Preoperative Plasma Fibrinogen: An Independent Predictor for Survival in Adult Patients with Xp11.2 Translocation Renal Cell Carcinoma

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Abstract

Background. Xp11.2 translocation renal cell carcinoma, a rare malignancy, is more common in children than in adults. It manifests with an aggressive course in adults and relatively indolent in children. Prognostic studies for adult patients are scare for the rarity of the disease; and the prognostic value of preoperative plasma fibrinogen awaits further illumination.

Methods. This retrospective single-center study enrolled 24 consecutive newly diagnosed Xp11.2 translocation RCC adult patients. Clinical presentations, baseline laboratory results and follow-up data were collected. Possible risk factors for progression free survival and overall survival were first scanned with chi-square tests and t-tests to compare patients who suffered from progression or death and who did not. Multivariate Cox regression was further utilized to identify independent risk factors.

Results. Twenty-four adult patients (median age 32, range 16-73), with a male-to-female ratio of 1:1, was included from 2010.4 to 2020.3. After a mean follow-up of 35.7months, seven patients died. With univariate analysis, higher C-reactive protein-to-albumin ratio (p=0.028), higher baseline fibrinogen (p=0.006), and presence of distant metastasis (p=0.007) were associated with progression of disease; higher preoperative fibrinogen (p=0.014) and distant metastasis (p=0.020) were associated with death. With multivariate Cox regression, only baseline fibrinogen level (p=0.001) was identified as an independent risk factor for progression free survival; meanwhile, fibrinogen level (p=0.048) and distant metastasis (p=0.043) were identified as independent risk factors for survival.

Conclusions. Preoperative plasma fibrinogen, a routinely tested parameter before surgery, is a promising tool for risk stratification in adult patients with Xp11.2 translocation renal cell carcinoma.

JIE et al: Preoperative plasma fibrinogen predicts outcome in Xp11.2 translocation RCC

Introduction

Xp11.2 translocation renal cell carcinoma (RCC) is a rare and unique subtype of RCC characterized by translocations involving the TFE3 gene [1–3]. It has been classified as a distinct entity in the 2004 World Health Organization renal tumor classification and is now regarded as an important subtype of RCC, especially in children [4, 5]. Compared to other subtypes of RCC, this neoplasm has more aggressive clinicopathologic features at diagnosis [5] and worse prognosis [3, 6]. In regard to the risk of disease re-occurrence and death, it is important to conduct prognostic studies to identify potential preoperative risk factors for disease progression and death which might help to guide interventions in the future. Moreover, prognostic researches for adult patients, should be especially encouraged due to at least three reasons: firstly, as a rare disease which mainly affects children [4], data for adult patients is scarce for the time being which awaits further illumination; secondly, this disease manifests with a more aggressive behavior in adults than in children [3] which suggests a possibly different prognostic features in adults; thirdly, prior prognostic studies, which revealed several possible risk factors as neutrophil-to-lymphocyte ratio (NLR),

C-reactive protein/albumin ratio (CRP/Alb ratio), platelet-to-lymphocyte ratio (PLR), tumor stage and inferior vena cava tumor thrombosis, included both child and adult patients [6, 7] for analysis which might bring bias. Therefore, it would be of importance to identify novel prognostic factors in adult XP11.2 translocation RCC patients.

Fibrinogen, a routinely tested parameter included in the preoperative coagulation examination, is a glycoprotein synthesized by hepatocytes with the function of blood coagulation. It also plays a crucial role in both inflammatory responses and cancer metastasis [8, 9]. Elevated fibrinogen levels have been reported to be associated with distant tumor metastasis and worse prognoses in many malignancies [8, 10], including renal cell carcinoma (RCC) [11, 12]. However, the role of preoperative plasma fibrinogen level for prognosis in XP11.2 translocation RCC patients has not been described. Herein, we embarked on a study to examine the prognostic value of fibrinogen for patients with newly diagnosed XP11.2 translocation RCC.

Patients And Methods

Patients

Between April 2010 and March 2020, patients diagnosed with XP11.2 translocation RCC after percutaneous renal mass biopsy or nephrectomy (radical or partial) at Peking Union Medical College Hospital (PUMCH) were included. Clinical information was retrieved from medical records from the department of urology. Pathological reports were carefully reviewed and TFE3 immunohistochemistry staining results were reconfirmed. The inclusion criteria were: 1) typical morphological pattern plus moderate-to-strong nuclear positivity with TFE3 immunohistochemistry staining results; 2) complete blood laboratory tests including blood routine test, blood biochemistry tests and coagulation test within one week before biopsy or nephrectomy; 3) adult patients defined as 16 years or older. The exclusion criteria were: pregnant women;<16 years old; with other inflammatory disease or a second tumor. This study was performed in accordance with relevant guidelines and regulations and was approved by the PUMCH Ethics Committee. Informed consent was achieved from all patients for the utilization of their medical records.

Demographic, clinical, laboratory, and treatment-related data, including age at the time of diagnosis, gender, symptoms at presentation, serological results, radiological findings, and treatment strategies were documented. Preoperative neutrophil count, lymphocyte count, platelet count, hemoglobin level, C-reactive protein (CRP) level, albumin level, lactic dehydrogenase (LDH) level, fibrinogen (Fbg) level were collected. Possible prognostic factors as NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), CRP/Alb (CRP/albumin ratio) [6] were calculated. Presence of tumor thrombus of inferior vena cava (IVC), lymph node metastasis and distant metastasis were confirmed from radiological examinations.

Follow-up

Patient follow-up was conducted via interviews at an outpatient clinic, telephone contacts, letters, and analyses of information documented in the hospital database. Patients were followed until March, 2020 and follow-up results were analyzed by two independent urologists to determine progression. Progression was defined as tumor relapse, enlargement of tumor mass or presence of new metastatic lesions. Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death from any cause. Overall survival (OS) was defined as the time from diagnosis to death from any cause.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, IL). Possible risk factors for progression-free survival and overall survival were firstly scanned with chi-square tests (for categorical covariates) and t-tests (for continuous covariates) to compare patients who suffered from progression (or death) and who did not. NLR, PLR and CRP/Alb were transcoded into categorical variables with cutoff values set at 2.45, 140 and 0.083 respectively according to a prior study [6]. Variables with $p < 0.10$ revealed by univariate comparison were further analyzed with multivariate Cox regression. A stepwise regression strategy with a backward method (criteria for entry and removal of variables were $p < 0.05$ and $p > 0.10$) was utilized with 1 variable eliminated at a time. Parameters with $p < 0.05$ were considered to represent independent predictors of PFS or OS. Dichotomous variables which were showed to be independent risk factors were further analyzed with Kaplan-Meier method for depicting survival curves using log rank tests for comparison. For the convenience of survival curve depicting, continuous variables revealed as independent risk factors via multivariate Cox regression were transcoded into dichotomous variables with cutoff values set according to ROC curve analysis.

Results

Patient Characteristics

A total of 4958 cases of adult RCC were diagnosed during the past ten years in our center. Of them, 24 patients were diagnosed as XP 11.2 translocation RCC with an overall proportion of 0.48%. Table 1 outlined clinical characteristics of these 24 patients, including 12 (50.0%) males and 12 (50.0%) females. The median age at diagnosis of XP 11.2 translocation RCC was 32 years (range, 16–73 years). At the time of diagnosis, eleven patients (45.8%) were symptomatic while 13 patients (54.2%) were asymptomatic. Tumors were found on 15 right kidneys (62.5%) and 9 left kidneys (37.5%) with a mean tumor size (maximum diameter) of 8.05 ± 5.13 cm. A large proportion of patients showed evidence of advanced stage at diagnosis: 45.8% patients with lymph node metastasis, 25% patients with distant metastasis, 20.8% patients with tumor thrombus of IVC. Two patients did not receive further surgery after percutaneous renal mass biopsy-proven diagnosis. Twenty-two patients underwent nephrectomy (radical 16/22 or partial 6/22). After a mean follow-up of 35.7 months, nine patients had a progression of disease and seven patients died. The estimated 3-year progression-free survival was 66% and 3-year OS was 88.1%.

Table 1
Clinical characteristics of patients with Xp11.2 translocation RCC

		Value	%
Gender			
	Male	12	50%
	Female	12	50%
Age (year)		42.7 ± 14.9	
Symptoms at onset			
	Symptomatic	11	45.80%
	Asymptomatic	13	54.20%
Location			
	Right	15	62.50%
	Left	9	37.50%
Tumor size (cm)		8.05 ± 5.13	
Lymph node metastasis			
	Positive	11	45.80%
	Negative	13	54.20%
Distant metastasis			
	Positive	6	25.00%
	Negative	18	75.00%
Tumor thrombus of IVC			
	Positive	5	20.80%
	Negative	19	79.20%
Surgical treatment			
	No surgery	2	8.30%
	Partical	6	25.00%
	Radical	16	66.70%
RCC = renal cell carcinoma; IVC = inferior vena cava			

Risk factors associated with progression

With univariate analysis (Table 2), higher C-reactive protein-to-albumin ratio (CRP/Alb) (p = 0.028), higher baseline fibrinogen (p = 0.006), and presence of distant metastasis (p = 0.007) were associated with progression of disease. All of them, with a p value less than 0.10, entered the multivariate Cox regression with a backward stepwise method. At the last step (Table 2), baseline fibrinogen level (HR 5.761; 95% confidence interval (CI) 1.958–16.949; p = 0.001) was identified as the only independent risk factor for PFS.

Table 2
Risk factors for disease progression in patients with Xp11.2 translocation RCC

	Univariate analysis			**Multivariate Cox regression (last step)**	
	Progression	No progession	P	HR (95% CI)	P
Gender,male (n)	4/9	8/15	0.673		
Age (year)	46.6 ± 17.7	40.4 ± 13.2	0.340		
Symptomatic patient (n)	6/9	5/15	0.113		
Right side (n)	5/9	4/15	0.157		
Tumor size (cm)	9.13 ± 5.82	7.40 ± 4.76	0.435		
NLR > 2.45	7/9	8/15	0.231		
PLR > 140	4/9	9/15	0.459		
CRP/Alb > 0.083	5/9	2/15	0.028		
LDH (U/L)	255.3 ± 101.8	201.0 ± 104.8	0.227		
Hemoglobin (g/L)	123.2 ± 23.3	132.8 ± 20.7	0.306		
Fbg (g/L)	3.95 ± 1.04	2.69 ± 0.47	0.006	5.761 (1.958–16.949)	0.001
Tumor thrombus of IVC	3/9	2/15	0.243		
Lymph node metastasis	6/9	5/15	0.113		
Distant metastasis	5/9	1/15	0.007		
Radical surgery *	5/7	11/15	0.926		

NLR = Neutrophil-to-lymphocyte ratio; PLR = Platelet-to-lymphocyte ratio; CRP/Alb = C-reactive protein/albumin ratio; LDH = lactic dehydrogenase; Fbg = Fibrinogen; IVC = inferior vena cava; * For patients who had surgical treamtent n = 22

Risk factors associated with overall survival

Univariate analysis revealed four candidates ($p < 0.10$) for further multivariate regression: CRP/Alb ($p = 0.053$), preoperative fibrinogen ($p = 0.014$), tumor thrombus of IVC ($p = 0.088$) and distant metastasis ($p = 0.020$). Of them, fibrinogen level and presence of distant metastasis were considered as statistically significant risk factors ($p < 0.05$) for death using univariate scanning. After multivariate analysis, fibrinogen level (HR 2.954; 95% CI 1.011–8.629; $p = 0.048$) and distant metastasis (HR 12.287; 95% CI 1.083-139.409; $p = 0.043$) were identified as independent risk factors for survival.

Survival curves

According to ROC curve analysis, the area under the curve (AUC) value of preoperative fibrinogen of overall survival was 0.861 ($p = 0.006$). The optimal cut-off value for fibrinogen was 3.84 g/L. Fibrinogen (Fbg), a continuous variable, was then transcoded into a dichotomous variable (Fbg ≥ 3.84 g/L versus Fbg < 3.84 g/L) for survival curve depicting. Figure 1a showed a significant difference of PFS ($p = 0.0006$) between patients with and without elevated (≥ 3.84 g/L) fibrinogen: the median PFS was not reached for patients with baseline Fbg < 3.84 g/L compared to 34 months in patients with elevated fibrinogen. Figure 1b revealed a significant difference of OS ($p = 0.0417$) between these two groups: median survival 56 months (Fbg < 3.84 g/L) versus. 48 months (Fbg ≥ 3.84 g/L).

Presence of distant metastasis, a dichotomous variable which was shown to be a risk factor for progression with univariate analysis and an independent risk factor for overall survival with multivariate analysis, was further used to delineate survival curves (Fig. 2). Significant difference was noted for PFS ($p = 0.0082$): median survival for patients without distant metastasis was 46 months compared with 22 months in patients with distant metastasis (Fig. 2a). Figure 2b showed a significant difference of survival curves for OS for patients with and without distant metastasis (median survival 48 months versus. 56 months, $p = 0.025$).

Discussion

XP11.2 translocation RCC accounts for 20–40% of pediatric RCC [13] and only 0.72–1.6% of adult RCC [5, 14]. This subtype of RCC in adults requires special attention and more intensive researches for its rarity, aggressiveness in nature [3, 13] and possible different treatment options (eg. m-TOR inhibitors or VEGF-targeted agents) [16, 17]. This single-center, retrospective study identified an overall incidence of 0.48% for XP11.2 translocation RCC out of all adult RCCs based on a ten-year data. This result was consistent with another Asian cohort [5] (0.72% in Korea) which further demonstrated the rarity of this disease in adults. Although a prior meta-analysis suggested a female gender predominance in adult XP11.2 translocation RCC [13], possibly due to its X-chromosome related nature, our study found an equal gender distribution as observed in children which might be explained by the absence of translocation on the Barr body (inactive X chromosome) or by the relatively small number of patients enrolled. Moreover, consistent with previous reports [7, 18] and for unknown reasons, right side prevalence was observed in our cohort.

Several attempts have been made to investigate the possible risk factors for survival [6, 7] which suggest several possible risk factors as NLR, CRP/Alb, PLR and tumor thrombosis of IVC and tumor stage.

However, disparities are noticed in different studies and these factors have never been externally validated. Moreover, these studies enrolled both children and adult patients which might hinder the accuracy of the prediction model as children present with relatively indolent disease course [3]. This study, according to our limited knowledge, is one of the first endeavors to validate those previously reported prognostic factors and to explore novel potential risk factors in adult patients with XP11.2 translocation RCC. In this study, previously reported risk factors as CRP/Alb [6], tumor thrombosis of IVC [7] showed statistical significance or borderline significance (Table 2 and Table 3) with univariate analysis; and distant metastasis, a parameter reflecting tumor stage, was showed to be an independent risk factor for OS with multivariate analysis. Moreover, preoperative plasma fibrinogen, a parameter routinely examined preoperatively but never tested for risk stratification in XP11.2 translocation RCC, was reported to be an independent risk factor for both PFS and OS.

Table 3
Risk factors for death in patients with Xp11.2 translocation RCC

	Univariate analysis			Multivariate Cox regression (last step)	
	Death	No death	P	HR (95% CI)	P
Gender,male (n)	4/7	8/17	0.653		
Age (year)	46.4 ± 19.7	41.2 ± 12.9	0.446		
Symptomatic patient (n)	4/7	7/17	0.476		
Right side (n)	4/7	5/17	0.202		
Tumor size (cm)	8.87 ± 6.47	7.71 ± 4.66	0.626		
NLR > 2.45	5/7	10/17	0.562		
PLR > 140	2/7	11/17	0.106		
CRP/Alb > 0.083	4/7	3/17	0.053		
LDH (U/L)	239.9 ± 107.8	213.8 ± 106.1	0.591		
Hemoglobin (g/L)	122.1 ± 23.2	132.1 ± 21.1	0.317		
Fbg (g/L)	4.16 ± 1.10	2.76 ± 0.47	0.014	2.954 (1.011–8.629)	0.048
Tumor thrombus of IVC	3/7	2/17	0.088		
Lymph node metastasis	5/7	6/17	0.106		
Distant metastasis	4/7	2/17	0.020	12.287 (1.083-139.409)	0.043
Radical surgery *	4/6	12/16	0.696		

NLR = Neutrophil-to-lymphocyte ratio; PLR = Platelet-to-lymphocyte ratio; CRP/Alb = C-reactive protein/albumin ratio; Fbg = Fibrinogen; LDH = lactic dehydrogenase; * For patients who had surgical treamtent n = 22

Elevated fibrinogen levels have been linked to poor outcomes in many types of cancer, including kidney malignancies [8–9, 11–12]. However, its role in predicting survival in XP11.2 translocation RCC has not been well illuminated. In this retrospective study, we not only demonstrated its independent nature to predict progression, but also suggested a crucial role to predict overall survival. There have been several theories to explain the association between fibrinogen and outcomes of malignancies: firstly, high fibrinogen level might be a reflection of tumor induced systemic inflammatory response [19]; secondly, fibrinogen can be endogenously synthesized by tumor cells and in return facilitates tumor growth and metastasis [11, 20]; thirdly, fibrinogen could activate tumor cell adhesion with platelets to form a dense fibrin ‘protective’ layer

around tumor cells from natural killer cells [21]. Aside from these common pathways, there might be another two distinct mechanisms to clarify the association between fibrinogen and outcomes of XP11.2 translocation RCC, a tumor which has been demonstrated to be related to VEGF and mTOR pathways [16, 17]: firstly, as an extracellular matrix element, fibrinogen could regulate growth of cancer cells by binding to VEGF[22]; secondly, fibrinogen may promote cell motility by inducing epithelial-mesenchymal transition via the p-AKT/p-mTOR pathway [23]. These mechanisms suggest a possible internal link between fibrinogen and this unique subtype of RCC and might explain the strong association found with a relatively small sample size.

Our study has limitations: first of all, TFE3 break-apart FISH analysis was not done for this cohort of patients. However, as TFE3 immunohistochemistry was also an accurate tool for diagnosis which had been accepted for prior studies [3, 6], we still utilized TFE3 immunohistochemistry stain as our inclusion criteria; second, the results of this study were not externally validated, future work focusing on the role of fibrinogen in XP11.2 translocation RCC might be helpful.

In conclusion, preoperative plasma fibrinogen, a routinely tested parameter before surgery, is a promising tool for risk stratification in adult patients with Xp11.2 translocation RCC.

Abbreviations

RCC
renal cell carcinoma
Fbg
fibrinogen
NLR
Neutrophil-to-lymphocyte ratio
PLR
Platelet-to-lymphocyte ratio
CRP/Alb
C-reactive protein/albumin ratio
PFS
progression-free survival
OS
overall survival

Declarations

Ethics approval This study was performed in accordance with relevant guidelines and regulations and was approved by the PUMCH Ethics Committee.

Patient consent for publication Informed consent was achieved from all patients for the utilization of their medical records.

Availability of data and materials The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no conflict of interest.

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Authors' contributions JD, WFX, ZGJ performed the research and collected clinical data; BJP reviewed the pathologies; JD wrote the manuscript; WFX and ZGJ supervised the study and revised the manuscript.

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Figures

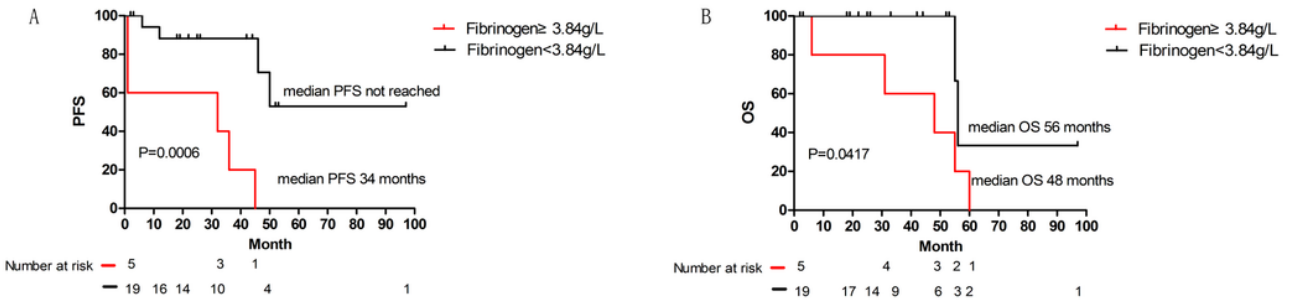

Figure 1

Survival curves of PFS (Fig 1a) and OS (Fig 1b) with a cutoff point of fibrinogen at 3.84g/L

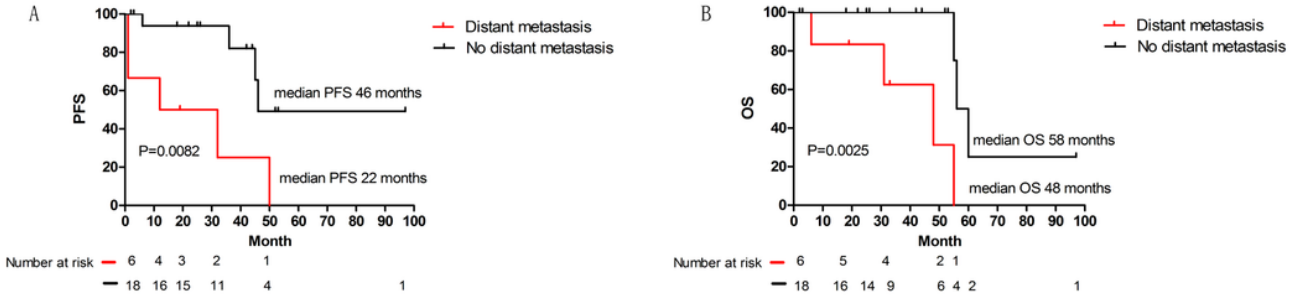

Figure 2

Survival curves of PFS (Fig 2a) and OS (Fig 2b) for patients with and without distant metastasis

Supplementary Files

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