting various disease groups have been shown in Table 4. T3 disease, MIBC and high-grade disease had statistically significant (p <0.05) AUC of ROC more than 0.7. When taking CA 19-9 level of 37IU/ml as a cut-off the sensitivity and specificity of CA 19-9 in predicting various disease states have been shown in Table 4.

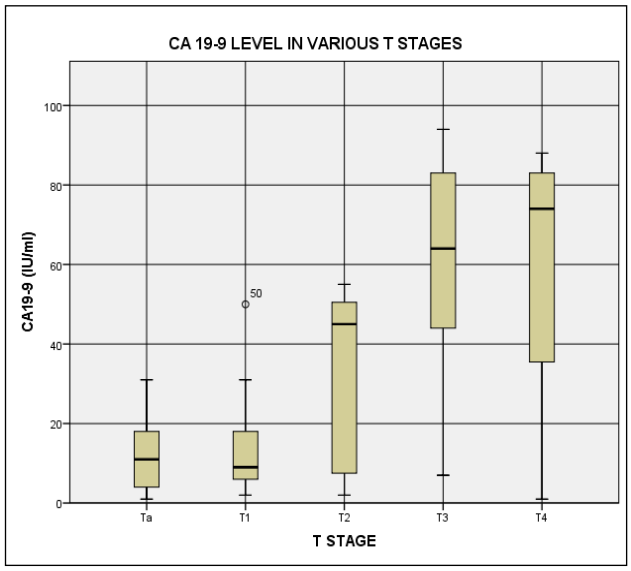

Figure 3: Relation of CA 19-9 level to various T stages.

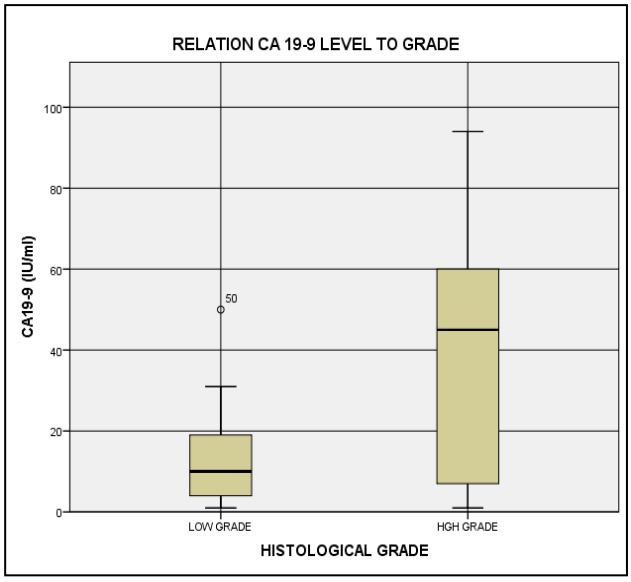

Figure 4: Relation of CA 19-9 level to histological grade.

Taking CA 19-9 level of ≤37IU/ml as normal value, and higher than that as a significant value, the distribution of the various disease groups with significant CA 19-9 level have been shown in Table 5.

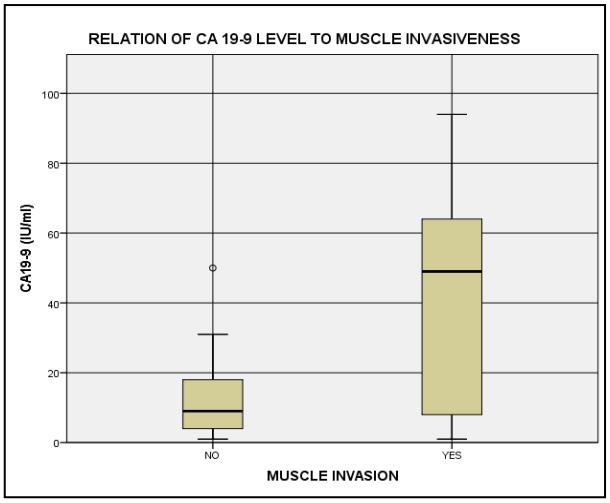

Figure 5: Relation of CA 19-9 level to muscle invasion status.

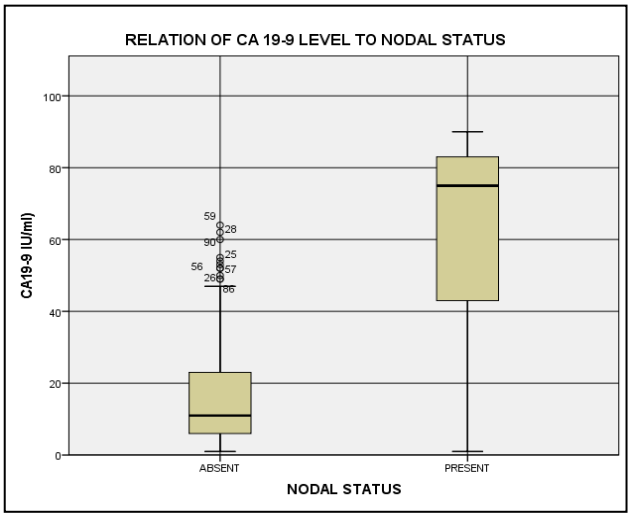

Figure 6: Relation of CA 19-9 level to nodal status.

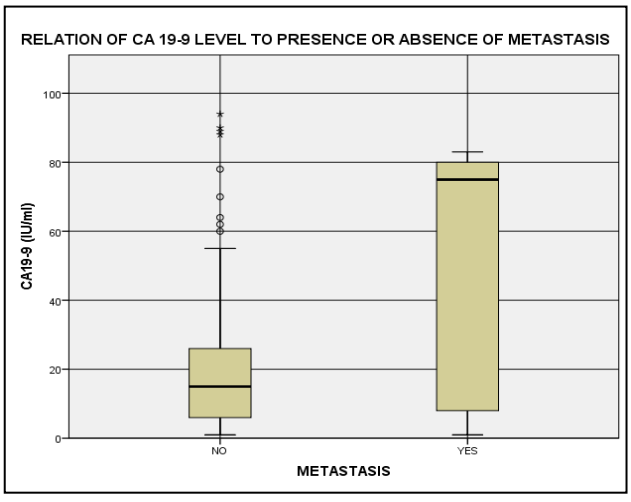

Figure 7: Relation of CA 19-9 level to presence or absence of metastasis.

Table 4: ROC curve analysis of ca 19-9 level for predicting the following disease groups.

Patient group	AUC	95% CI	P value	Using cut-off as 37 IU/ml to predict disease groups	
				Sensitivity (%)	Specificity (%)
Ta	0.345	0.247-0.443	0.006	-	-
T1	0.374	0.273-0.475	0.031	-	-
T2	0.629	0.484-0.773	0.071	60	84.2
T3	0.804	0.615-0.992	0.002	80	84
T4	0.722	0.320-1	0.133	75	78.4
Node present	0.816	0.650-0.981	0.084	78.6	84.2
Metastasis	0.654	0.308-1	0.247	60	78.2
Grade	0.726	0.619-0.832	<0.001	57.8	98.6
Muscle invasion	0.788	0.679-0.898	<0.001	70.3	98.7

Table 5: Distribution of patients among the various disease groups when CA 19-9 level of 37 ≤ IU/ml is taken as normal.

Patient group	Patients with CA 19-9 ≤ 37 IU/ml (n)	Patients with CA 19-9> 37 IU/ml (n)	p value	Pearson's R
Ta	42	0	<0.001	0.710
T1	35	1		
T2	8	12		
T3	2	11		
T4	1	3		
N0	85	16	<0.001	0.484
N1	3	11		
M0	86	24	0.049	0.184
M1	2	3		
Low grade	69	1	<0.001	0.649
High grade	19	26		
NMIBC	77	1	<0.001	0.760
MIBC	11	26		

DISCUSSION

TCC bladder is the second most common cancer of the genitourinary tract. Bladder cancer is associated with field change effect which can involve any part of urothelium resulting in synchronus and metachronus lesions in the tract.[25]Although a significant percentage of TCC are superficial, most of them have a high recurrence rates even after adequate resection. In patients with muscle invasive disease or progressive disease the prognosis is guarded and a greater part of management depends on upon regular surveillance and early detection of recurrent or persistent disease.[26] The greatest difficulty after treatment of NMIBC is to decrease or prevent progression to MIBC. In patients with MIBC the 5 year overall survival drops to 36% to 48% even after radical cystoprostatectomy.[27,28] MIBC poses a significant risk of progression to either nodal or distant metastasis.

Cystoscopy is regarded as the standard mode of follow up although most of the patients find significant discomfort in it. The overall sensitivity and specificity of urine cytology for detection of malignant cells is poor.[29] The combination of cystoscopy and urine cytology for malignant cells as the standard surveillance protocol for bladder cancer recurrence is actually followed by only 40% of patients.[30,31]

An ideal tumour marker that can be used for TCC of bladder should be sensitive, specific, non-invasive, cost effective and easily available. Recently several biomarkers from peripheral blood or urine, have been investigated for diagnosis of urothelial cancer like BTA stat (Polymedco, Cortlandt Manor, NY), BTA TRAK, NMP22 Bladder Chek Test (Matritech, Newton, MA) and UroVysion (Abbott Molecular, Chicago, IL). However, the sensitivity and specificity of these markers are far below that of standard cystoscopy.[32,33,31]

Although CA 19-9 and CEA are not approved as markers, many studies have reported the association of serum CEA and CA 19-9 level with the clinical course and prognosis of bladder cancer.[24,21] Therefore, there is a need for an ideal tumor marker or combination of these for the

bladder cancer patients. Association of CA 19-9 with TCC bladder is sporadically reported in literature and the diagnostic significance of CA 19-9 in bladder cancer have also been reported.[24,21,34]

Presence of CA 19-9 antigen in blood in tested by using a monoclonal antibody against it. It has proved its usefulness against cancers of digestive system particularly pancreatic cancer.[35,36]

We have found a significant correlation increased levels of CA 19-9 with increasing T stage, nodal presence, presence of muscle invasive disease and high grade bladder cancer. Statistically significant association between CA 19-9 and metastasis was not found. This may be probably due to the low number of cases with metastasis and a number of outliers. When CA 19-9 level >37IU/ml was taken as cut-off for a positive test, sensitivity of detecting T3 disease, T4 disease, MIBC, presence of positive nodes and high grade tumour were 80%, 75%, 70.3%, 78% and 57.8% respectively. All these results indicate the usefulness of CA 19-9 in prognostification of bladder cancer during follow up.

The clinical utility of monitoring the serum levels of CA 19-9 in TCC bladder is scarcely described in literature. The studies available so far have reported different conclusions. Kurokawa and colleagues (1993) found no significant difference in levels of CA 19-9 in bladder carcinoma, benign disease and controls. Thirteen percent of the control group, 13.8% of the TCC bladder and 57.1% of the upper urinary tract cancer had elevated levels of CA 19-9. Although there was no correlation of increased levels of marker with tumor size, depth of invasion, and degree of differentiation, but there was a significant association with size of tumour.[37] Hegele and colleagues (2010) found that increased CA19-9 and CEA levels in bladder cancer correlate well with tumour invasion and higher grade of malignancy.[21] Pectasides and colleagues (1996) have suggested that CA 19-9 levels increased significantly in bladder cancer patients. They found that higher tumour depth and higher stages had significantly increased CA 19-9 values.[24] Mahender and colleagues (2012) in their series of 75 patients with TCC bladder found a significantly higher level of CA 19-9 in higher disease stages and metastatic disease.[22]

However, a few reported that CA 19-9 levels are not associated with tumour invasion.[38] Increased CA 19-9 can be used for prediction of prognosis during follow up of bladder cancer.[26,22]

Insights from our study and various other studies it can be postulated that there is a significant association of high CA 19-9 level with regard to presence of metastases, depth of invasion, higher TNM stage and high histological grade. However, there is less or no value of CA 19-9 as a screening test for bladder cancers, but has a significant role in evaluating the effects of treatment and detecting the recurrence or metastasis at an early stage during follow up.

CONCLUSION

CA 19-9 is not useful in the primary diagnosis of urothelial cancer. It is elevated in increasing T stage, presence of nodes, muscle invasive disease and high grade bladder cancer. When CA 19-9 level >37IU/ml is taken as cut-off for a positive test disease progression to a higher stage or recurrence during follow up can be predicted with good sensitivity. However, the usefulness of CA19-9 serum levels monitoring as a prognostic marker as well as marker for response to therapy has to be evaluated by carrying forward this study in larger series.

Recommendations

The important points of reference on the posterolateral surface of the skull are asterion, inion, apex of the mastoid process and suprameatal crest. The objectives of the present study were to determine the type of asterion depending on the presence or absence of sutural bone, to measure the linear distances of asterion from various bony landmarks, the nearest distance of the same from sigmoid and transverse sinus and also the thickness at the centre of the asterion that may be of importance to anthropologists, anatomists, forensic pathologists and neurosurgeons.

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