Original Article

Plasma fibrinogen as prognostic predictor in patients with metastatic renal cell carcinoma receiving target therapy

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Background: The purpose of this work was to detect the influence of plasma fibrinogen level on the prognosis of patients with metastatic renal cell carcinoma (mRCC) before treatment of targeted therapy.

Methods: We identified mRCC patients who received first-line therapy of sorafenib or sunitinib between January 2006 to December 2016 in Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Kaplan-Meier method was used to estimate the progression-free survival (PFS) and overall survival (OS); log-rank test was used to compare the survival outcomes between patients with low and high fibrinogen level; and cox proportional hazard regression model was used to estimate the prognostic value. Prognostic accuracy was determined using Harrell concordance index (C-index) and receiver operating curve (ROC) analysis.

Results: Patients with high fibrinogen level both had significantly shorter median PFS (6 *vs.* 15 months, P<0.001) and OS (17 *vs.* 44 months, P<0.001) than those with low fibrinogen level. Multivariate analysis showed that pretreatment plasma fibrinogen was an independent predictor of PFS (HR 2.873, P<0.001) and OS (HR 3.213, P<0.001). The model built by the addition of fibrinogen improved predictive accuracy of PFS and OS compared with the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model [Harrell C-index: 0.74 and 0.76, AUC (area under the ROC curve): 0.863, P<0.001].

Conclusions: High pretreatment plasma fibrinogen could be a significant risk factor for mRCC patients receiving target therapy and increase the prognostic accuracy of established prognostic model.

Keywords: Fibrinogen; metastatic renal cell carcinoma (mRCC); prognosis; sorafenib; sunitinib

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Introduction

Targeted therapy has brought significant changes and great benefits to metastatic renal cell carcinoma (mRCC) patients. Different from Western targeting therapy, sunitinib and sorafenib are recommend as first-line treatment by Chinese guidelines on the management of RCC (1) and these two agents are the most widely used first-line targeted drug for mRCC in China (2). The median survival time of patients with mRCC is improved, and the goal is to achieve better long-term survival (3). However, most patients with mRCC will develop to secondary drug resistance after targeted therapy of about 6 to 12 months (4). Therefore, to find pretreatment clinical markers that can effectively predict the prognosis of targeted therapies and can accurately identify patients who will benefit are important research directions for target therapy of mRCC. Although several prognostic

models such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model (5) and Memorial Sloan-Kettering Cancer Center (MSKCC) model (6) were well designed to better appropriate management decisions in patients with mRCC receiving targeted therapy, more nutritional and inflammatory markers are being added to make the traditional prognostic model more accurate recently.

Systemic inflammation is closely related to the development of the tumor (7). There are many clinical hematological indicators which could reflect body inflammation levels. Routine laboratory inflammation indexes such as CRP (8), albumin (9) were proved to be important prognostic indicators for mRCC patients receiving target therapy. Recently, some new combined indexes like neutrophil to lymphocyte ratio (NLR) (10), platelet to lymphocyte ratio (PLR) (11,12), prognostic nutritional index (PNI) (13) were also found to be effective prognostic biomarkers. Fibrinogen is a kind of glycoprotein which is synthesized and secreted by the liver, and it is a common and important blood coagulation test index in clinic. Similarly, fibrinogen is also highly expressed in different tumors and closely related to tumor activity (14). High fibrinogen level was proved to be a risk factor in non-mRCC (15) and localized upper tract urothelial carcinoma (16). And for mRCC patients treated by interleukin-2, high fibrinogen levels were also found to be independently associated with the tumor responses and survival outcomes (17). However, the prognostic evidence of fibrinogen in mRCC patients treated with targeted therapy remains elusive.

Thus, in this study, we conducted a large retrospective study to analyze the prognostic role of fibrinogen in metastatic RCC patients receiving target therapy and added fibrinogen to IMDC model to prove its prognostic efficiency.

Methods

Study design and population

The electronic medical records and laboratory data of mRCC patients from March 2006 to December 2016 at the Department of Urology in Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine were analyzed retrospectively. Ethical ratification was authorized by the clinical research ethics committee of Renji Hospital. This study involved patients who was confirmed as renal cell cancer with metastasis histologically or cytologically and received first-line targeted treatment of sunitinib or sorafenib. The blood routine, liver and kidney function and fibrinogen of whom were recorded within one to two weeks before targeted treatment. Patients who did not conform to the above criteria and who with incomplete clinical medical records or follow-up data were excluded from this study.

Clinical and pathological evaluation

We retrieved the patient's clinical pathology and examination information from the medical records database. Pre-treatment baseline assessment was performed before target treatment began, including hematology and radiographic examination. Fuhrman nuclear grade and clinical staging based on the AJCC 2010 TNM classification. IMDC focuses on 6 principal adverse prognostic factors: Karnofsky performance status (KPS) score less than 80; neutrophilia; low hemoglobin; elevated corrected calcium; thrombocytosis; and the time from diagnosis to treatment less than 1 year. Zero risk factor belongs to favorable IMDC group; 1–2 risk factors belong to intermediate IMDC group and 3–6 belong to poor group (5).

Treatment and follow up

Sorafenib was taken 400 mg BID orally in cycles of 4 weeks and sunitinib was taken 50 mg QD orally for the first 4 weeks in a 6-week cycle (4-week on, 2-week off-4/2 schedule). Dose adjustments, including dose increase or dose reduction will be based on adverse events experienced by the individual patient. After the target treatment began, the patients were followed up monthly and the imaging examination was reviewed every 2–3 months until the patient was lost to follow up or died. Progression-free survival (PFS) was defined as the time from onset of target therapy to first documentation of objective tumor progression or the last visiting day recorded if the disease did not progress. overall survival (OS) was defined as the time from date of onset of target therapy to date of death due to any cause or the last visiting day recorded if the patients were alive.

Statistical analyses

All analyses were performed using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and R (R version 3.4.3). Pearson's Chi-squared test was used to compared categorical

variables. Receiver operating curve (ROC) analysis was used to determine the best cutoff point of plasma fibrinogen levels to separate patients' survival outcomes. The optimal threshold of fibrinogen value was determined on the ROC curve with a maximum Youden index. Kaplan-Meier method was used to describe survival curve and log-rank test was used to compare the PFS and OS. Cox regression analysis and Cox's proportional hazard model was used to calculate prognostic value of different variables. C-index and ROC analysis were used to estimate predictive ability of survival outcomes. All statistical tests were two-sided, and the level of significant P was <0.05. The C-index was built based on training set with the R package "survival".

Results

Clinical characteristics

A total of 318 cases of mRCC who treated with targeted therapy were retrospectively retrieved from medical records. Of these patients, 164 patients were complied with our inclusion criteria and included in this study. The clinical characteristics were shown in *Table 1*. ROC analysis to determine the cutoff point of fibrinogen was shown in *Figure 1* and the best cutoff value of fibrinogen was 2.940 g/L. Ninety-four patients constituted low fibrinogen group (<2.940 g/L) and 70 patients constituted high fibrinogen (≥2.940 g/L) groups. Our final cohort included 122 men (74.4%) and 42 women (25.6%). Median age was 60 years (24–82 years). Of them, 7 patients Furman grade could not be found in the database. Seventy-four (45.1%) patients belonged favorable IMDC group, 64 (39.0%) belonged intermediate IMDC group and 26 (15.9%) belonged poor IMDC group. Sorafenib was administered as first-line therapy in 101 (61.6%) patients whereas sunitinib was 63 (38.4%).

Correlation between fibrinogen and clinical and pathological characteristics

The median (range) pretreatment plasma fibrinogen level was 2.76 (1.98–4.56) g/L. No significant difference was found in sex, age, histology, prior cytokines therapy or nephrectomy, Fuhrman grade and the kind of first-line targeted agents between two groups. In the high fibrinogen level group, there were more patients with ≥2 metastasis sites (38.6% *vs.* 23.4%, P=0.036) and more patients with poorer IMDC risk grade (P=0.003).

Correlation between pretreatment fibrinogen and survival outcomes

The median follow-up period was 26 months. The overall median PFS of all 164 patients was 10 months (95% CI, 8–12 months), and the median OS was and 28 months (95% CI, 23–33 months). One-year survival rate was 71.3% and 2-year survival rate was 45.1%. As shown in *Figure 2*, median PFS (6 *vs.* 15 months, P<0.001) and OS (17 *vs.* 44 months, P<0.001) in the high plasma fibrinogen group were significantly shorter than low plasma fibrinogen group. We further compared the survival outcomes between high and low plasma fibrinogen level groups in different IMDC risk patients in *Figure 3*. In the sub-group of favorable, intermediate or poor IMDC, the median PFS and OS were also significant shorter in high plasma fibrinogen group than low.

The prognostic value of diffident clinical pathological parameters on PFS and OS was shown in *Tables 2* and *3*. Multivariate analysis revealed that Fuhrman grade, number of metastasis sites, IMDC were significant predictor of PFS and OS. We also identified that plasma fibrinogen (<2.940 and ≥2.940 g/L) remained a significant predictor of shorter OS (HR 3.213, 95% CI, 2.138–4.827, P<0.001) and PFS (HR 2.873, 95% CI, 2.002–4.123, P<0.001) in the multivariate analysis. Further, when fibrinogen was analyzed as continuous variable, plasma fibrinogen was remaining as a significant predictor for PFS (HR 2.035, 95% CI, 1.519–2.726, P<0.001) and OS (HR 1.968, 95% CI, 1.475–2.627, P<0.001) (data not shown).

Predictive accuracy of pretreatment fibrinogen and IMDC

C-index was presented in *Table 4*. The C-index of fibrinogen (<2.940 and ≥2.940 g/L) for PFS and OS was 0.65 (95% CI, 0.60–0.70) and 0.66 (95% CI, 0.61–0.71). After the adding fibrinogen to the base IMDC model, C-index for PFS was improved from 0.68 of IMDC model to 0.74, and for OS, it was improved from 0.69 to 0.76. The ROC curve of the IMDC and combined model to predict the prognosis was plotted in *Figure 4*. The AUC was also improved form the 0.793 (95% CI, 0.722–0.852) of IMDC to 0.863 (95% CI, 0.801–0.921, P<0.001) after the addition of fibrinogen level.

Discussion

Several established prognostic models are used to predict the clinical outcomes of mRCC. According to the IMDC model, pretreatment anemia, thrombocytosis, neutrophilia, KPS and time from diagnosis to first-line targeted therapy

Table 1 Patient baseline and clinicopathological characteristics

Variables	Number (%) (N=164)	Fibrinogen <2.940 g/L (%) (N=94)	Fibrinogen ≥2.940 g/L (%) (N=70)	P value
Sex				0.737
Male	122 (74.4)	69 (73.4)	53 (75.7)	
Female	42 (25.6)	25 (26.6)	17 (24.3)	
Age				0.737
<65	122 (74.4)	69 (73.4)	53 (75.7)	
≥65	42 (25.6)	25 (26.6)	17 (24.3)	
Histology				0.950
Clear cell	156 (95.1)	90 (95.7)	66 (94.3)	
Others	8 (4.9)	4 (4.3)	4 (5.7)	
Prior nephrectomy				0.876
Yes	135 (82.3)	77 (81.9)	58 (82.9)	
No	29 (17.7)	17 (18.1)	12 (17.1)	
Prior cytokines				0.267
Yes	60 (36.6)	31 (33.0)	29 (41.4)	
No	104 (63.4)	63 (67.0)	41 (58.6)	
Fuhrman grade				0.151
1–2	92 (56.1)	58 (61.7)	34 (48.6)	
3–4	65 (39.6)	32 (34.0)	33 (47.1)	
Unknown	7 (4.3)	4 (4.3)	3 (4.3)	
Number of metastasis sites				0.036
1	115 (70.1)	72 (76.6)	43 (61.4)	
≥2	49 (29.9)	22 (23.4)	27 (38.6)	
Metastatic site				
Lung	119 (72.6)	67 (71.3)	52 (74.3)	0.669
Lymph node	44 (26.8)	21 (22.3)	23 (32.9)	0.133
Bone	19 (11.6)	8 (8.5)	11 (15.7)	0.154
Liver	15 (9.1)	10 (10.6)	5 (7.1)	0.248
Others	13 (7.9)	9 (9.6)	4 (5.7)	0.365
IMDC				0.003
Favorable	74 (45.1)	50 (53.2)	24 (34.3)	
Intermediate	64 (39.0)	35 (37.2)	29 (41.4)	
Poor	26 (15.9)	9 (9.6)	17 (24.3)	
First-line therapy				0.773
Sorafenib	101 (61.6)	57 (60.6)	44 (62.9)	
Sunitinib	63 (38.4)	37 (39.4)	26 (37.1)	

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium model.

are prognostic factors for mRCC. Moreover, system inflammation markers like CRP (8), NLR (10) an PLR (11) represent new independent survival outcomes predictors of mRCC patients. Fibrinogen was also proved to be a prominent prognostic indicator in different cancers such as hepatocellular carcinoma (18), esophageal squamous cell carcinoma (19) and localized renal cell carcinoma (20). Tsimafeyeu *et al.* (17) have compared OS time between two groups of mRCC patients with and without hypercoagulability then found that hypercoagulability was an independent risk factor for mRCC. However, they have not analyzed the fibrinogen level separately. The number of patients was limited in their study and they have not specifically included patients who receive targeted therapy. Therefore, the potential prognostic significance of fibrinogen is still limited in target treatment of mRCC. New biomarker for prognosis is important since they would guide clinical judgment and treatment for individual patient. To the best of our knowledge, this work is the first to demonstrate the prognostic value of pretreatment plasma fibrinogen level in mRCC patients receiving target therapy. Finally, we found that fibrinogen could accurately predict the clinical outcomes of mRCC and increase the accuracy of prognostic prediction of IMDC model.

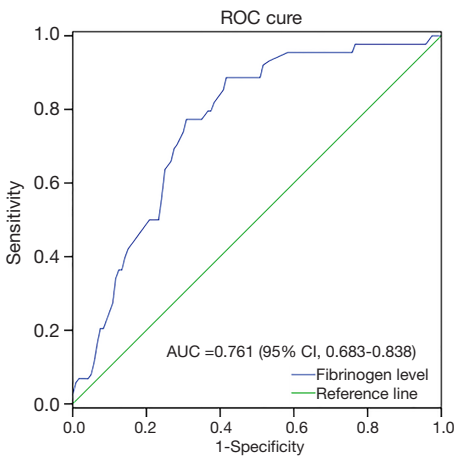

Figure 1 Receiver operating characteristic (ROC) analysis of optimal fibrinogen cutoff level.

Systemic inflammation is an important risk factor for tumor progression. The change of plasma fibrinogen is associated with abnormal coagulation and inflammation of the body (20). Renal cell carcinoma cells may activate the coagulation cascade, and thus increase the plasma fibrinogen level and promote the hematogenous metastasis (20). Fibrinogen can be synthesized endogenously through the tumor cell and it can regulate the growth of cancer cells by binding to VEGF, FGF-2 and PDGF (21). In addition, VEGF can also conversely stimulate the endothelial cells, activate the coagulation cascade, and increase the fibrinogen level (22). Blocking the VEGF and PDGF signaling pathways may reverse the physiological processes of *VHL* gene function and thus inhibit tumor growth, which is the rationale for anti-angiogenic therapy for mRCC (23). Thus, on one hand, high plasma fibrinogen might be related to the progress of renal cancer, and on the other hand it is related to drug resistance of target therapy.

As to clinic-pathological parameters, the higher clinical stages of multiple tumors were reported to be accompanied with an increased plasma fibrinogen level (24-26). Du *et al.* (27) found that a higher plasma fibrinogen level was significantly correlated to higher Fuhrman grade, pathologic T stage and larger tumor diameter in non-mRCC. Further, Pichler *et al.* (15) and Obata *et al.* (20) found it also predicts worse survival endpoints in localized renal cell carcinoma. In

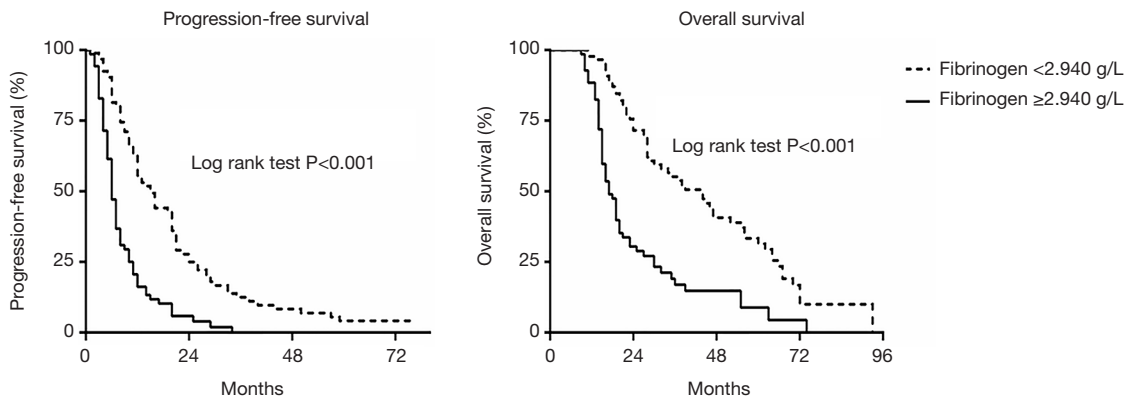

Figure 2 Progression-free survival (PFS) and overall survival (OS) of patients with high plasma fibrinogen *vs.* low high plasma fibrinogen.

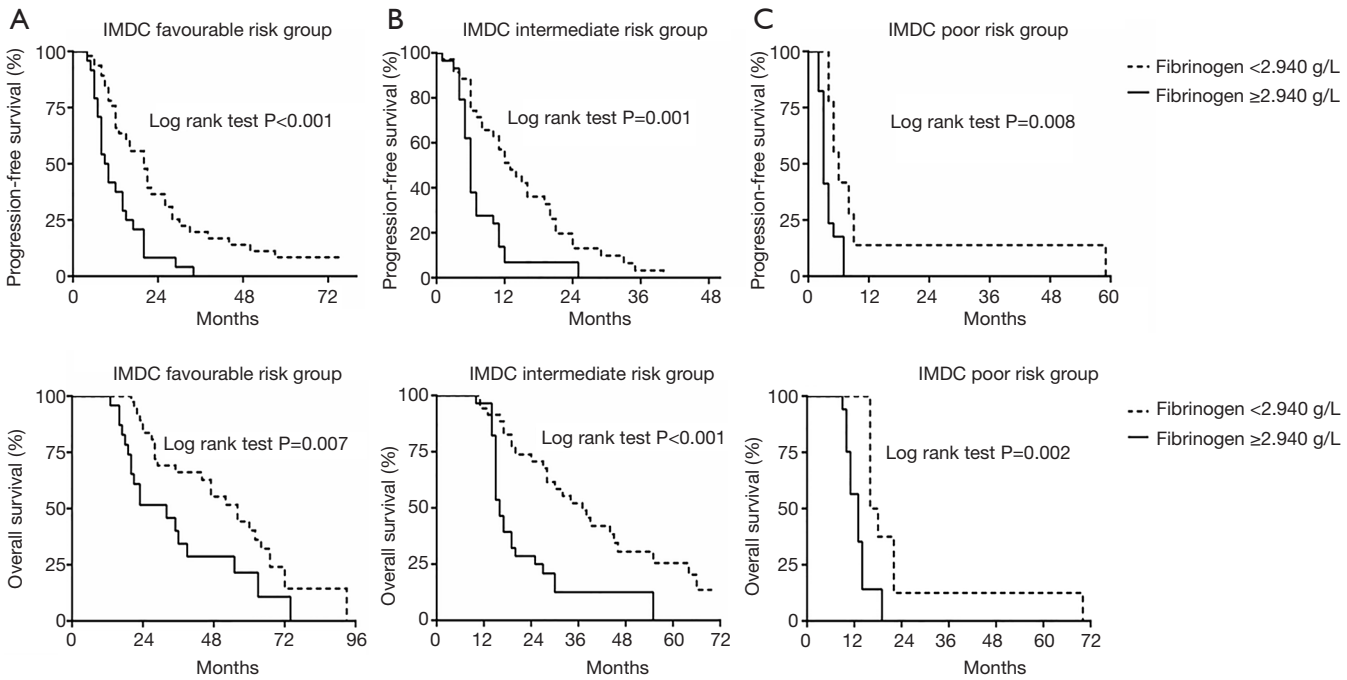

Figure 3 Kaplan-Meier survival curves stratified by IMDC risk model. (A) Favorable risk; (B) intermediate risk; (C) poor risk. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium model.

Table 2 Univariable and multivariable Cox regression models to predict PFS

Variables	Univariable		Stepwise analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male versus female)	0.999 (0.689–1.450)	0.998	–	–
Age (≥65 *vs*. <65)	1.016 (0.699–1.476)	0.934	–	–
Pathology (nccRCC *vs*. ccRCC)	1.714 (0.745–3.943)	0.205	–	–
History of nephrectomy (no *vs*. yes)	1.530 (0.998–2.346)	0.051	–	–
History of cytokines (no *vs*. yes)	1.308 (0.927–1.845)	0.126	–	–
Fuhrman grade		0.003		0.003
1–2	Ref	–	Ref	–
3–4	1.662 (1.187–2.328)	0.003	1.747 (1.229–2.481)	0.002
Unknown	0.521 (0.190–1.428)	0.205	0.628 (0.223–1.769)	0.378
Number of metastasis sites (2 or more *vs*. 1)	1.572 (1.104–2.239)	0.012	1.650 (1.136–2.394)	0.008
Heng risk grade		<0.001		<0.001
Favourable	Ref	–	Ref	–
Intermediate	1.796 (1.252–2.576)	0.001	1.740 (1.202–2.518)	0.003
Poor	4.183 (2.554–6.850)	<0.001	4.873 (2.967–8.390)	<0.001
Fibrinogen (≥2.940 *vs*. < 2.940 g/L)	2.754 (1.949–3.892)	<0.001	2.873 (2.002–4.123)	<0.001
Drug category (sunitinib *vs*. sorafenib)	1.056 (0.755–1.476)	0.751	–	–

PFS, progression-free survival; ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma.

Table 3 Univariable and multivariable Cox regression models to predict OS

Variables	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male *vs.* female)	1.103 (0.730–1.665)	0.641	–	–
Age (≥65 *vs*. <65)	1.035 (0.678–1.579)	0.874	–	–
Pathology (nccRCC *vs*. ccRCC)	2.796 (1.200–6.515)	0.017	1.073 (0.429–2.682)	0.881
History of nephrectomy (no *vs*. yes)	1.183 (0.728–1.924)	0.497	–	–
History of cytokines (no *vs*. yes)	1.104 (0.754–1.617)	0.610	–	–
Fuhrman grade		<0.001		<0.001
1–2	Ref	–	Ref	–
3–4	2.106 (1.446–3.067)	<0.001	2.279 (1.529–3.396)	<0.001
Unknown	0.815 (0.295–2.256)	0.694	0.998 (0.348–2.863)	0.997
Number of metastasis sites (1 *vs*. 2 or more)	1.936 (1.317–2.846)	0.001	2.055 (1.366–3.091)	0.001
Heng risk grade		<0.001		<0.001
Favourable	Ref	–	Ref	–
Intermediate	1.915 (1.260–2.911)	0.002	2.026 (1.313–3.125)	0.001
Poor	6.090 (3.581–10.358)	<0.001	8.914 (4.893–16.239)	<0.001
Fibrinogen (≥2.940 *vs*. < 2.940 g/L)	2.791 (1.916–4.066)	<0.001	3.213 (2.138–4.827)	<0.001
Drug category (sunitinib *vs*. sorafenib)	1.039 (0.720–1.499)	0.838	–	–

OS, overall survival; ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma.

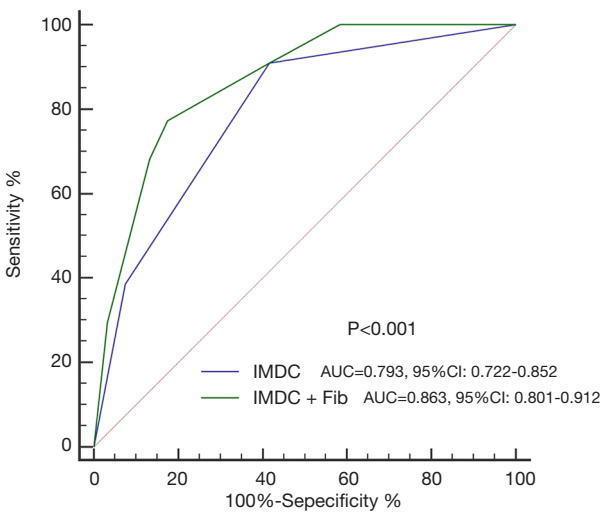

Figure 4 Receiver operating characteristic (ROC) analysis to predict survival: plasma fibrinogen + IMDC *vs.* IMDC. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium model.

Table 4 C-index of IMDC and IMDC with fibrinogen

Variables	C-index (std)	
	PFS	OS
IMDC	0.68 (0.027)	0.69 (0.028)
Fibrinogen	0.65 (0.025)	0.66 (0.026)
IMDC + fibrinogen	0.74 (0.029)	0.76 (0.031)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium model; PNI, prognostic nutritional index; PFS, progression-free survival; OS, overall survival.

mRCC, we also found that the proportion of patients with more metastatic sites in the high fibrinogen level group was higher than the low group (P=0.036). Clinical studies suggest that hypercoagulability is common in the blood of patients with malignant tumors and it can accelerate the metastasis of tumor then ultimately affect the prognosis of patients (14), which was consistent with our research. More metastatic sites might mean a higher plasma fibrinogen level. We also found that there were more patients with poorer IMDC risk patients

in high fibrinogen group. In order to better compare the fibrinogen level with the basic IMDC model and eliminate this interference, we separately analyzed the survival curves of the high and low fibrinogen level in each subgroup of IMDC. The results showed that both the PFS and the OS in the high plasma fibrinogen level group were significantly lower than the low fibrinogen group whether in favorable, intermediate or poor risk IMDC group. Similarly, in multifactor analysis, except other interfering factors, fibrinogen remained an independent risk factor for survival outcomes.

At present, the commonly used prognostic models like IMDC show good accuracy and applicability in clinical application of targeted therapy in mRCC (4). With further research on the mechanism of inflammation, tumor occurrence and development, and new-found prognostic factors of mRCC, more accurate and adaptable prognosis models for target treatment of mRCC are expected to be developed and applied. In this work, we found that adding fibrinogen to base model was able to raise the predictive accuracy. The C-index of IMDC for FPS and OS was 0.68 and 0.69, and the AUC was 0.793. After adding fibrinogen to it, predictive accuracy increased to 0.74 and 0.76. AUC could also be improved to 0.863. Fibrinogen is easy to assess and could be routinely measured before target therapy. Addition of fibrinogen can help predict the prognosis of clinical more accurately, and further to help scientifically develop the next target treatment strategy.

This study had several limitations. Firstly, this is a single-center retrospective study. Despite we have analyzed the data which were strictly included according to criteria, some confounding and bias were still inevitable. Secondly, different patients would choose different second- or third-line treatment which might have significant inference on OS time. Thus, Future researches are recommended to study the prognostic role of plasma fibrinogen level, reveal its underlying mechanisms and improve predictive accuracy of traditional model in order to a better guide for targeted therapy in mRCC.

Conclusions

This study showed basal plasma fibrinogen status could be used as an independent prognostic parameter for the PFS and OS of patients with mRCC receiving target therapy. It could also be an important complement to the traditional prognostic model. Monitoring the fibrinogen status is not only an effective measure to detect coagulation status, but also play an important role in controlling the development and predicting prognosis of target treatment in mRCC.

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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.2018.10.20). 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. Ethical ratification was authorized by the clinical research ethics committee of Renji Hospital (2005-RJ006). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Renji Hospital and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The written informed consent was waived due to the retrospective nature of the study.

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