Original Article

A retrospective analysis of the correlation between AXL expression and clinical outcomes of patients with urothelial bladder carcinoma

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Background: Immunohistochemistry (IHC) analysis of primary tumors revealed that AXL expression is associated with survival in patients with different cancers. The objective of our study is to investigate the relationship between the expression of AXL and clinical outcomes of patients with bladder carcinoma (BC).

Methods: A total of 407 samples from The Cancer Genome Atlas (TCGA) database and 203 patients with clinical and pathological diagnosis of BC in our hospital were used to assess the association of AXL and clinical outcomes of BC patients. IHC was performed to evaluate the expression of AXL in tumor tissue collected after surgical treatment.

Results: Data from TCGA showed that *AXL* mRNA expression was significantly associated with poor clinical-pathological characters and short overall survival (OS) of BC patients. In our study, AXL was significantly related to worse pathological T-stage (pT), lymph node metastasis (pN), and tumor grade. In univariate analysis, abundant AXL was significantly associated with the worse OS. In multivariate analysis, AXL, as well as pT, pN, and Ki67, was an independent prognostic factor in predicting the survival of patients.

Conclusions: AXL was an unfavorable prognostic factor, which was associated with poor clinical outcomes of BC patients.

Keywords: AXL; bladder carcinoma (BC); prognosis; The Cancer Genome Atlas (TCGA)

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Introduction

Urothelial bladder carcinoma (BC) is a common malignancy in genitourinary tract worldwide, with an estimated 81,190 new cases and 17,240 deaths in USA, 2018 (1). Approximately 70–75% of newly diagnosed patients are non-muscle invasive BC (NMIBC) and 25–30% are invasive (MIBC) (2). Although NMIBC patients have a better prognosis than MIBC, 15–70% of NMIBC will recur, and a significant proportion of high-risk NMIBC patients will develop into MIBC within 5 years (3,4). The current prognostic models for NMIBC rely on pathologic features, which are obtained after invasive surgical examination and do not reach sufficient accuracy to identify the patients most likely to benefit from early radical cystectomy (RC) (5). Therefore, there is an urgent need to identify effective markers for predicting the prognosis of BC patients.

AXL, a member of the TAM (Tyro3, Axl, MerTK) family of receptor tyrosine kinase (RTKs), is involved in the regulation of cell survival, adhesion, and migration in many cancers, such as prostate cancer (6). In BC, it was reported that *AXL* depletion significantly inhibited the migration of tumor cells (7,8). Multiple and selective targeted tyrosine kinase inhibitors have a blocking effect on the progression of BC cells (9). Most AXL signaling occurs in a Gas6-mediated ligand-dependent manner (10). When bound to its ligand Gas6, AXL will induce the multiple downstream pathways, which has been found to play an important role in cancer development and progression (11,12).

Immunohistochemistry (IHC) analysis of primary tumors revealed that AXL expression is associated with metastasis and/or poor survival in patients with different cancers, such as breast cancer, hepatocellular and renal cell carcinoma (13-15). Few studies about prognostic value of AXL in BC have been published and the role of AXL in BC is still unclear. IHC in Yeh *et al.*'s study showed that AXL is non-significantly related to the clinical features and survivals of BC patients, but Hattori *et al.*'s study showed that AXL is associated with cancer-specific survival (CSS) of patients (8,16). The objective of our study is to investigate the prognostic value of AXL in predicting the clinical outcome of BC patients, which may help risk-based individuals adopt better treatment strategies.

Methods

TCGA database

The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov), an online bioinformatics database, provides extensive biological information for different carcinomas, including BC (17,18). A total of 407 BC patients with *AXL* mRNA expressional data (mRNASeq-count.txt) and sufficient clinical information to be used for analysis were obtained from TCGA database in our study.

Patients and specimens

A total of 203 patients with clinical and pathological diagnosis with BC in the 2nd hospital of Tianjin medical university (Tianjin, China) from June 2011 to December 2014 were included in our research. Tumor tissue of patients was obtained after first surgical treatment. Clinical data including the age, gender, smoking state, tumor grade, size, number, pathological T-stage (pT), lymph node metastasis (pN) and recurrence rate of patients were retrospectively recorded. Tumors were classified according to 2009 UICC TNM staging and 2004 WHO/ISUP classification (19,20). Overall survival (OS) of patients was followed-up. The whole study was approved by Human Ethics Committee of Tianjin medical university (Tianjin, China) (No.KY2016K010) and written informed consent was obtained from all participants. All patient's personal data has been protected.

IHC

Paraffin-embedded tissues collected after surgical treatment were sliced into 4 μm sections and heated for 30 min at 65 ℃. Then, tissue sections were performed with EDTA (pH =8.0) and 3% hydrogen peroxide in methanol. Slides were incubated with AXL Polyclonal Antibody (HPA037422, Sigma-Aldrich, USA) at 4 ℃ overnight. The second antibody (Solarbio, USA) was then incubated at room temperature for 30 min. For each IHC sample, five random fields were selected at low magnification (100×) and evaluated at high magnification (200×). The process was finished by two workers independently. For the results, H-sore method was applied to evaluate the expression of AXL protein (21). The staining intensity was divided as follows: no staining as 0; weak staining as 1; moderate staining as 2; strong staining as 3. The percentages of positive cells were categorized as follows: no staining as 0; 1–25% of stained cells as 1; 25–50% as 2; 51–85% as 3; 85–100% as 4. The score was calculated as follows: staining index = staining intensity × percentages of positive cells. The cutoff value of AXL expression was determined by distribution of scores.

Statistical analysis

All data were analyzed by SPSS.20.0 statistics software. Quantitative date was evaluated by mean ± SD. According to whether the variance was homogeneity, parameter test and non-parametric test were used respectively. Relationship between the expression of AXL and the clinicopathological features was evaluated using χ^2 tests. The prognostic value of AXL was estimated by Kaplan-Meier method and Cox-regression analysis. For the results, $P<0.05$ for the difference was considered as significant.

Table 1 χ^2 tests analysis of association between *AXL* mRNA expression and clinical features of BC patients from TCGA database

Clinical-pathological features	AXL mRNA expression			OR	95% CI	P value
	Low	High	Total			
Age						
<75	190	106	296	13.51	7.23–25.25	<0.001*
≥75	13	98	111			
Sex						
Male	156	144	300	1.38	0.89–2.16	0.152
Female	47	60	107			
Race						
White	148	175	323	N	N	0.008*
Asian	31	13	44			
Black	10	13	23			
pT						
T2	70	49	119	N	N	0.01*
T3	81	112	193			
T4	25	33	58			
pN						
No	127	110	237	1.86	1.20–2.89	0.005*
Yes	49	79	128			
Grade						
Low	16	5	21	3.43	1.23–9.54	0.013*
High	185	198	383			
Recurrence						
Yes	90	83	173	1.22	0.78–1.90	0.391
No	66	74	140			

*, P<0.05. BC, bladder carcinoma; TCGA, The Cancer Genome Atlas; OR, odds ratio; N, no odds ratio analysis was performed in the multi-group analysis; pT, pathological T-stages; pN, lymph node metastasis.

Results

Relationship between expression of AXL gene mRNA and clinical outcomes of patients with BC from TCGA database

A total of 407 of BC samples from TCGA database were used to investigate the relationship between *AXL* expression and clinical-pathological characters of BC patients. *AXL* was associated with the patient's age, pT, pN, and grade of tumors. Patients over 75-year-old were more likely to have high *AXL* expression (P<0.001). Increased *AXL* was associated with a worse pathological tumor grade, pT, and pN (P<0.05) (*Table 1*). Therefore, high expression of AXL was related to the unfavorable pathological features of BC patients.

For prognostic value, univariate and multivariate analyses were performed to evaluate the relationship between these features and the OS of patients. In univariate analysis, high expression of *AXL* was associated with short OS (P=0.048); however, there was no significant difference in multivariate analysis (P=0.218). In addition, tumor pT and pN were significantly associated with OS (P<0.01) (*Table 2*). In conclusion, from TCGA database, we found that AXL was

Table 2 Univariate and multivariate analysis association between clinical features and OS of BC patients from TCGA database

Clinical features	Median	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age					
<75	35.3	1.372 (0.999–1.885)	0.051	1.253 (0.881–1.783)	0.210
≥75	26.9				
Sex					
Male	34.9	1.123 (0.811–1.555)	0.485	1.210 (0.836–1.752)	0.313
Female	30.9				
Race					
White	32	0.984 (0.742–1.305)	0.912	1.185 (0.873–1.608)	0.277
Asian	54.8				
Black	22.8				
pT					
T2	86.7	1.731 (1.376–2.177)	<0.001*	1.483 (1.134–1.939)	0.004*
T3	27				
T4	17.1				
pN					
No	64.7	2.233 (1.629–3.060)	<0.001*	1.819 (1.281–2.582)	0.001*
Yes	19.4				
Grade					
Low	29.7	2.965 (0.734–11.985)	0.109	2.645 (0.358–19.546)	0.341
High	32.9				
AXL					
Low	44.2	1.349 (1.003–1.816)	0.048*	1.273 (0.882–1.735)	0.218
High	28.2				

*, P<0.05. OS, overall survival; BC, bladder carcinoma; TCGA, The Cancer Genome Atlas; HR, hazard ratio; pT, pathological T-stages; pN, lymph node metastasis.

associated with poor clinical outcomes in BC patients.

AXL was associated with clinical-pathological features of BC patients

A total of 203 patients diagnosed with BC were included in our study. The details of these patients are summarized in *Table 3*. IHC was performed to assess the expression of AXL in tumor tissues. The typical staining of AXL is shown in *Figure 1*. Consistent with TCGA, our results showed that abundant AXL was significantly related to worse pathological tumor grade, pT and pN of patients (P<0.05). However, there was also a correlation between AXL and patients' gender (P=0.018) and tumor size (P=0.021) (*Table 3*).

High expression of AXL was related to a worse OS of BC patients

Kaplan-Meier analysis was performed to investigate prognostic value of AXL in OS of patients. High AXL was significantly associated with a short OS (P<0.001) (*Figure 2*).

Table 3 The association between AXL expression and clinical-pathological features of 203 BC patients from our hospital

Characters	Numbers	Percentage	AXL expression			
			Low	High	OR (95% CI)	P value
Ages						
<70	118	58.1	66	52	1.08 (0.61–1.89)	0.798
≥70	85	41.9	46	39		
Gender						
Male	170	83.7	100	70	2.50 (1.16–5.41)	0.018*
Female	33	16.3	12	21		
Smoking						
No	114	56.2	66	48	1.29 (0.74–2.25)	0.377
Yes	89	43.8	46	43		
Grade						
Low	79	38.9	62	17	5.40 (2.83–10.29)	<0.001*
High	124	61.1	50	74		
pT						
Ta, T1	117	57.6	79	38	3.34 (1.87–5.98)	<0.001*
T2–T4	86	42.4	33	53		
pN						
No	174	85.7	102	72	2.69 (1.18–6.13)	0.016*
Yes	29	14.3	10	19		
Ki67						
Low	102	50.2	58	44	1.15 (0.66–2.00)	0.626
High	101	49.8	54	47		
Tumor sizes						
<2 cm	114	56.2	71	43	1.93 (1.10–3.40)	0.021*
≥2 cm	89	43.8	41	48		
Tumor numbers						
Single	85	41.9	45	40	0.86 (0.49–1.50)	0.587
Multiple	118	58.1	67	51		
Recurrence						
No	117	57.6	62	55	0.81 (0.46–1.42)	0.466
Yes	86	42.4	50	36		

*, P<0.05. BC, bladder carcinoma; OR, odds ratio; pT, pathological T-stages; pN, lymph node metastasis.

Then, we divided the samples into different groups according to tumor grade and pT. AXL was related to the OS in patients with NMIBC (P=0.018), but not MIBC (P=0.060) (*Figure 3*). There was a relationship between AXL and OS in patients with high tumor grade (P=0.007), but not low tumor grade (P=0.225) (*Figure 4*).

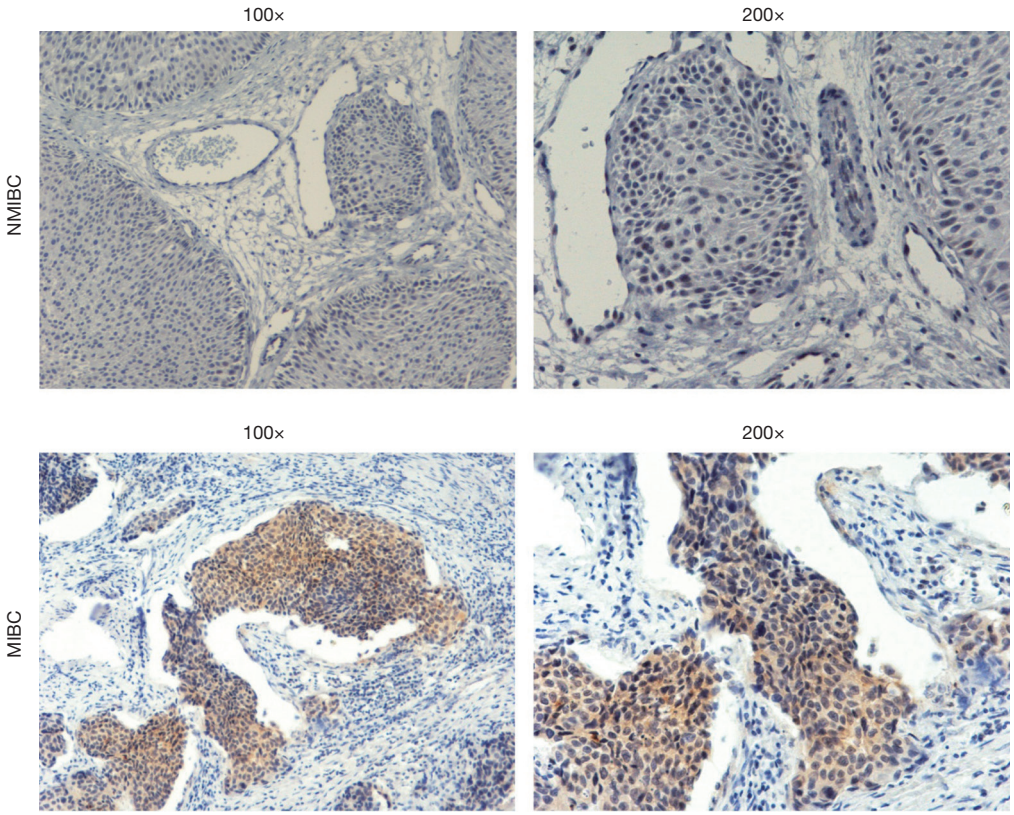

Figure 1 The typical staining of high and low expression of AXL in BC tissues. All samples were stained by IHC. NMIBC, non-muscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; BC, bladder carcinoma; IHC, immunohistochemistry.

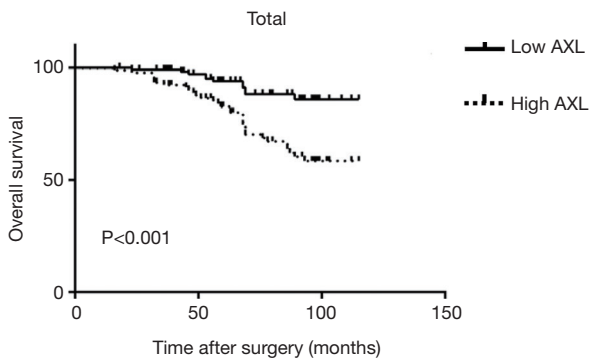

Figure 2 Kaplan-Meier analysis of association between AXL and OS of patients. OS, overall survival.

In univariate analysis, pathological tumor grade, pT, PN, Ki67 and AXL were significantly associated with a worse OS (P<0.05). In multivariate analysis, AXL, as well as pathological pT, pN, and Ki67, was an independent prognostic factor in predicting the survival of BC patients (P<0.05) (*Table 4*).

Discussion

With the high rates of recurrence, short progress and death time, monitoring BC patients' survival is extremely important and brings a giant economic burden worldwide (22). Despite the combination of RC and chemotherapy, only 30–40% of patients with MIBC survive 5 years or longer (23). Cystoscopy is the standard diagnostic tool of BC, but it is expensive, time consuming, invasive and leads to infection in more than 16% of patients (24). Many biomarkers have been found to play a role in BC and could predict the survival of patients (25). However, the strategy based on these markers was unsatisfied. Therefore, novel biomarkers need to be researched.

RTK plays a key role in cell signaling and is involved in tumor progression. In 1991, AXL was first identified as an RTK in patients with chronic myeloid leukemia (26). The TAM family of RTKs comprises three transmembrane receptors: TYRO-3, AXL, and MER. There are two main ligands for TAM receptors, growth arrest-specific gene 6 (*Gas6*) and protein S (PROS) (27,28). In the past

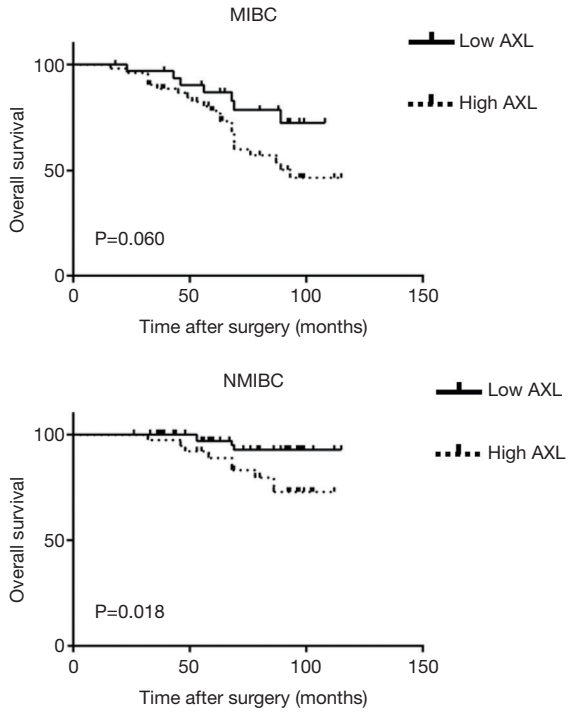

Figure 3 Kaplan-Meier analysis of association between AXL and OS of patients with MIBC and NMIBC. MIBC, muscle invasive bladder cancer; NMIBC, non-muscle invasive bladder cancer; OS, overall survival.

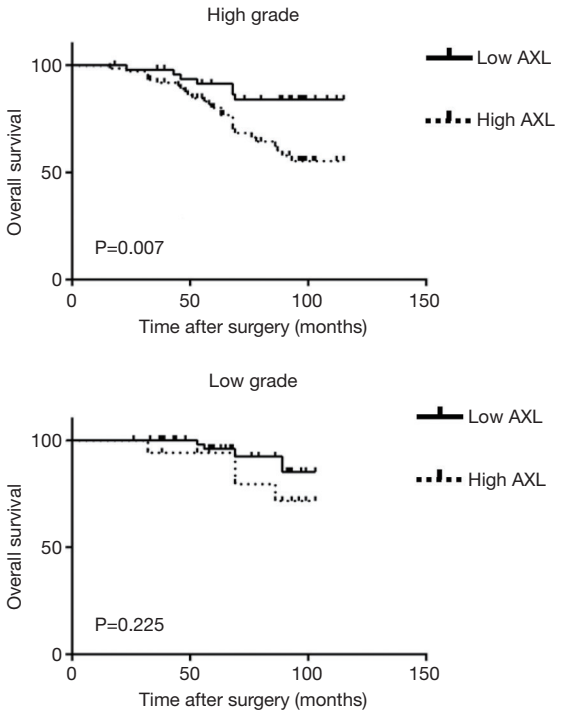

Figure 4 Kaplan-Meier analysis of association between AXL and OS of patients with high and low tumor grades. OS, overall survival.

decades, the TAM family has become an important factor in controlling tissue homeostasis and innate immune responses. Dysregulation of TAM signaling is associated with chronic inflammation, autoimmune diseases and cancers (29).

Overexpression of AXL has been found in multiple carcinomas and is often associated with poor prognosis (10,30). In our study, we first used TCGA data to analyze the relationship between *AXL* expression and clinical characters of BC patients. The results showed that *AXL* expression was associated with the poor clinical-pathological characters, such as T-stage, pN, and tumor grade, and a worse OS of patients. Then, 203 samples from our hospital were used to research the prognostic value of AXL. Consistent with the result of TCGA, we found that abundant AXL was related to the poor clinical outcomes. AXL was an independent prognostic factor in predicting the survival of BC patients. However, in our study, the relationship between AXL expression and the survival of MIBC patients was non-significant (P=0.06). The difference of results between our study and TCGA might be due to the sample size limit in our study [86], but 407 MIBC samples were included in TCGA database. Therefore, a large sample number and multi-center study is needed in the future.

In the previous Hattori *et al.*'s study, the results showed that AXL were independently associated with lower CSS. In a subgroup analysis of patients with NMIBC, no significant difference in CSS was observed between patients with weak expression and strong expression of AXL (31). However, in the current study, our results exhibited that the expression of AXL was significantly related to OS in patients with NMIBC. The discrepancy may be due to differences in the type of specimens, the number of samples, or IHC assessment method. As a retrospective study, the sample size was small and all patients were obtained from only one center. In the future, a large sample multi-center research is necessary to confirm our conclusions. Other states, such as distant metastasis, intravesical Bacillus Calmette Guerin (BCG) treatment and chemotherapy, which may influence the survival of patients, were not analyzed by subgroup in our study. This may potentially cause discrepancy in results.

In conclusion, our results demonstrated that AXL

Table 4 Univariate and multivariate analysis of associations between clinical characters and OS of 203 BC patients from our hospital.

Characters	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Ages	1.850	1.007–3.398	0.047*	1.730	0.911–3.287	0.094
Genders	1.826	0.917–3.636	0.087	–	–	–
Smoking	0.865	0.463–1.616	0.650	–	–	–
Grade	2.399	1.109–5.190	0.026*	1.082	0.480–2.439	0.849
pT	3.345	1.739–6.437	<0.001*	2.131	1.057–4.297	0.034*
pN	6.567	3.555–12.131	<0.001*	4.369	2.288–8.342	<0.001*
Ki67	1.979	1.053–3.722	0.034*	2.366	1.222–4.581	0.011*
Tumor sizes	0.718	0.388–1.328	0.291	–	–	–
Tumor numbers	1.301	0.697–2.430	0.408	–	–	–
AXL	3.328	1.673–6.624	0.001*	2.193	1.058–4.545	0.035*

*, P<0.05. OS, overall survival; BC, bladder carcinoma; HR, hazard ratio; pT, pathological T-stages; pN, lymph node metastasis.

expression was significantly associated with the prognosis of patients with BC. Patients with abundant AXL were more likely to have a poor clinical outcome. The result will contribute to better understand AXL as a biomarker for BC and provide a better strategy for clinical treatment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The whole study was approved by Human Ethics Committee of Tianjin medical university (Tianjin, China) (No.KY2016K010) and written informed consent was obtained from all participants.

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