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ORIGINAL RESEARCH

Prognostic Role of Prothrombin Time Activity, Prothrombin Time, Albumin/Globulin Ratio, Platelets, Sex, and Fibrinogen in Predicting Recurrence-Free Survival Time of Renal Cancer

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Zichen Bian[1,*]
Jialin Meng[1,*]
Qingsong Niu[1]
Xiaoyan Jin[2]
Jinian Wang[3]
Xingliang Feng[1]
Hong Che[4]
Jun Zhou[1]
Li Zhang[1]
Meng Zhang[1,5]
Chaozhao Liang[1]

[1]Department of Urology, The First Affiliated Hospital of Anhui Medical University; Anhui Province Key Laboratory of Genitourinary Diseases, Anhui Medical University; The Institute of Urology, Anhui Medical University, Hefei, People's Republic of China; [2]The Second Clinical College of Anhui Medical University, Hefei, Anhui, People's Republic of China; [3]Clinical Skills Training Center, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui, People's Republic of China; [4]Department of Cardiac Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China; [5]Institute of Urology of Shenzhen University, The Third Affiliated Hospital of Shenzhen University, Shenzhen Luohu Hospital Group, Shenzhen 518000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chaozhao Liang; Meng Zhang
Email liang_chaozhao@ahmu.edu.cn; zhangmeng1930@126.com

Background: To help with the clinical practice of renal cancer patients, prognostic models are urgently warranted. We hunted and identified prognostic variables associated with recurrence-free survival (RFS) for renal cancer patients.

Patients and Methods: In this retrospective study, 187 renal cancer patients who had received curative radical/partial nephrectomy between November 2011 and January 2017 were enrolled in the current study. These patients were randomly split into the training (n = 95) and validation sets (n = 92) by the ratio of 1:1. Univariate and multivariable Cox regression analyses were used to establish the nomogram, which was then evaluated by receiver operating characteristic (ROC) and Kaplan-Meier (K-M) analyses.

Results: Patient characteristics and outcomes were well balanced between the training and validation sets; the median RFS values were 54.1 months and 58.9 months for the training and validation cohorts, respectively. The final nomogram included six independent prognostic variables (prothrombin time (%), prothrombin time (second), albumin/globulin ratio, platelets, sex and fibrinogen). The mean values of RFS for the low- and high-risk groups defined by a prognostic formula were 56.22 ± 18.50 months and 49.54 ± 23.57 months, respectively, in the training cohort and were 59.00 ± 19.50 months and 53.32 ± 19.95 months, respectively, in the validation cohort. The significance and stability of the model were tested by the time-dependent K-M model and ROC curves, respectively.

Conclusion: Our validated prognostic model incorporates variables routinely collected from renal cancer patients, identifying subsets of patients with different survival outcomes, which provides useful information for patient care and clinical trial design.

Keywords: renal cancer, recurrence, nomogram

Introduction

Renal cancer is the sixth most frequent cancer in men and the 10th in women around the world.[1] Most renal cancers can be diagnosed at an early stage, but tumour-specific mortality has continuously increased in the past decades. Moreover, there are approximately 1/5 to 3/10 renal cancer patients who will step into the metastasis stage after the initial radical or partial nephrectomy.[2] On the other hand, renal cancer is insensitive to radiotherapy and chemotherapy; therefore, the prognosis of renal cancer patients is unfavourable, and a great number of patients die from the disease.[3] Thus, more effective biomarkers that could forecast disease progression are warranted.

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Currently, numerous publications have reported the prognosis predictive value of clinical parameters among different tumours,[4–6] as well as renal cancer.[7] The clinical parameters are usually used to evaluate the basic stability of the internal environment of the human body, and the abnormal results always indicated the unbalanced internal environment that was associated with several diseases. Globulin (GLO) is one of the significant components of serum proteins and always responds to chronic inflammation with an increase in serum levels.[8] Elevated serum GLO plays an essential role in several diseases,[9] such as cancer, chronic liver disease, rheumatoid diseases, diabetes mellitus, and nephrotic syndrome. Moreover, the counts of several blood cells or their ratios were also reported as prognostic biomarkers for cancer. Platelets are regarded as multifunctional cells and participate in the immune response, allergy, tissue regeneration, inflammation, and lymphangiogenesis processes. The platelet count (PLT) has been reported to be associated with the prognoses of pancreatic cancer,[10] cervical cancer,[11] and gallbladder cancer.[12] Some studies have been done by categorizing the relationship between cancer and coagulation function. Cancer cells are able to activate the coagulation system, while haemostatic factors also play a role in tumour progression.[13,14] For example, the high pretreatment fibrinogen and D-dimer levels are reportedly related to poor overall survival (OS) in endometrial cancer patients.[15,16] Thus, the clinical haematological parameters-based prognostic signatures are easily obtained as the prognosis forecast tools for patients with tumours.[7]

In the current study, we focused on the establishment and validation of a haematological parameters-based prognostic signature for renal cancer patients. A total of 187 renal cancer patients were registered. The basic information, haematological parameters, and follow-up data were all recorded and analysed. We built a nomogram to help the patients be aware of the recurrence risk by themselves as well.

Patients and Methods

Patients and Inclusion Criteria

The retrospective study involved 187 patients with renal cancer who were treated at the Department of Urology, The First Affiliated Hospital of Anhui Medical University between November 2011 and January 2017. Patients with the completed laboratory results and demographic and pathological data were enrolled, as well as the acquirable follow-up information. The patients who lacked any of the above mentioned data were not suitable for the current study. The current study was approved by the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University (anyiyifuyuanlunshen-kuai-PJ-2019-09-11).

Follow-Up Record

The follow-up evaluations included clinical laboratory tests and radiological examinations. All patients were followed-up via telephone interviews. The last follow-up was completed on 1 November 2019. The observed endpoint of renal cancer patients was tumour recurrence determined by the result based on radiological examination. The other patients were set as censored or recurrence-free ones.

Clinical and Laboratory Parameters

All clinicopathological data, including laboratory data, tumour stage, and demographic settings, were retrieved from the electronic medical records at our hospital. The American Joint Committee on Cancer (AJCC) TNM staging system (8th edition) was executed to determine the tumour stage. The characterizations of the laboratory parameter were demonstrated as below:

Absolute neutrophil count (NEUT); absolute lymphocyte count (LYMPH); red blood cell count (RBC); haemoglobin (HGB); haematocrit value (HCT); platelet count (PLT); neutrophil-to-lymphocyte ratio (NLR); albumin (ALB); globulin (GLO); albumin to gamma-glutamyltransferase ratio (AGR); direct bilirubin (DBIL); indirect bilirubin (IBIL); alanine transaminase (ALT); aspartate aminotransferase (AST); blood urea nitrogen (BUN); creatinine (CRE); uric acid (UA); plasma prothrombin time (PT (sec)); "international normalized ratio (INR); plasma prothrombin time activity (PT-%); activated partial thromboplastin time (APTT); thrombin time (TT (sec)); fibrinogen (FIB (g/l)); pathological stage-T (stage-T); pathological stage-N (stage-N); and the AJCC staging system. The classifications of these laboratory characteristics are demonstrated in Table S1.

Statistical Analysis

All the enrolled samples were 1:1 random sampling without replacement by using sample() R package. The randomizing process was blind to the demographic information or laboratory test results, which can ensure that the training and validation cohorts are independent to clarify the key points we focused on. Univariate analysis was applied to determine the significance of variables concerning RFS. A multivariate Cox regression model was implemented to establish the model for the prediction of RFS. We used the Kaplan-Meier (K-M) method and the Log rank test to

compare the patients' clinical endpoints. In addition, the time-dependent receiver operative characteristic (tROC) curve and time-dependent area under the curve (tAUC) were applied to determine the stability of the classifier. We used R (http://www.R-project.org) software to make all statistical analyses. A two-sided $P < 0.05$ was considered statistically significant.

Results

Clinicopathological Features

Baseline demographics and disease characteristics were balanced between the training set (n = 95) and the validation set (n = 92) (Figure 1). Table 1 summarizes the patients' characteristics in both the training and validation cohorts. Overall, the age of the enrolled patients was 56.72 ± 12.68 years old. Of them, 118 (63.0%) were male and 69 (37.0%) were female. In all, 154, 19, 12, and 2 patients were at stage I, II, III and IV, respectively. The median follow-up time from diagnosis was 54.609 months (range 1 month to 97.2 months). Forty patients were diagnosed with a recurrence during the follow-up period.

Univariate Analysis Indicted the Potential Prognostic Factors

We performed the univariate analysis to determine the RFS-related candidates from the 29 elements. The results indicated that age (HR = 4.537, 95% CI: 1.653–12.459, $P < 0.05$), PT (sec) (HR = 6.806, 95% CI: 1.972–23.483, $P < 0.05$), PT-INR (HR = 8.572, 95% CI: 1.942–37.844, $P < 0.05$), PLT (HR = 3.154, 95% CI: 1.252–7.946, $P < 0.05$), stage (HR = 3.795, 95% CI: 1.271–11.331, $P < 0.05$), FIB (g/l) (HR = 2.160, 95% CI: 1.010–4.618, $P < 0.05$) and stage-T (HR = 3.795, 95% CI: 1.271–11.331, $P < 0.05$) were the risk factors for recurrence, while the PT -% (HR = 0.115, 95% CI: 0.039–0.345, $P < 0.05$), AGR (HR = 0.155, 95% CI: 0.046–-0.525, $P < 0.05$), HCT (HR = 0.286, 95% CI: 0.125–0.652, $P < 0.05$), LYMPH (HR = 0.246, 95% CI: 0.090–0.677, $P < 0.05$), HGB (HR = 0.343, 95% CI: 0.151–0.777, $P < 0.05$), and sex (HR = 0.250, 95% CI: 0.074–0.849, $P < 0.05$) were the protective factors for recurrence (Table 2).

As mentioned above, the analysis by means of a univariate method identified thirteen prognostic instances related to unfavourable RFS. The subsequent multivariate analysis found that the PT (%), PT (sec), AGR, PLT, sex and FIB (g/l) were still statistically significant (Table 3). Based on these findings, subsequent analyses were performed.

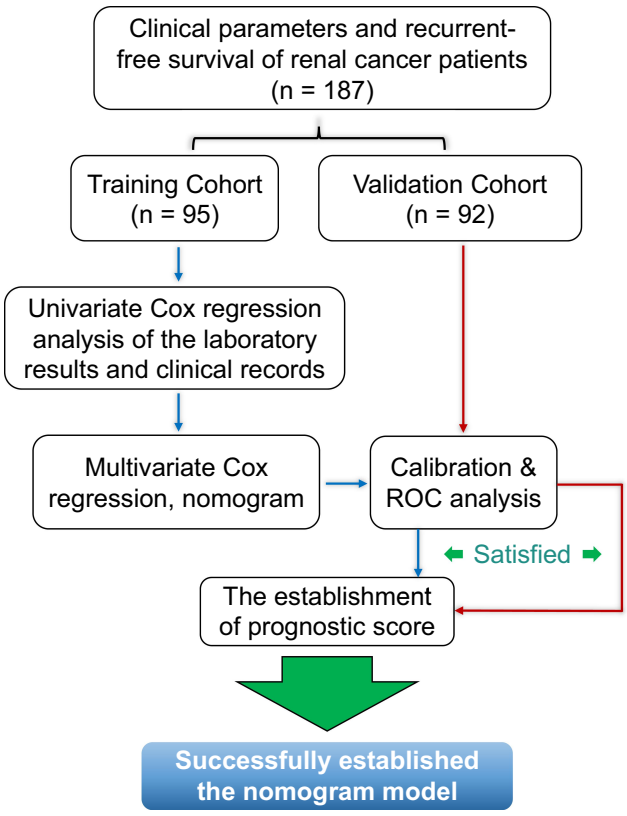


Figure 1 Flow chart showed the designation of current study.

Prognostic Nomogram for the RFS of Renal Cancer Patients

To integrate the data that contains all vital independent factors of RFS in the testing syngeneic group, a prognostic nomogram was made (Figure 2A). The C-index for the prediction of RFS was 0.810 in the training set. The prediction of the nomogram was optimally accorded with the actual observed value in the validation and training groups by calibration plot of the feasibility of 3- or 5-year survival after surgery (Figure 2B–E).

ROC and K-M Analyses

Concordance for predicting RFS as assessed by the tAUC scores for the four-variable model was 0.768, 0.852 and 0.790 at 1–, 3– and 5–year RFS in the training set, respectively, while the tAUC scores were 0.683, 0.756, and 0.695 at 1–, 3– and 5–year RFS in the validation set, respectively (Figure 3). Although the multivariate analysis excluded the clinicopathological features, we performed the nomogram by combining the six variable-based classifier, age and tumour stage; the results suggested that our classifier showed the best predictive values compared to the tumour stage, and

Table 1 Clinicopathological Features of the Enrolled Renal Cancer Patients

Parameters	Training Cohort (n = 95)	Percent (%)	Validation Cohort (n = 92)	Percent (%)	P-value
Age (mean ± SD)	56.790 ± 13.268		56.663 ± 12.126		0.946†
Gender					0.880§
Male	59	62.10%	59	64.13%	
Female	36	37.90%	33	35.87%	
pT status					0.588§
T1 + T2	89	93.68%	84	91.30%	
T3 + T4	6	6.32%	8	8.70%	
pN status					0.117§
N0	95	100%	89	96.74%	
N1	0	0.00%	3	3.26%	
pM status					1.000§
M0	95	100.00%	92	100.00%	
M1	0	0.00%	0	0.00%	
pTNM stage					0.588§
I + II	89	93.68%	84	91.30%	
III + IV	6	6.32%	8	8.70%	
Age					0.771§
≤ 55	47	49.47%	48	52.17%	
> 55	48	50.53%	44	47.83%	

Notes: †Student *T*-Test; §Fisher Exact Probability Test.
Abbreviations: SD, standard deviation; ccRCC, clear cell renal cell carcinoma.

the combination of classifier, age and tumour stage showed better predictive values (Figure 4).

A risk score was determined by regression coefficients from the training set for the six variables. An algorithm was established accordingly. Patients who were in the training group were stratified as being at high- and low-risk of recurrence according to the score of median risk (Figure 5A–C). The mean RFS among low-risk patients was 56.22 ± 18.50 months, whereas among high-risk patients, the mean RFS was 49.54 ± 23.57 months. In addition, our findings were further proved in an internal validation set. The patients who were validated were also stratified as being high- and low-risk for recurrence (Figure 5D–F), which refers to the median risk score that came from the training group. The mean RFS among the low- and high-risk patients was 59.00 ± 19.50 months and 53.32 ± 19.95 months, respectively, in the validation cohort.

Discussion

The incidence of renal cancer has rapidly increased by approximately 2% worldwide during the last decades.[17] Although advancements have been made in managing renal masses, long-term survival remains unsatisfactory; most patients with renal cancer still die of this disease. Therefore, renal cancer patients should receive close follow-up; at the same time, reliable prognostic biomarkers that evaluate postoperative risk and guide individualized treatment for renal cancer patients are equally necessary.

In recent years, numerous studies have investigated a wide variety of prognostic factors, such as TNM stage,[17] Fuhrman's grade, and tumour size.[18] However, these prognostic variables cannot always display the accurate predictions due to the limitation of significant tumour heterogeneity in renal cancer patients.[19] Thus, novel biomarkers that can distinguish the high-risk renal cancer patients and improve clinical outcomes are desperately needed. In the past few years, nomograms have had a high development and been more precise than the traditional staging methods for predicting prognosis with regard to some cancers.[20,21] Here, we performed univariate and multivariate Cox regression analyses and finally identified six RFS-related factors, including PT (%), PT (sec), AGR, PLT, sex and FIB (g/l). Subsequently, we constructed a precise prognostic nomogram for renal cancer

Table 2 Univariate Analysis Based on the Training Set

Variables	HR	95% Low	95% High	*P*-value
Sex	0.250	0.074	0.849	0.026*
Age	4.538	1.653	12.459	0.003*
BP	0.845	0.330	2.167	0.727
NEUT	1.990	0.671	5.899	0.215
LYMPH	0.246	0.090	0.677	0.007*
NLR	2.197	0.859	5.619	0.101*
RBC	0.546	0.234	1.270	0.160
HGB	0.343	0.151	0.777	0.010*
HCT	0.286	0.125	0.652	0.003*
PLT	3.154	1.252	7.946	0.015*
ALB	0.492	0.200	1.208	0.121
AGR	0.155	0.046	0.525	0.003*
GLO	1.521	0.510	4.536	0.452
DBIL	1.352	0.464	3.941	0.580
IBIL	0.921	0.335	2.529	0.873
ALT	0.532	0.137	2.060	0.360
AST	0.704	0.262	1.891	0.486
BUN	1.317	0.533	3.257	0.551
CRE	0.978	0.408	2.344	0.960
UA	0.933	0.406	2.147	0.871
PT (sec)	6.806	1.972	23.483	0.002*
PT-INR	8.572	1.942	37.844	0.005*
PT (%)	0.115	0.039	0.345	< 0.001*
APTT	1.384	0.340	5.630	0.650
FIB (g/l)	2.160	1.010	4.618	0.047*
TT (sec)	0.806	0.016	41.853	0.915
Pathological T	3.795	1.271	11.331	0.017*
Pathological N	NA	NA	NA	NA
Stage	3.795	1.271	11.331	0.017*

Note: *P < 0.05.

Abbreviations: HR, hazard ratio; BP, blood pressure; NEUT, absolute neutrophil count; LYMPH, absolute lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit value; PLT, platelet count; ALB, albumin; AGR, albumin to gamma-glutamyltransferase ratio; GLO, globulin; DBIL, direct bilirubin; IBIL, indirect bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRE, creatinine; UA, uric acid; PT (sec), plasma prothrombin time; PT-INR, international normalized ratio; PT (%), plasma prothrombin time activity; APTT, activated partial thromboplastin time; FIB (g/l), fibrinogen; TT (sec), thrombin time.

Table 3 Multivariable Analysis of Prognostic Variables in the Training Set

Variables	Co-ef	Exp (co-ef)	Se (co-ef)	z	*P* value
PT (%) (Normal)	4.577	0.010	0.576	7.949	<0.001*
PT (sec) (Normal)	1.576	4.834	0.643	2.451	0.014*
PT (sec) (High)	1.366	0.255	0.643	2.125	0.034*
AGR (High)	1.746	0.174	0.629	2.777	0.005*
PLT (High)	2.735	15.410	0.490	5.581	<0.001*
Sex (Female)	1.960	0.141	0.626	3.130	0.002*
FIB (g/l) (Normal)	1.648	5.197	0.429	3.845	<0.001*

Note: *P < 0.05.

Abbreviations: Co-ef, co-efficient; Exp (co-ef), exponent of the coefficient; PT (%), plasma prothrombin time activity; PT (sec), plasma prothrombin time; AGR, albumin to gamma-glutamyltransferase Ratio; PLT, platelet count; FIB (g/l), fibrinogen (gram/liter).

patients. The nomogram played a good part in predicting the rate of survival, and the prediction gains support from the C-index (0.810 and 0.765 for the training and validation cohorts, respectively) and the calibration curve. The nomogram predicts RFS survival more accurately than the AJCC staging system. Although the multivariate analysis excluded tumour stage as an independent factor for the prediction of RFS, we performed an additional nomogram (nomogram2) by combining the six laboratory-based classifier, tumour stage and age. The results suggested nomogram2 had an increasing predictive value compared to these variables alone.

Notably, it has already been shown that the haemostatic activities induced by cancer could promote tumour metastasis, development, and progression.[22–24] Actually, the connection between tumour spread, progression and the aberrant parameter of fibrinolytic haemostasis may reduce overall survival (OS) of patients with tumours.[25] In the study by Li et al,[26] they pointed out that the reduction in pretreatment thrombin time (TT) has something to do with the lessening of oesophageal carcinoma (ESCC) survival. Tas et al[27] also expounded that the international normalized ratio (INR) and the prothrombin time (PT) have some prognostic values in lung cancer. In addition, some original studies indicated that hyperfibrinogenaemia was also considered an independent prognostic predictor of melanoma[28] and gallbladder cancer.[29] Fibrinogen (FIB) is a kind of clotting factor[30] and has been proven to have prognostic value in breast cancer.[31] Here, we first reported that the PT (%), PT (sec) and FIB could serve as independent risk factors for prediction of RFS.

As ALB and GLO are the two major serum proteins in the human body, low levels of ALB and high levels of GLO reflect malnutrition and a chronic inflammatory state.[32,33] Equally, the AGR can also reflect the nutritional and inflammatory status. Malnutrition influences the function of the immune system, mediating the growth and metastasis of tumours, and negatively influences the prognosis of cancer patients. The AGR has been recognized as a classic factor for the prediction of prognosis in renal cancer.[34,35] In this study, our results have verified that

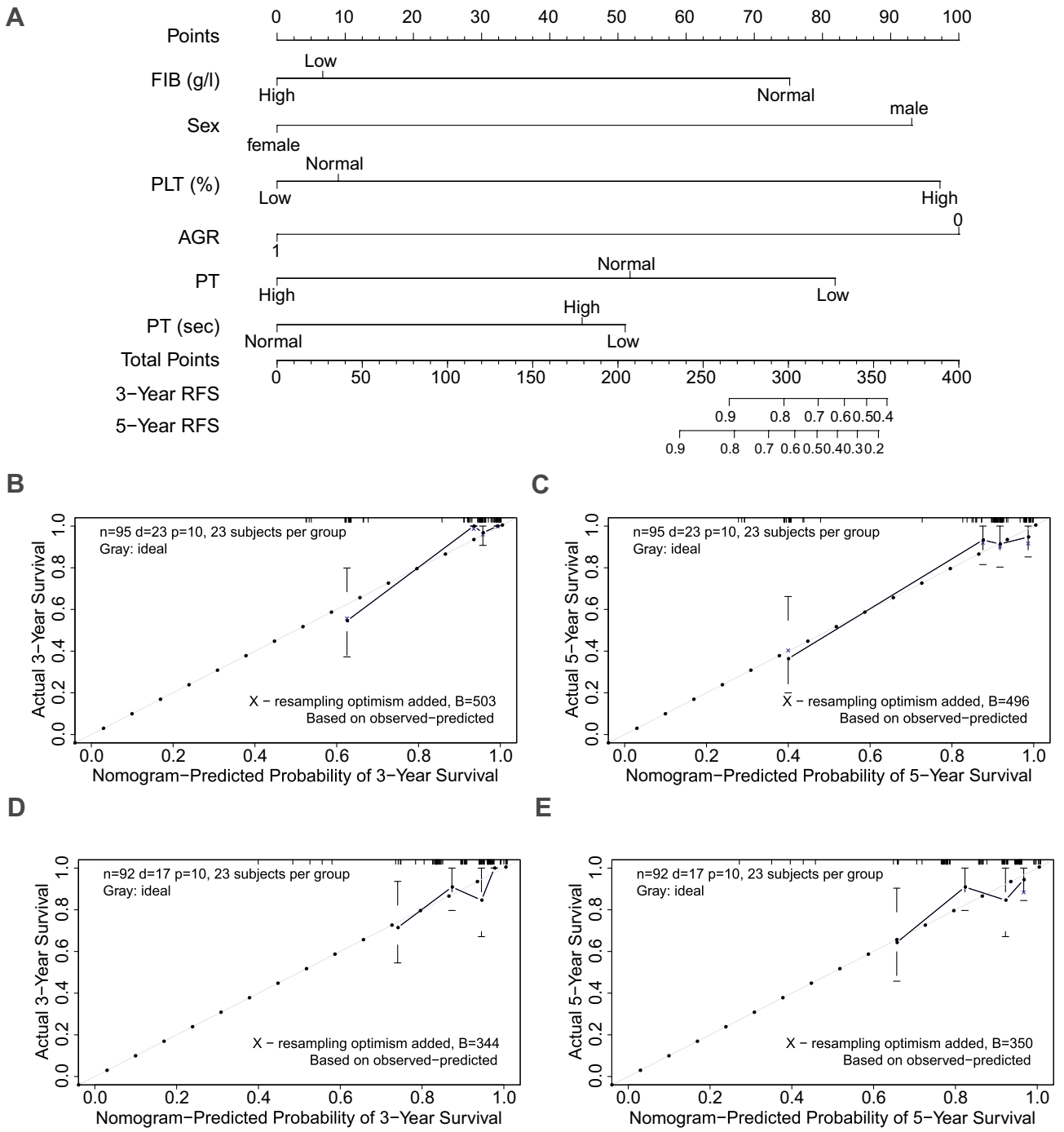


Figure 2 Construction of a nomogram for recurrence-free survival predicting. (**A**) Nomogram combining signature with laboratory results and clinicopathological features. (**B**–**E**) Calibration plot displaying that the nomogram model predicted recurrence-free survival probabilities was proved consistent with the actual observed proportions.

a low AGR may represent the poor prognosis of patients with renal cancer.

Elevated blood platelets could be considered a potential risk factor in the development of kidney cancer. Thrombocytosis is most likely associated with the neuroendocrine activity of tumour cells. There is evidence of the protective effect of platelets in relation to circulating tumour cells. They escaped the regulation of the immune system by hiding their recognition and facilitating their integration into the endothelium.[21] Platelets potentially influence tumour growth by generating growth factors, such as PDGF and VEGF. Studies have indicated that the renal cancer patients who have thrombocytosis mostly have unfavourable prognoses after surgery.[21,30,36] Our

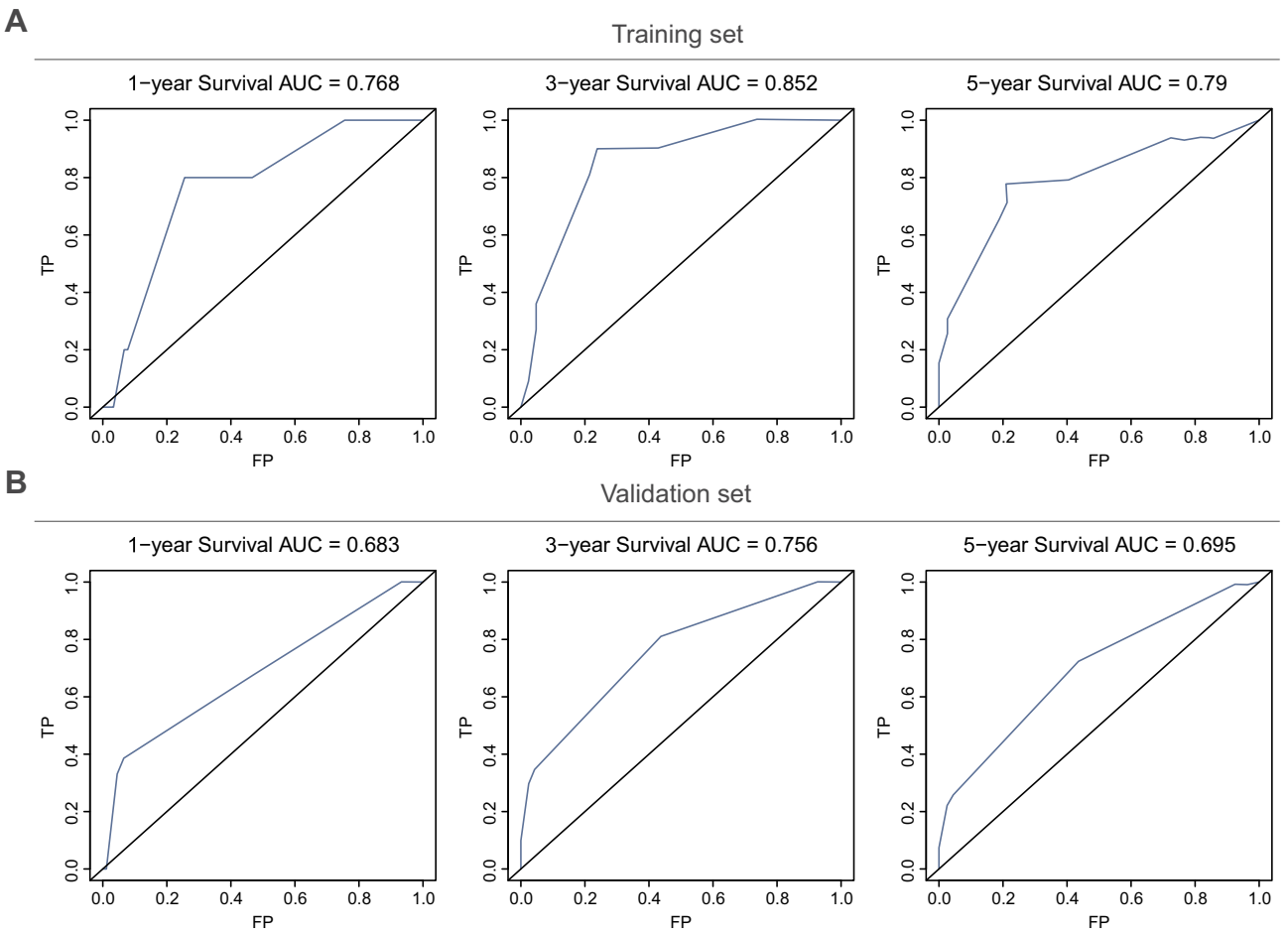


Figure 3 ROC curve analyses for the nomogram in predicting recurrence-free survival. (**A**) ROC curves showed satisfied predictive values of the nomogram in the training cohort at 1-, 3- and 5-year. (**B**) ROC curves showed satisfied predictive values of the nomogram in the validation cohort at 1-, 3- and 5-year.
Abbreviation: ROC, receiver operating characteristic.

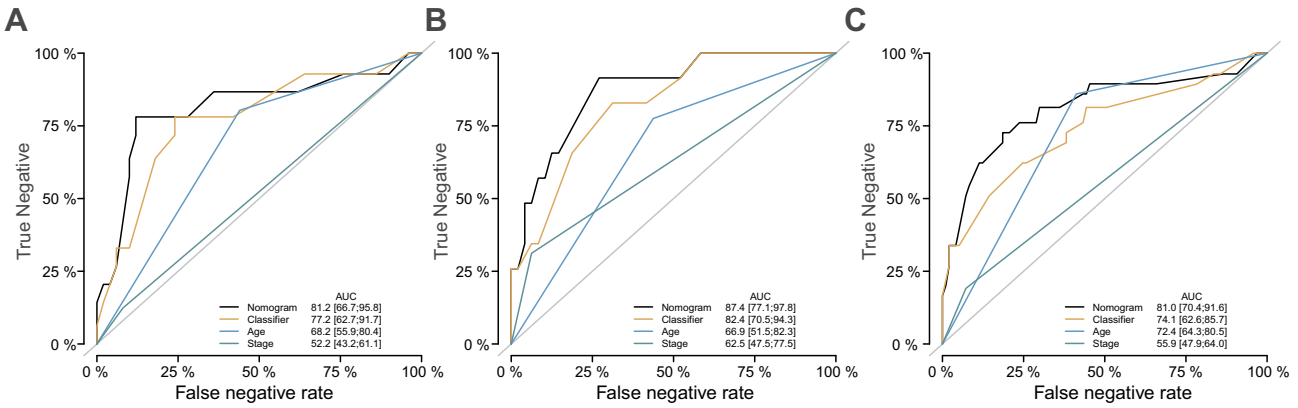


Figure 4 Nomogram (version 2) showed increased predictive values by combining the six-variables-based classifier and clinicopathological features in the training (**A**), validation (**B**) and overall datasets (**C**).

study has indicated that a high level of PLT could be a risk factor for the recurrence of renal cancer.

As the incidence of most cancers increases along with the age, cancer is considered an age-associated disease and begins to rise faster in middle age. Some biological mechanisms which regulate ageing might also be involved in the pathogenesis of age-related diseases, such as cancer. In addition, gender has also been proven to be associated with the

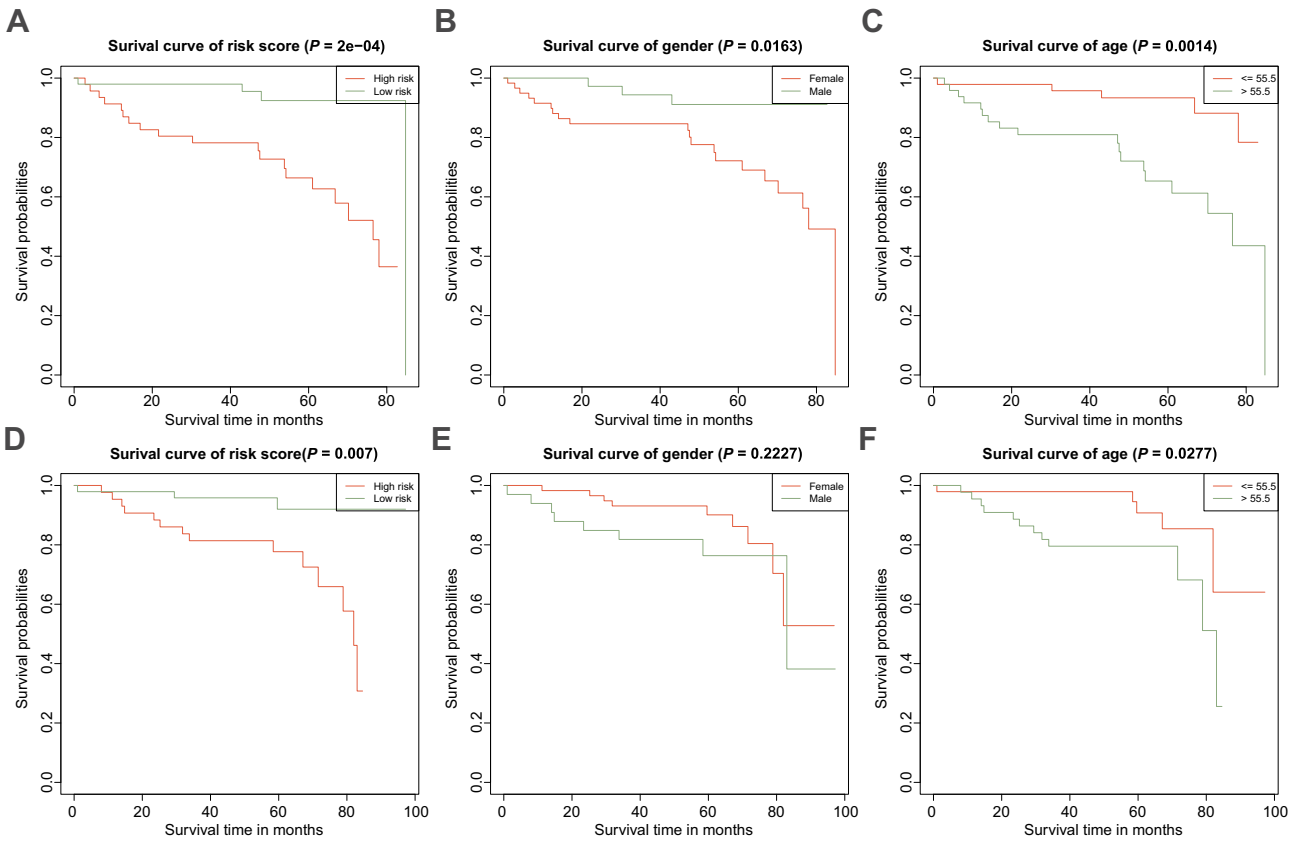


Figure 5 Survival analyses of the nomogram in predicting recurrence-free survival of renal cancer patients. (**A**–**C**) Stratified survival analyses based on the risk score, gender and age in the training cohort. (**D**–**F**) Stratified survival analyses based on the risk score, gender and age in the validation cohort.

prognosis of renal cancer patients. In our study, we found female patients had a better RFS status than male patients. Qu et al[37] suggested that, for these young and premenopausal women, they mostly had good survival status, which might be conferred by the oestrogen axis. In addition, the protective effect of the oestrogen axis on prognosis has also been observed in other cancers, such as colorectal cancer.[38] Previous basic research found that the oestrogen-ERβ axis inhibits the proliferation and induces the apoptosis of renal cancer cells.[38] Thus, increased circulating levels of oestrogen may enhance the tumour suppressor function of ERb, improving the prognosis of female patients with renal cancer.

Advantages are obvious for the current study. We defined a novel method to obtain a more accurate prediction of the recurrence of renal cancer after surgery. All the enrolled factors, including the results of blood coagulation factors, are normally tested and recorded for the inpatient patients, so there is no extra economic burden. However, we could use these results to get a better prediction of the prognosis for renal cancer patients. Better prediction means better preparation for the precise treatment. Limitations of this study exist in the cohort design and its retrospective nature, thereby allowing intrinsic biases that may affect the results. Patients with renal cancer are a heterogeneous group, from which we have a relatively small sample size and a diverse range of histology. Our findings that rely on the pathological features and laboratory test results require external validation. Currently, few established prognostic models are completely foolproof, even if they have enough ability to predict prognosis. In this case, more accurate markers are continually being searched for. The different biologic behaviours underlying the different clinical scenarios unveiled by molecular events may help make the risk-stratified clinical decision and provide personal prognostication.[39] In the targeted therapies epoch, localized and metastatic renal cancer patients demand the latest models and new prognostic factors.[40]

In conclusion, the nomogram, as proposed in the current study, objectively and accurately predicts the RFS of renal cancer patients after surgery. Multicentre prospective studies are warranted to validate our findings.

Data Sharing Statement

The anonymized data used and/or analysed during the current study are available from the corresponding authors on reasonable request.

Ethics Approval and Consent to Participate

The contents and methods of the research were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (anyiyi-fuyuanlunshen-kuai-PJ-2019-09-11). This study only collecting limited data that is known only to researchers, and the results of the research will not affect clinical care of the individuals, since they will already have left the hospital. Therefore, the consent to review the medical records were not required by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Patient information and clinical records were anonymized and de-identified prior to analysis. The study was conducted in compliance with the Declaration of Helsinki principles.

Consent for Publication

All authors have read and approved the manuscript being submitted and published, and agree to its submitted journal.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All the authors state they have no conflicts of interest.

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