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Original Article

Combination of preoperative plasma fibrinogen and neutrophil-to-lymphocyte ratio to predict the prognosis for patients undergoing laparoscopic nephrectomy for renal cell carcinoma

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Abstract: This study was conducted to investigate the prognostic significance of a combination of fibrinogen and neutrophil-to-lymphocyte ratio (NLR) named the F-NLR score as a novel indicator and further create nomograms for predicting the prognosis of patients with renal cell carcinoma (RCC) treated with laparoscopic nephrectomy. A total of 425 patients with RCC who underwent laparoscopic nephrectomy were included in this study. Then, we divided the patients based on the cut-off values of their F-NLR score into three categories: F-NLR 2 (both high fibrinogen and NLR), F-NLR 0 (both low fibrinogen and NLR), and F-NLR 1 (remaining patients). Cox regression analysis was performed to investigate the predictive performance of the F-NLR score on overall survival (OS) and cancer-specific survival (CSS). Predictive nomograms of F-NLR were established and internally validated. Time-dependent receiver operating characteristic (ROC) curve analysis was performed to assess the predictive accuracy of the nomogram, NLR, and fibrinogen as prognostic markers. The F-NLR 0, 1, and 2 groups included 226 (53.2%), 147 (34.6%), and 52 (12.2%) patients, respectively. Cox regression analysis showed that a high F-NLR score was significantly associated with poor prognosis and acted as an independent prognostic factor for OS and CSS (all $P < 0.05$). Predictive nomograms with F-NLR for OS (C-index: 0.773) and CSS (C-index: 0.838) were well developed. Time-dependent ROC results showed that nomograms containing F-NLR had better predictive performance than NLR and fibrinogen. F-NLR score was a novel effective prognostic biomarker for patients with RCC undergoing laparoscopic nephrectomy.

Keywords: F-NLR score, renal cell carcinoma, laparoscopic nephrectomy, prognostic biomarker

Introduction

Renal cell carcinoma (RCC), one of the common urological tumors, accounts for approximately 3% of adult malignancies [1]. Over the past few decades, the incidence of RCC has increased at a rate of 2% per year, while the prognosis for RCC patients is poor, especially for those with metastases [2]. For the reason that the RCC disease process is usually asymptomatic, approximately one-third of the patients present with metastatic lesions at first diagnosis [3]. Since RCC is insensitive to radiotherapy and chemotherapy, surgical resection remains the main treatment modality; however, it is associated with a 10% recurrence rate of patients after surgery [4]. Therefore, identifying an accurate predictor of RCC recurrence or poor prognosis, will help improve individualized treatment for patients with RCC.

Inflammation is often the culprit in the development of various cancers [5]. The inflammatory environment promotes tumor progression by

facilitating cell proliferation, attenuating vascular barriers, and enhancing immune cell migration [6]. The neutrophil to lymphocyte ratio (NLR), a biological indicator of inflammation, has been reported to enhance the prognosis in both localized and metastatic renal cancer [7]. Similarly, elevated systemic immune-inflammation index (SII) and platelet-lymphocyte ratio (PLR) are associated with poor survival outcomes in patients with RCC [8, 9]. Tumor-related disorders of the coagulation system the development, progression, and metastasis of tumors and indicate poor prognosis. Fibrinogen is an important regulator of the coagulation system. It can predict well the recurrence-free survival of patients with RCC [10]. The preoperative fibrinogen-albumin ratio also improves postoperative prognosis in RCC [11]. The combination of plasma fibrinogen and neutrophil to lymphocyte ratio (F-NLR) score have been used as a new tumor prognostic marker to predict the prognosis of patients with gastric cancer [12], rectal cancer [13] and non-small cell lung cancer [14]. Compared to invasive tests, these hematological indicators are more accessible and demonstrate prognostic value in clinical individualized treatment. Therefore, it is crucial to find a biological marker that can effectively predict the prognosis of RCC patients undergoing laparoscopic nephrectomy. To our knowledge, the prognostic value of the F-NLR score in RCC patients undergoing laparoscopic nephrectomy is not backed by relevant clinical research. In addition, we compare F-NLR with existing predictive models such as, NLR, PLR, SII, and TNM stage, and the results indicate that F-NLR has a superior prognostic value.

In this study, we combined preoperative plasma fibrinogen level and NLR to establish a novel prognostic marker i.e., F-NLR, and further investigated its relationship with clinicopathological parameters, overall survival (OS) and cancer-specific survival (CSS). Finally, the clinical significance of F-NLR score in the prognosis for patients with RCC undergoing laparoscopic nephrectomy was evaluated by establishing a nomogram.

Patients and methods

Patients

The retrospective study included 590 patients with RCC who underwent laparoscopic nephrectomy at Zhongda Hospital Southeast University, Shanghai Tenth People's Hospital and Shidong Hospital between January 2014 and December 2019. This study complied with the criteria outlined in the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee and Institutional Review Board of all participating institutions (SHSY-IECKY-4.0/18-68/01 and ZDKYSB077). Signed informed consent was provided by all patients and their relatives who enrolled in this study.

The patient inclusion criteria were as follows: 1. age over 18 years; 2. pathologically diagnosed with RCC; 3. received laparoscopic nephrectomy. The exclusion criteria were as follows: 1. received other anticancer treatments prior to nephrectomy such as transcatheter arterial chemoembolization; 2. diagnosed with other malignancies that could seriously affect survival; 3. had incomplete medical records or follow-up data were missing. Based on the above criteria, 165 patients were excluded, and 425 patients were eventually included in this study.

Data collection and follow-up

All related clinicopathological data of all patients were reviewed and collected from the electronic medical records in Zhongda Hospital Southeast University, Shanghai Tenth People's Hospital and Shidong Hospital, including age, gender, body mass index [BMI, calculated by weight (kg)/height^2 (m^2)], hypertension, diabetes, cardiovascular disease, smoking, TNM stage, and Fuhrman grade. Relevant blood samples were preoperatively obtained and further analyzed. Patients who underwent nephrectomy and were discharged from the hospital were followed up on an outpatient basis or by telephone. Relevant hematological inflammatory indicators included NLR, PLR (ratio of platelets to lymphocytes), and systemic SII (ratio of platelets multiplied by neutrophil to lymphocytes ratio). The optimal cut-off values for fibrinogen, NLR, PLR, and SII were obtained using X-tile program (http://www.tissuearray.org/rimmlab/). According to the cut-off values, the F-NLR score was defined as follows: patients with neither hyperfibrinogenemia nor hyper-NLR were included in F-NLR 0 group; patients with either hyperfibrinogenemia or hyper-NLR were included in F-NLR 1 group and patients with both hyperfibrinogenemia and hyper-NLR

Table 1. Univariate analysis of Cox regression model of hematological predictors for overall survival (OS) and cancer-specific survival (CSS)

Factors	Overall Survival		Cancer-specific Survival	
	Unadjusted HR (95% CI)	*P* value	Unadjusted HR (95% CI)	*P* value
Preoperative fibrinogen	2.531 (1.469-4.359)	0.001	3.315 (1.688-6.511)	0.001
Preoperative NLR	2.284 (1.338-3.901)	0.002	2.715 (1.377-5.355)	0.004
Preoperative PLR	1.858 (0.908-3.802)	0.090	2.166 (0.838-5.598)	0.111
Preoperative SII	1.864 (1.089-3.191)	0.023	1.856 (0.942-3.657)	0.074

Abbreviations: OS, Overall survival; CSS, Cancer-specific survival; HR, Hazard ratio; CI, Confidence interval; NLR Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; SII, Systemic immune-inflammation index.

were included in F-NLR 2 group [13]. OS was defined as the time between the date of surgical treatment to the date of death or the last follow-up. CSS was defined as the time between the date of therapeutic resection to the date of death due to RCC.

Statistical analysis

All data were analyzed using SPSS software (version 24.0) and RStudio software (version 1.2.5033), and differences were considered statistically significant when $P < 0.05$.

The *chi-square* test or Fisher's exact test was used to analyze categorical variables, and Student's *t*-test was used to analyze continuous variables. The *chi-square* test or Kruskal-Wallis test was performed to assess the correlation between F-NLR score and clinicopathological characteristics. The effects of fibrinogen levels, NLR, and F-NLR on survival outcomes were evaluated using Kaplan-Meier curves and log-rank test to determine the differences. The time-dependent receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to compare the ability of fibrinogen levels, NLR, PLR, SII, and F-NLR score to predict OS and CSS. Univariate and multivariate Cox regression models were applied to evaluate the risk factors for OS and CSS. Multivariate Cox regression analysis was used to determine the relationship of fibrinogen level, NLR, and F-NLR score with OS and CSS by constructing three models and calculating the associated unadjusted hazard ratio (HR) and 95% confidence interval (CI). All independent prognostic factors were integrated to establish a predictive nomogram associated with OS and CSS using RStudio software. The predictive performance of the nomogram was evaluated by applying decision curve analysis (DCA) and ROC curve analysis. Bootstrap resampling and 10-fold cross-validation were used for internal and external verification of the nomogram. Harrell's concordance index (C-index) and calibration curve were used to evaluate the performance of the nomogram.

Results

Comparison of the prognostic value of preoperative fibrinogen and inflammation-related indicators

The prognostic value of fibrinogen, NLR, PLR and SII on OS and CSS was evaluated by univariate analysis of the Cox regression model. As the results in **Table 1** indicated, preoperative plasma fibrinogen level was significantly associated with OS (unadjusted HR = 2.531, 95% CI 1.469-4.359, $P = 0.001$) and CSS (unadjusted HR = 3.315, 95% CI 1.688-6.511, $P = 0.001$). Moreover, NLR was significantly correlated with OS (unadjusted HR = 2.284, 95% CI 1.338-3.901, $P = 0.002$, respectively) and CSS (unadjusted HR = 2.715, 95% CI 1.377-5.355, $P = 0.004$, respectively). Nevertheless, preoperative SII was independently associated with OS (unadjusted HR = 1.864, 95% CI 1.089-3.191, $P = 0.023$), but not CSS (unadjusted HR = 1.856, 95% CI 0.942-3.657, $P = 0.074$).

Correlations of preoperative fibrinogen, NLR and F-NLR score with clinicopathological characteristics

The average follow-up time among the patients included in this study was 32.71 months, with a 3-year average survival rate of 86.0% and a 5-year average survival rate of 81.6%. The optimal cut-off values of preoperative fibrinogen, NLR, PLR and SII were 4.3 g/L, 2.9, 99.3 and 657.4, respectively (Figure S1). Patients were

Table 2. Clinical characteristics of the patients according to preoperative fibrinogen and NLR

Characteristic	All patients	Fibrinogen		*P* value	NLR		*P* value
		Low group	High group		Low group	High group	
	N = 425	N = 326	N = 99		N = 273	N = 152	
Age categorized, y				0.314			0.640
≤ 65	305 (71.8)	230 (70.6)	75 (75.8)		198 (72.5)	107 (70.4)	
> 65	120 (28.2)	96 (29.4)	24 (24.2)		75 (27.5)	45 (29.6)	
Gender				0.154			0.759
Male	284 (66.8)	212 (65.0)	72 (72.7)		181 (66.3)	103 (67.8)	
Female	141 (33.2)	114 (35.0)	27 (27.3)		92 (33.7)	49 (32.2)	
BMI categorized, kg/m^2				0.027			0.320
< 25	238 (56.0)	173 (53.1)	65 (65.7)		148 (54.2)	90 (59.2)	
≥ 25	187 (44.0)	153 (46.9)	34 (34.3)		125 (45.8)	62 (40.8)	
Hypertension				0.501			0.973
No	240 (56.5)	187 (57.4)	53 (53.5)		154 (56.4)	86 (56.6)	
Yes	185 (43.5)	139 (42.6)	46 (46.5)		119 (43.6)	66 (43.4)	
Diabetes				0.830			0.792
No	355 (83.5)	273 (83.7)	82 (82.8)		229 (83.9)	126 (82.9)	
Yes	70 (16.5)	53 (16.3)	17 (17.2)		44 (16.1)	26 (17.1)	
Cardiovascular diseases				0.900			0.327
No	375 (88.2)	288 (88.3)	87 (87.8)		244 (89.4)	131 (86.2)	
Yes	50 (11.8)	38 (11.7)	12 (12.1)		29 (10.6)	21 (13.8)	
Smoking				0.047			0.869
No	354 (83.3)	278 (85.3)	76 (76.8)		228 (83.5)	126 (82.9)	
Yes	71 (16.7)	48 (14.7)	23 (23.2)		45 (16.5)	26 (17.1)	
T-stage				< 0.001			0.002
T1	323 (76.0)	259 (79.4)	64 (64.6)		222 (81.3)	101 (66.4)	
T2	27 (6.4)	15 (4.6)	12 (12.1)		17 (6.2)	10 (6.6)	
T3	64 (15.1)	41 (12.6)	23 (23.2)		28 (10.3)	36 (23.7)	
T4	11 (2.6)	11 (3.4)	0 (0.0)		6 (2.2)	5 (3.3)	
N-stage				0.303			0.826
N0	407 (95.8)	314 (96.3)	93 (93.9)		261 (95.6)	146 (96.1)	
N1	18 (4.2)	12 (3.7)	6 (6.1)		12 (4.4)	6 (3.9)	
M-stage				< 0.001			0.011
M0	408 (96.0)	320 (98.2)	88 (88.9)		267 (97.8)	141 (92.8)	
M1	17 (4.0)	6 (1.8)	11 (11.1)		6 (2.2)	11 (7.2)	
Fuhrman grade				0.001			0.030
I	69 (16.2)	59 (18.1)	10 (10.1)		52 (19.0)	17 (11.2)	
II	265 (62.4)	204 (62.6)	61 (61.6)		172 (63.0)	93 (61.2)	
III	81 (19.1)	60 (18.4)	21 (21.2)		45 (16.5)	36 (23.7)	
IV	10 (2.4)	3 (0.9)	7 (7.1)		4 (1.5)	6 (3.9)	

Abbreviations: NLR, Neutrophil-to-lymphocyte ratio; BMI, Body mass index; AJCC, American Joint Committee on Cancer.

then classified into high fibrinogen (> 4.3 g/L; n = 99) or low fibrinogen (≤ 4.3 g/L; n = 326) groups according to cut-off values. Moreover, patients were categorized into high NLR (> 2.9; n = 152) and low NLR (≤ 2.9; n = 273) groups. The correlations of preoperative fibrinogen and NLR with other clinicopathological characteristics are summarized in **Table 2**. The results indicate that a high fibrinogen level was related to elevated BMI level (P = 0.027), smoking (P = 0.047), more advanced T-stage (P < 0.001), M-stage (P < 0.001) and Fuhrman grade (P =

Table 3. Baseline characteristics of the patients according to F-NLR score in the training group

Characteristic	F-NLR score			*P* value
	0	1	2	
	N = 226	N = 147	N = 52	
Age, y				0.842
≤ 65	162 (71.7)	104 (70.7)	39 (75.0)	
> 65	64 (28.3)	43 (29.3)	13 (25.0)	
Gender				0.459
Male	145 (64.2)	103 (70.1)	36 (69.2)	
Female	81 (35.8)	44 (29.9)	16 (30.8)	
BMI categorized, kg/m^2				0.059
< 25	120 (53.1)	81 (55.1)	37 (71.2)	
≥ 25	106 (46.9)	66 (44.9)	15 (28.8)	
Hypertension				0.711
No	131 (58.0)	79 (53.7)	30 (57.7)	
Yes	95 (42.0)	68 (46.3)	22 (42.3)	
Diabetes				0.405
No	192 (85.0)	118 (80.3)	45 (86.5)	
Yes	34 (15.0)	29 (19.7)	7 (13.5)	
Cardiovascular diseases				0.196
No	204 (90.3)	124 (84.4)	47 (90.4)	
Yes	22 (9.7)	23 (15.6)	5 (9.6)	
Smoking				0.006
No	188 (83.2)	130 (88.4)	36 (69.2)	
Yes	38 (16.8)	17 (11.6)	16 (30.8)	
T-stage				< 0.001
T1	186 (82.3)	109 (74.1)	28 (53.8)	
T2	12 (5.3)	8 (5.4)	7 (13.5)	
T3	22 (9.7)	25 (17.0)	17 (32.70)	
T4	6 (2.7)	5 (3.4)	0 (0.0)	
N-stage				0.665
N0	218 (96.5)	139 (94.6)	50 (96.2)	
N1	8 (3.5)	8 (5.4)	2 (3.8)	
M-stage				< 0.001
M0	225 (99.4)	137 (93.20)	46 (88.5)	
M1	1 (0.4)	10 (6.8)	6 (11.5)	
Fuhrman grade				0.002
I	45 (19.9)	21 (14.3)	3 (5.8)	
II	140 (61.9)	96 (65.3)	29 (55.8)	
III	40 (17.7)	25 (17.0)	16 (30.8)	
IV	1 (0.4)	5 (3.4)	4 (7.7)	

Abbreviations: F-NLR score, Fibrinogen and neutrophil-to-lymphocyte ratio; BMI, Body mass index; AJCC, American Joint Committee on Cancer.

0.001). Similarly, patients with an elevated NLR level were associated with more advanced T-stage (P = 0.002), M-stage (P = 0.011) and Fuhrman grade (P = 0.030).

Based on the above F-NLR scoring criteria, patients were categorized into F-NLR 0 group (53.2%; n = 226), F-NLR 1 group (34.6%; n = 147) and F-NLR 2 group (12.2%; n = 52). We found that, higher F-NLR score was correlated with advanced T-stage ($P < 0.001$), M-stage ($P < 0.001$) and Fuhrman grade ($P = 0.002$). However, other clinicopathological characteristics were not significantly related to F-NLR score (all $P > 0.05$). All complete data results are presented in **Table 3**.

Prognostic impact of preoperative fibrinogen, NLR and F-NLR score on survival outcomes

As shown in **Figure 1**, the Kaplan-Meier survival curves were utilized to evaluate the prognostic impact of preoperative fibrinogen, NLR and F-NLR score on survival outcomes. Low fibrinogen (> 4.3 g/L) and NLR levels (> 2.9) were both significantly correlated with improved OS ($P < 0.001$ for both; **Figure 1A**, **1C**) and CSS ($P < 0.001$ for both; **Figure 1B**, **1D**). Furthermore, the F-NLR 0 group had better OS and CSS than the F-NLR 1 and F-NLR 2 groups. However, there was no significant difference between F-NLR 1 group and F-NLR 2 group in terms of OS and CSS (all $P < 0.001$ **Figure 1E**, **1F**). Therefore, elevated expression of either fibrinogen or NLR, either of the two, predicts terrible OS and CSS.

Subsequently, the prognostic value of the above factors was further evaluated by ROC analysis. The AUC of F-NLR score was larger than that of fibrinogen, NLR, PLR and SII, both in terms of OS and CSS (**Figure 2**). Thus, the prognostic value of F-NLR score was superior to that of other indicators and provided a

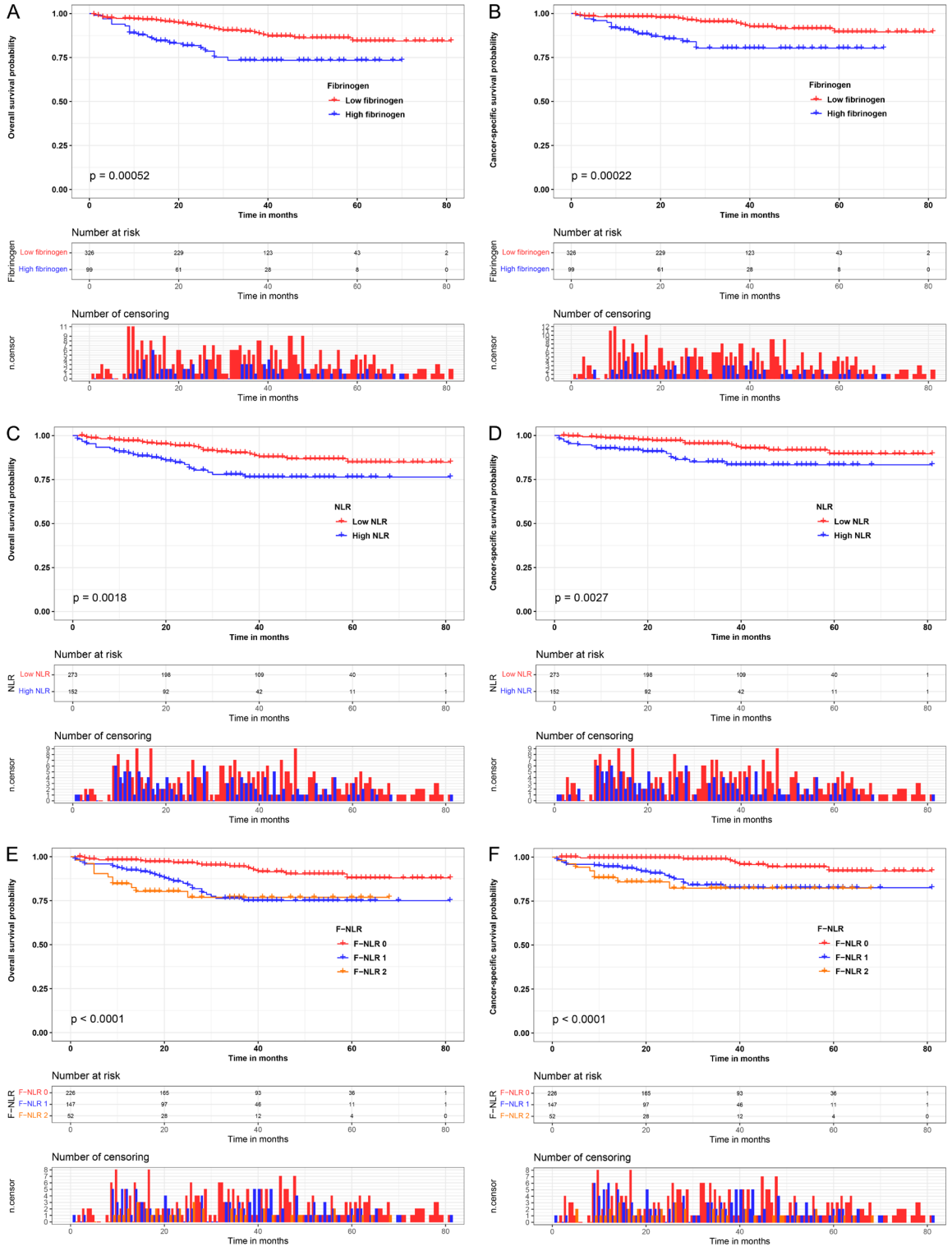

Figure 1. Kaplan-Meier curves for overall survival (OS) and cancer-specific survival (CSS) in patients with renal cell carcinoma (RCC) after laparoscopic nephrectomy stratified based on preoperative fibrinogen level (A, B), neutrophil-to-lymphocyte ratio (NLR) (C, D) and F-NLR score (E, F).

better prediction of OS (AUC: 0.649, 95% CI: 0.629-0.778) and CSS (AUC: 0.684; 95% CI: 0.596-0.772) in patients with RCC undergoing laparoscopic nephrectomy (**Table 4**).

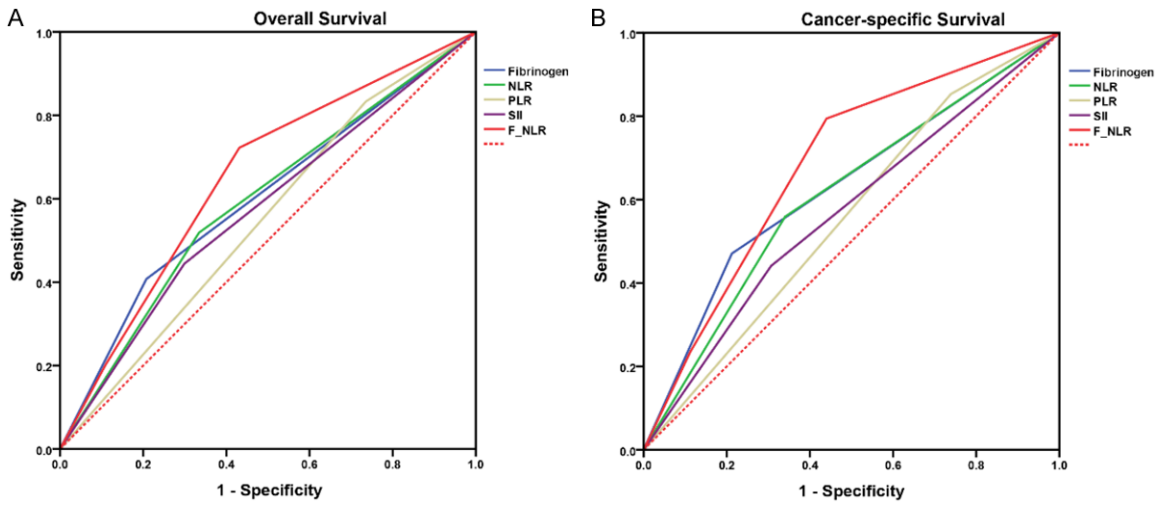

Figure 2. Receiver operating characteristic (ROC) curves for the predictive ability of F-NLR score compared to fibrinogen, neutrophil-to-lymphocyte ratio (NLR), platelets to lymphocytes ratio (PLR) and systemic immune-inflammation index (SII) for overall survival (OS) (A) and cancer-specific survival (CSS) (B) in patients with renal cell carcinoma (RCC) after laparoscopic nephrectomy.

Table 4. Analysis of predictive accuracy through the evaluation of the area under the curve (AUC)

	Overall Survival			Cancer-specific Survival		
	AUC	95% CI	*P* value	AUC	95% CI	*P* value
Fibrinogen	0.600	0.514-0.685	0.018	0.629	0.524-0.734	0.012
NLR	0.592	0.509-0.675	0.029	0.609	0.509-0.710	0.034
PLR	0.549	0.470-0.627	0.247	0.557	0.462-0.652	0.271
SII	0.573	0.489-0.657	0.084	0.567	0.464-0.670	0.194
F-NLR score	0.649	0.573-0.726	< 0.001	0.684	0.596-0.772	< 0.001

Abbreviations: AUC, Area under the curve; CI, Confidence interval; OS, Overall survival; CSS, Cancer-specific survival; NLR Neutrophil-to-lymphocyte ratio; PLR Platelet-to-lymphocyte ratio; SII, Systemic immune-inflammation index; F-NLR score, Fibrinogen and neutrophil-to-lymphocyte ratio.

Independent prognostic factors for OS and CSS

Univariate analysis demonstrated that T-stage, N-stage, M-stage, Fuhrman grade, fibrinogen, SII, and F-NLR score were significantly associated with OS and CSS (**Tables 5** and **6**). The above parameters were then subjected to multivariate Cox regression analysis to assess the correlation with OS and CSS. The results of univariate analysis revealed that T-stage, N-stage, M-stage and F-NLR score (F-NLR 1 group: HR = 2.232, 95% CI: 1.142-4.362, *P* = 0.019; F-NLR 2 group: HR = 3.103, 95% CI: 1.359-7.081, *P* = 0.007) were independent prognostic factors for OS in patients with RCC undergoing laparoscopic nephrectomy (**Table 5**). Nevertheless, T-stage, M-stage and F-NLR score were considered as independent risk factors for CSS (F-NLR 1 group: HR = 3.465, 95% CI: 1.383-8.682, *P* = 0.008; F-NLR 2 group: HR = 4.572, 95% CI: 1.536-13.607, *P* = 0.006), and the other variables did not exhibit significant results (**Table 6**).

Establishment and validation of predictive nomograms-based F-NLR score

Based on the results of Cox regression analyses, nomograms predicting 3-year and 5-year OS (**Figure 3**) and CSS (**Figure 4**) in RCC patients undergoing laparoscopic nephrectomy were established. To verify whether there is a better prediction performance of nomograms compared with traditional TNM staging system, we created a nomogram of the traditional TNM staging system without the F-NLR score predicting 3-year, 5-year OS (Figure S2) and CSS

Table 5. Univariate and multivariate analyses of factors associated with overall survival (OS)

Characteristics	Univariate analyses		Multivariate analyses	
	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Age, y				
≤ 65	Reference			
> 65	1.563 (0.904-2.702)	0.110		
Gender				
Male	Reference			
Female	1.101 (0.630-1.925)	0.736		
BMI categorized, kg/m^2				
< 25	Reference			
≥ 25	0.530 (0.295-0.951)	0.033		
Hypertension				
No	Reference			
Yes	1.026 (0.598-1.760)	0.926		
Diabetes				
No	Reference			
Yes	0.769 (0.347-1.701)	0.516		
Cardiovascular diseases				
No	Reference			
Yes	1.080 (0.488-2.391)	0.849		
Smoking				
No	Reference			
Yes	1.130 (0.568-2.245)	0.728		
T-stage				
T1	Reference		Reference	
T2	1.984 (0.686-5.741)	0.206	1.616 (0.548-4.763)	0.384
T3	5.774 (3.234-10.309)	< 0.001	2.722 (1.336-5.548)	0.006
T4	4.733 (1.634-13.708)	0.004	2.804 (0.912-8.625)	0.072
N-stage				
N0	Reference		Reference	
N1	5.018 (2.451-10.273)	< 0.001	2.424 (1.110-5.296)	0.026
M-stage				
M0	Reference		Reference	
M1	13.522 (7.281-25.115)	< 0.001	4.275 (1.978-9.241)	< 0.001
Fuhrman grade				
I	Reference		Reference	
II	1.718 (0.662-4.456)	0.266	-	0.778
III	3.421 (1.250-9.361)	0.017	-	0.863
IV	16.906 (4.781-59.776)	< 0.001	-	0.087
Fibrinogen				
Low group	Reference		Reference	
High group	2.531 (1.469-4.359)	0.001	-	0.945
NLR				
Low group	Reference		Reference	
High group	2.284 (1.338-3.901)	0.002	-	0.945
PLR				
Low group	Reference			
High group	1.858 (0.908-.3802)	0.090		

SII				
Low group	Reference		Reference	
High group	1.864 (1.089-3.191)	0.023	-	0.947
F-NLR score				
0	Reference		Reference	
1	3.232 (1.724-6.058)	< 0.001	2.232 (1.142-4.362)	0.019
2	4.085 (1.872-8.914)	< 0.001	3.103 (1.359-7.081)	0.007

Abbreviations: OS, Overall survival; CSS, Cancer-specific survival; CI, Confidence interval; BMI, Body mass index; AJCC, American Joint Committee on Cancer; SII, Systemic immune-inflammation index; F-NLR score, Fibrinogen and neutrophil-to-lymphocyte ratio.

Table 6. Univariate and multivariate analyses of factors associated with cancer-specific survival (CSS)

Characteristics	Univariate analyses		Multivariate analyses	
	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Age, y				
≤ 65	Reference			
> 65	1.346 (0.666-2.720)	0.408		
Gender				
Male	Reference			
Female	0.840 (0.401-1.757)	0.643		
BMI categorized, kg/m^2				
< 25	Reference			
≥ 25	0.607 (0.296-1.246)	0.174		
Hypertension				
No	Reference			
Yes	1.771 (0.899-3.490)	0.098		
Diabetes				
No	Reference			
Yes	0.892 (0.345-2.305)	0.814		
Cardiovascular diseases				
No	Reference			
Yes	0.708 (0.216-2.316)	0.568		
Smoking				
No	Reference			
Yes	1.280 (0.557-2.940)	0.561		
T-stage				
T1	Reference		Reference	
T2	4.045 (1.286-12.721)	0.017	3.700 (1.168-11.717)	0.023
T3	8.022 (3.675-17.513)	< 0.001	3.229 (1.247-8.364)	< 0.001
T4	9.712 (3.083-30.595)	< 0.001	5.172 (1.434-18.652)	< 0.001
N-stage				
N0	Reference		Reference	
N1	5.451 (2.254-13.184)	< 0.001	-	0.080
M-stage				
M0	Reference		Reference	
M1	21.375 (10.384-44.002)	< 0.001	6.835 (2.726-17.135)	< 0.001
Fuhrman grade				
I	Reference		Reference	
II	2.541 (0.583-11.078)	0.214	-	0.230
III	6.648 (1.483-29.798)	0.013	-	0.477

IV	37.021 (6.535-209.745)	< 0.001	-	0.837
Fibrinogen				
Low group	Reference		Reference	
High group	3.315 (1.688-6.511)	0.001	-	0.445
NLR				
Low group	Reference		Reference	
High group	2.715 (1.377-5.355)	0.004	-	0.445-
PLR				
Low group	Reference			
High group	2.166 (0.838-5.598)	0.111		
SII				
Low group	Reference			
High group	1.856 (0.942-3.657)	0.074		
F-NLR score				
0	Reference		Reference	
1	4.762 (1.998-11.348)	< 0.001	3.465 (1.383-8.682)	0.008
2	6.506 (2.351-18.004)	< 0.001	4.572 (1.536-13.607)	0.006

Abbreviations: OS, Overall survival; CSS, Cancer-specific survival; CI, Confidence interval; BMI, Body mass index; AJCC, American Joint Committee on Cancer; SII, Systemic immune-inflammation index; F-NLR score, Fibrinogen and neutrophil-to-lymphocyte ratio.

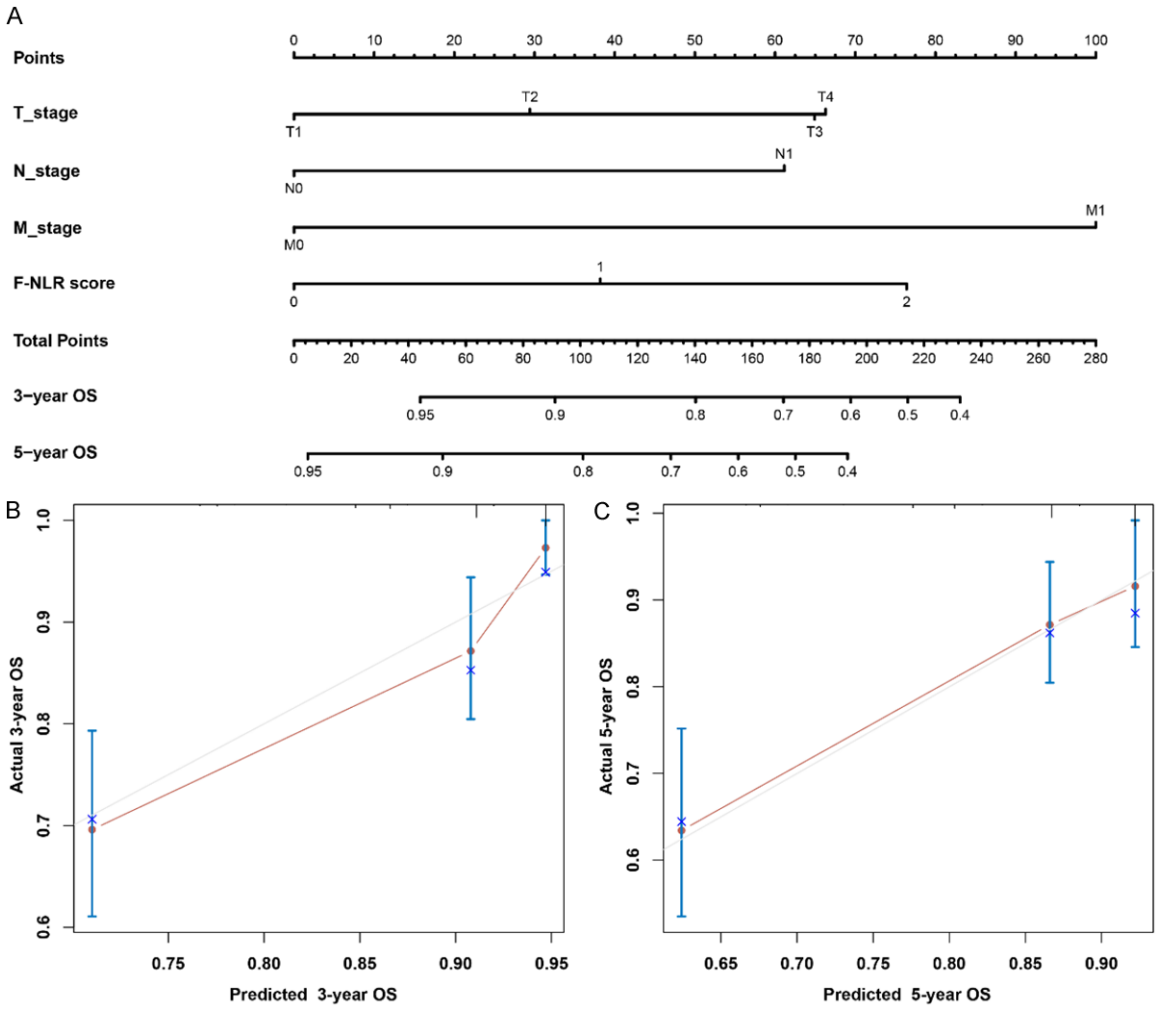

Figure 3. Nomogram for predicting the 3-year and 5-year overall survival (OS) in patients with renal cell carcinoma (RCC) after laparoscopic nephrectomy (A). Calibration curves for 3-year (B) and 5-year (C) OS for internal validation.

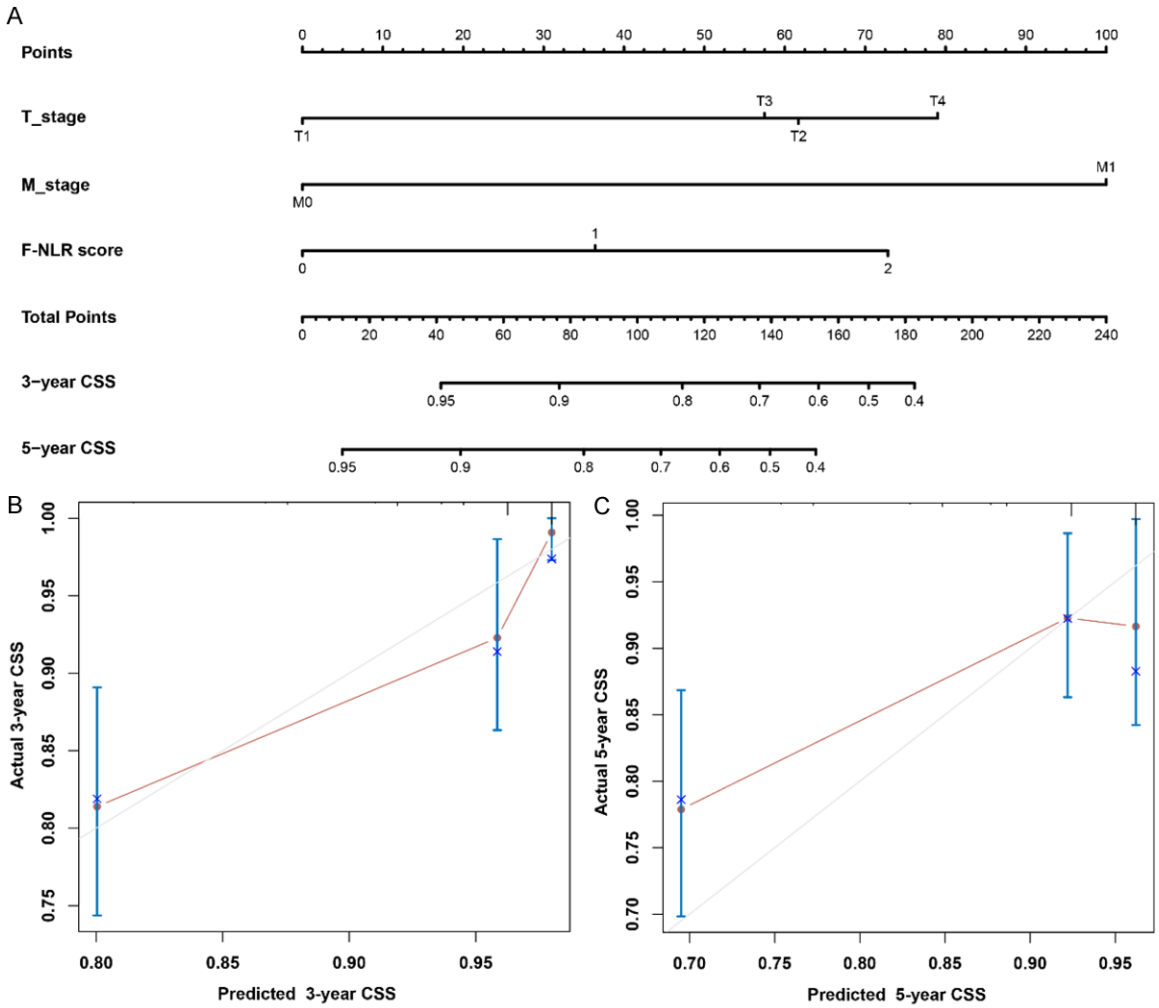

Figure 4. Nomogram for predicting the 3-year and 5-year cancer-specific survival (CSS) in patients with renal cell carcinoma (RCC) after laparoscopic nephrectomy (A). Calibration curves for 3-year (B) and 5-year (C) CSS for internal validation.

(Figure S3). The C-index of the nomogram integrating F-NLR score was 0.773 (95% CI: 0.708-0.838) for OS and 0.838 (95% CI: 0.771-0.905) for CSS to internally validate the performance. The C-index of the nomogram without the F-NLR score was 0.729 (95% CI: 0.657-0.801) for OS and 0.810 (95% CI: 0.730-0.890) for CSS, which were worse than those for the nomogram integrating F-NLR score. Calibration curves for 3-year and 5-year OS and CSS demonstrated considerable agreement between OS (**Figure 3B**, **3C**) and CSS (**Figure 4B**, **4C**) predicted by the nomograms and the actual probabilities of OS (Figure S2B, S2C) and CSS (Figure S3B, S3C), indicating that the nomograms were well-calibrated. We then compared the F-NLR score with other prediction models, including NLR, SII, PLR and fibrinogen (**Figure 5**). The ROC curves for OS and CSS showed that the AUC of the F-NLR score nomogram was 0.819 and 0.789, respectively, higher than those for other prediction models, indicating that the nomogram could more accurately predict the prognosis for patients with RCC undergoing laparoscopic nephrectomy. The AUCs of the 3-year OS and 5-year OS nomograms were 0.808 and 0.781, respectively, and the AUCs of the 3-year CSS and 5-year CSS nomograms were 0.855

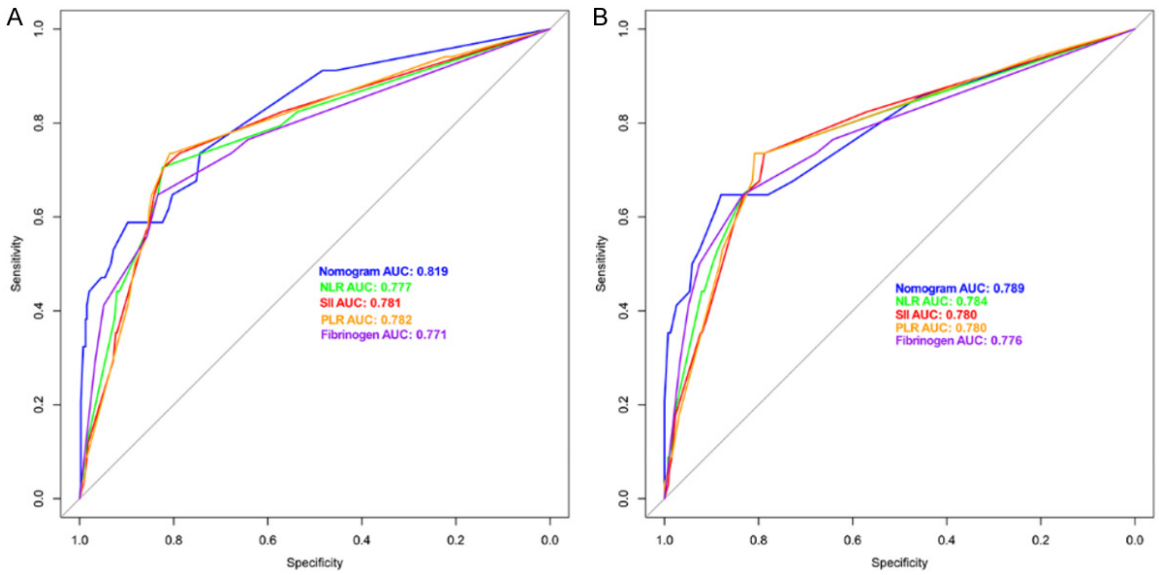

Figure 5. Time-dependent receiver operating characteristic curves of fibrinogen, neutrophil-to-lymphocyte ratio (NLR), and nomogram for overall survival (OS) (A) and cancer-specific survival (CSS) (B) in patients with renal cell carcinoma (RCC) undergoing laparoscopic nephrectomy.

and 0.721, respectively, suggesting that the nomograms could accurately predict the 3-year and 5-year OS and CSS in patients with RCC undergoing laparoscopic nephrectomy (**Figure 6A**, **6B**). The DCA curves demonstrated that the 3-year and 5-year OS and CSS predicted by the nomogram had excellent calibration results (**Figure 6C**, **6D**). Time-dependent AUC curves demonstrated that the nomograms were superior to NLR and fibrinogen over a broad time period, indicating that the nomograms were preferable to other blood indicators in predicting OS and CSS in RCC patients undergoing laparoscopic nephrectomy (**Figure 7**).

Discussion

In this study, the prognostic significance of preoperative fibrinogen and inflammation-related indicators, including NLR, PLR, and SII, was retrospectively investigated in patients with RCC undergoing laparoscopic nephrectomy. Based on preoperative fibrinogen and NLR, we constructed a novel index (F-NLR score) and developed nomograms to evaluate its ability to predict OS and CSS. F-NLR score was found to be an objective and accessible prognostic indicator of OS and CSS compared to the conventional TNM staging system. Hence, we can use the F-NLR score to accurately predict the prognosis of patients with RCC undergoing laparoscopic nephrectomy for achieving precise treatment outcomes.

As a multifunctional protein, fibrinogen was essential for the coagulation cascade and played an important role in tumorigenesis and metastasis [15]. Fibrinogen levels would increase to different degrees in response to various pathophysiological conditions in the body, including infection, inflammation, and cancers [16]. Fibrinogen can promote the metastasis of malignant tumors by stabilizing adhesion between cancer cells, endothelial cells, and platelets and impeding natural killer cells from eliminating cancer cells [16, 17]. In addition, it promoted tumor development and angiogenesis by interacting with fibroblast growth factor-2 and vascular endothelial growth factor [18]. Previous studies have confirmed that high fibrinogen levels were associated with poor prognosis for different malignancies [19], consistent with the results of this study. A high preoperative level of fibrinogen in RCC patients undergoing laparoscopic nephrectomy was significantly associated with poor clinical prognosis.

Systemic inflammation can lead to tumor development and promote various stages of tumorigenesis, providing us with a new approach to predict the prognosis for patients with RCC

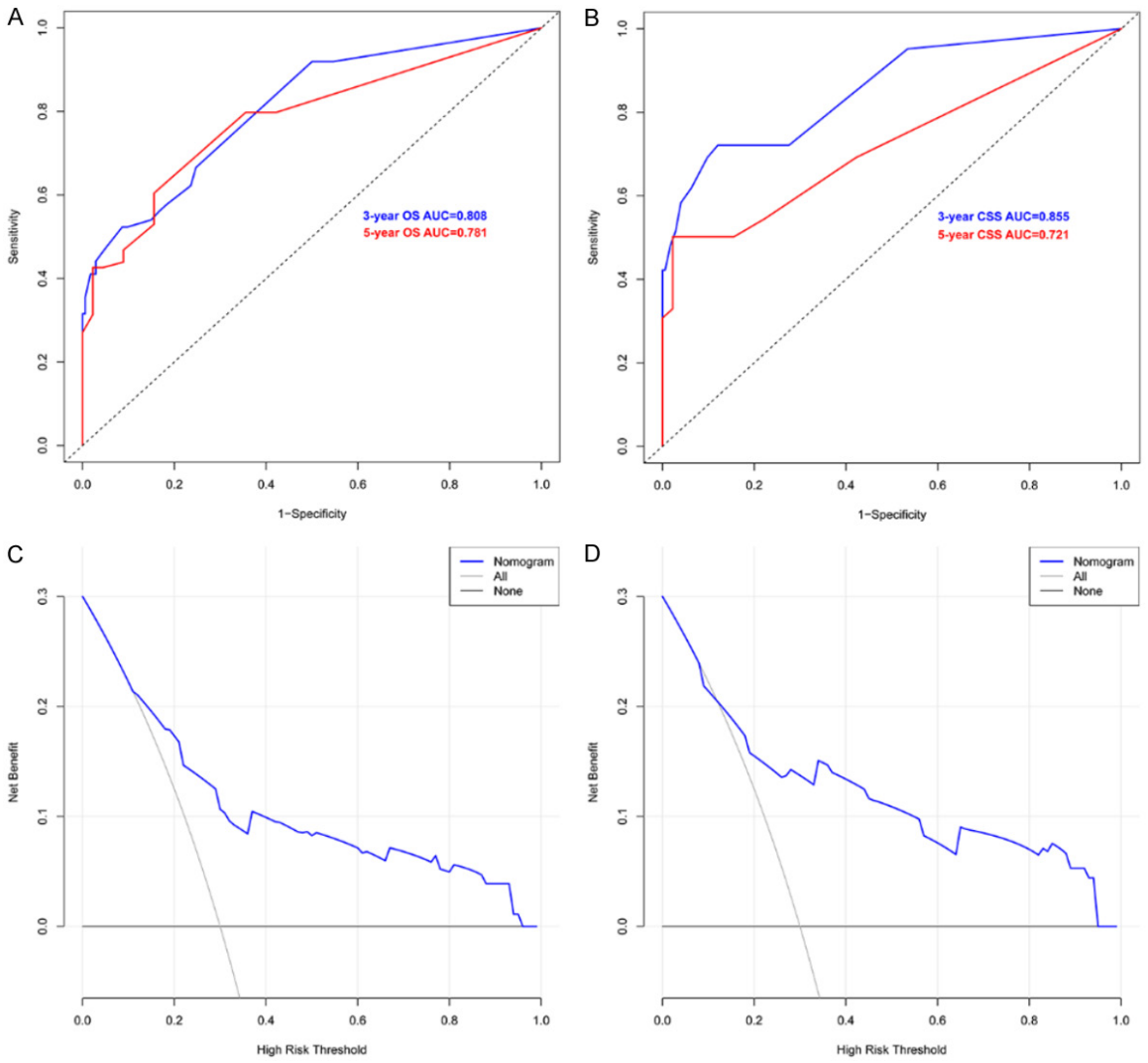

Figure 6. Receiver operating characteristic (ROC) curve analysis of the prognostic accuracy of nomograms for 3-year and 5- year overall survival (OS) (A) and 3-year and 5-year cancer-specific survival (CSS) (B) in patients with renal cell carcinoma (RCC) undergoing laparoscopic nephrectomy. Decision curve analysis (DCA) of nomogram for survival benefit in terms of OS (C) and CSS (D) in patients with renal cell carcinoma (RCC) undergoing laparoscopic nephrectomy.

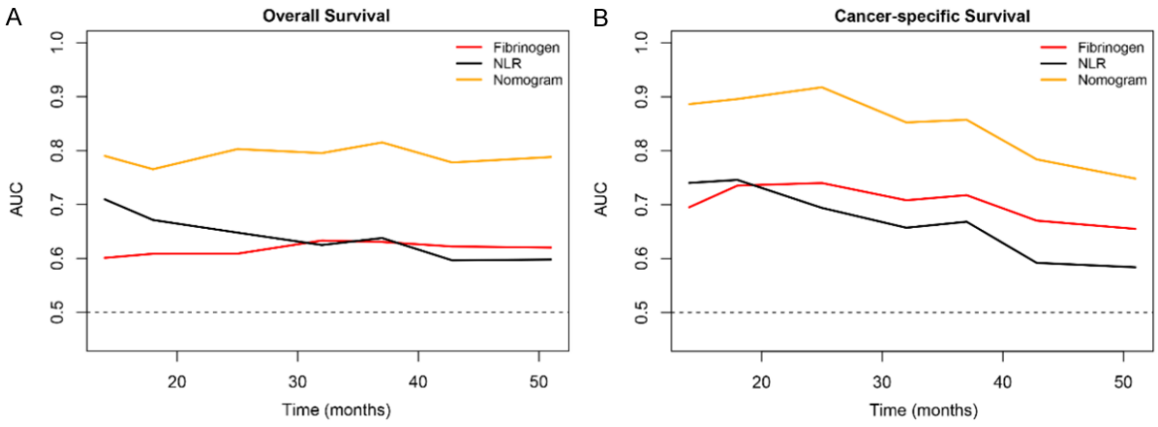

Figure 7. Receiver operating characteristic (ROC) curve analysis of the nomogram, NLR, SII, PLR, and fibrinogen for predicting overall survival (OS) in patients with renal cell carcinoma (RCC) undergoing laparoscopic nephrectomy (A). Nomogram and ROC analysis of NLR, SII, PLR, and fibrinogen for cancer-specific survival (CSS) in patients with RCC undergoing laparoscopic nephrectomy (B).

undergoing laparoscopic nephrectomy [20]. Local inflammation mainly induces immune responses in the tumor microenvironment, while systemic inflammation causes paraneoplastic symptoms by increasing the production of inflammatory mediators such as cytokines in the blood [21]. Tumors can also cause inflammatory changes in hematological indicators such as lymphocytes, monocytes and hemoglobin [22]. While details of the relationship between systemic inflammation and tumors are unclear, it is worthy of further research. NLR, as an important blood indicator of systemic inflammatory status, has been demonstrated to be correlated with recurrence and poor prognosis in various malignancies [23]. Our univariate analysis indicated that NLR was associated with OS and CSS in patients with RCC undergoing laparoscopic nephrectomy.

In recent years, increasing studies revealed that the interaction between coagulation and inflammation can promote the progression of malignancies [24]. Therefore, reducing the fibrinogen level and establishing validated therapies can reduce the probability of cancer development and avoid cancer-related death [25, 26]. The F-NLR score can serve as a reliable prognostic biomarker for non-small cell lung cancer [14], gastric cancer [27], and epithelial ovarian cancer [28].

Nomograms are extremely effective for predicting the survival of patients with cancer [29]. In the present study, F-NLR score, as a new prognostic indicator combining coagulation and inflammation indicators, could effectively predict the prognosis for patients with RCC after laparoscopic nephrectomy. Time-dependent ROC analysis indicated that F-NLR is more accurate than NLR and fibrinogen in separately predicting the prognosis of RCC patients undergoing laparoscopic nephrectomy. It is worth noting that the nomogram of F-NLR score could better predict OS and CSS than the traditional TNM staging. Therefore, the F-NLR score can be used as a noninvasive and reproducible prognostic indicator for RCC patients treated with laparoscopic nephrectomy due to its excellent prognostic value.

Nevertheless, there are several limitations in this study. First, this was a retrospective study with a small sample size, and selection bias cannot be ruled out. Second, although every effort was made to control for potential confounding factors, it is barely possible to control for other comorbidities or medical effects due to drug treatment, which could affect the biomarker values. Third, external validation using data from an additional medical center is required prior to using the F-NLR score nomograms. Considering these limitations, further large-scale prospective studies are required to validate our conclusions.

Conclusion

The F-NLR score, a novel prognostic indicator combining coagulation and inflammatory systems, has been demonstrated as a potential predictor of the prognosis for patients with RCC undergoing laparoscopic nephrectomy. The predictive nomograms based on the F-NLR score were more accurate and reliable in evaluating the risk stratification and prognosis for patients with RCC than the traditional TNM staging system. This score will assist urologists in clinical decision-making and developing rational and personalized treatment plans.

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Disclosure of conflict of interest

None.

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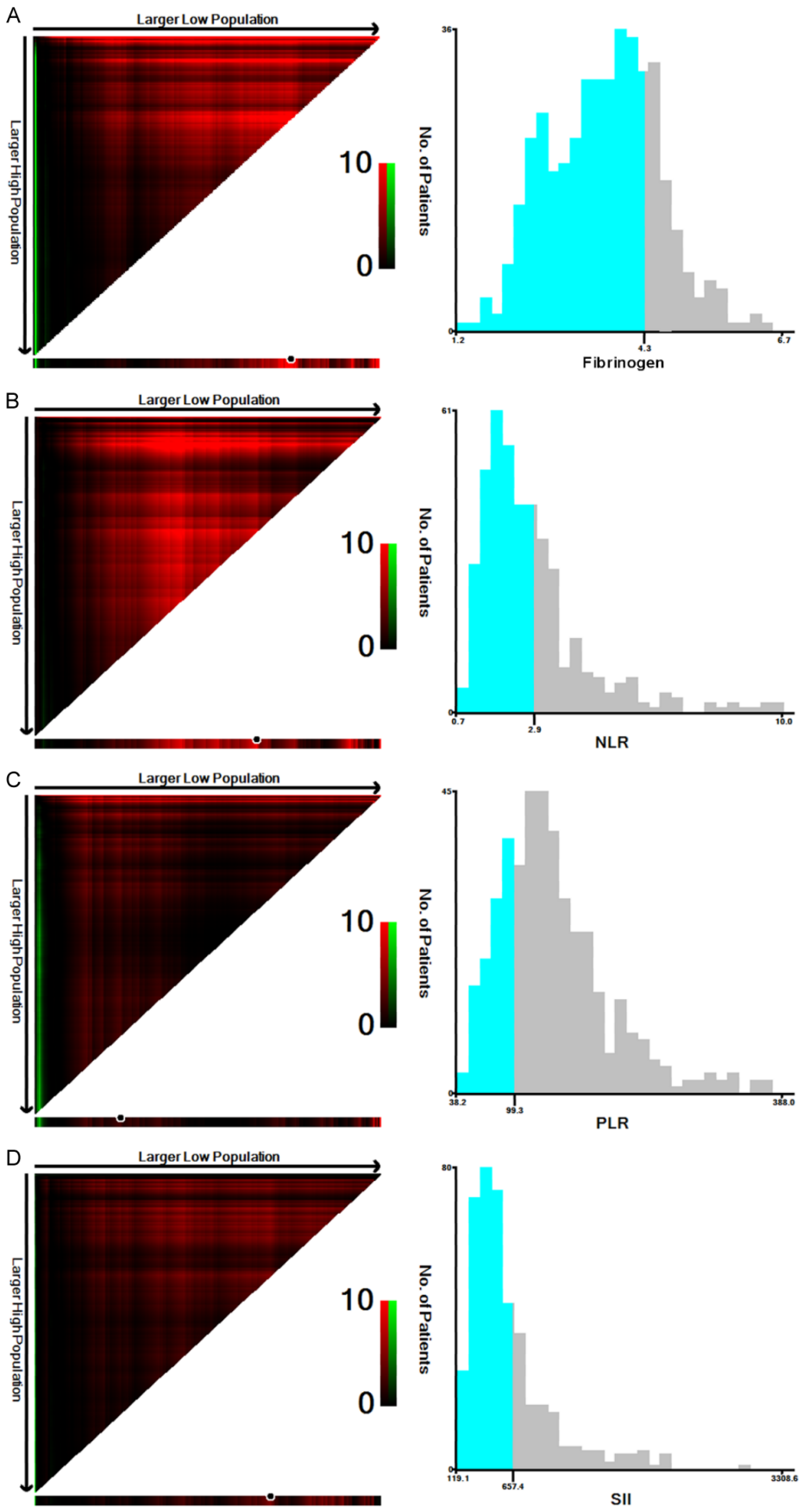
A
Larger Low Population
Larger High Population
10
0
No. of Patients
36
0
1.2
4.3
6.7
Fibrinogen
B
Larger Low Population
Larger High Population
10
0
No. of Patients
61
0
0.7
2.9
10.0
NLR
C
Larger Low Population
Larger High Population
10
0
No. of Patients
45
0
38.2
99.3
388.0
PLR
D
Larger Low Population
Larger High Population
10
0
No. of Patients
80
0
119.1
657.4
3308.6
SII

Figure S1. Optimal cut-off values for fibrinogen (A), neutrophil-to-lymphocyte ratio (NLR) (B), platelet-to-lymphocyte ratio (PLR) (C), and systemic immune inflammatory index (SII) (D) were determined based on receiver operating characteristic (ROC) analysis with the X-tile program.

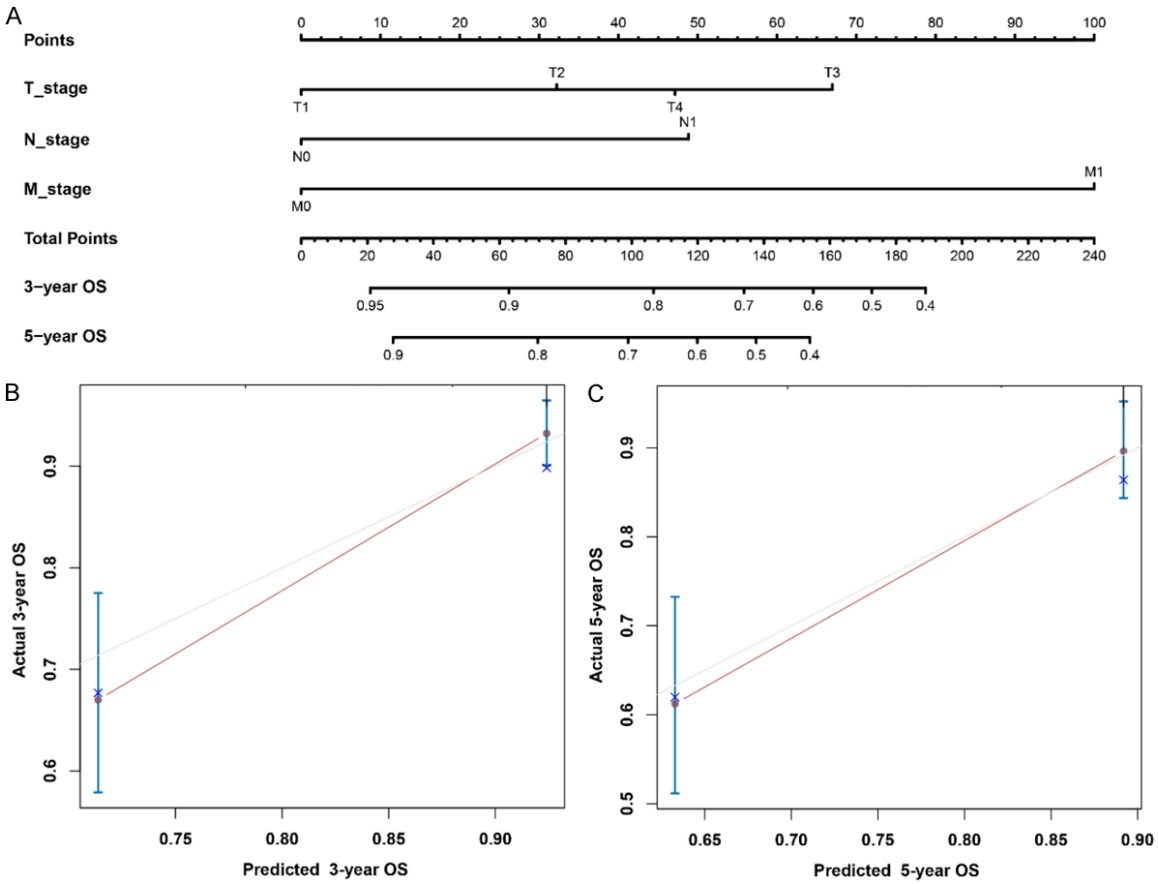

Figure S2. A nomogram of the traditional TNM staging system without the F-NLR score for predicting the 3-year and 5-year overall survival (OS) in patients with renal cell carcinoma (RCC) after laparoscopic nephrectomy (A). Calibration curves for 3-year (B) and 5-year (C) OS for internal validation.

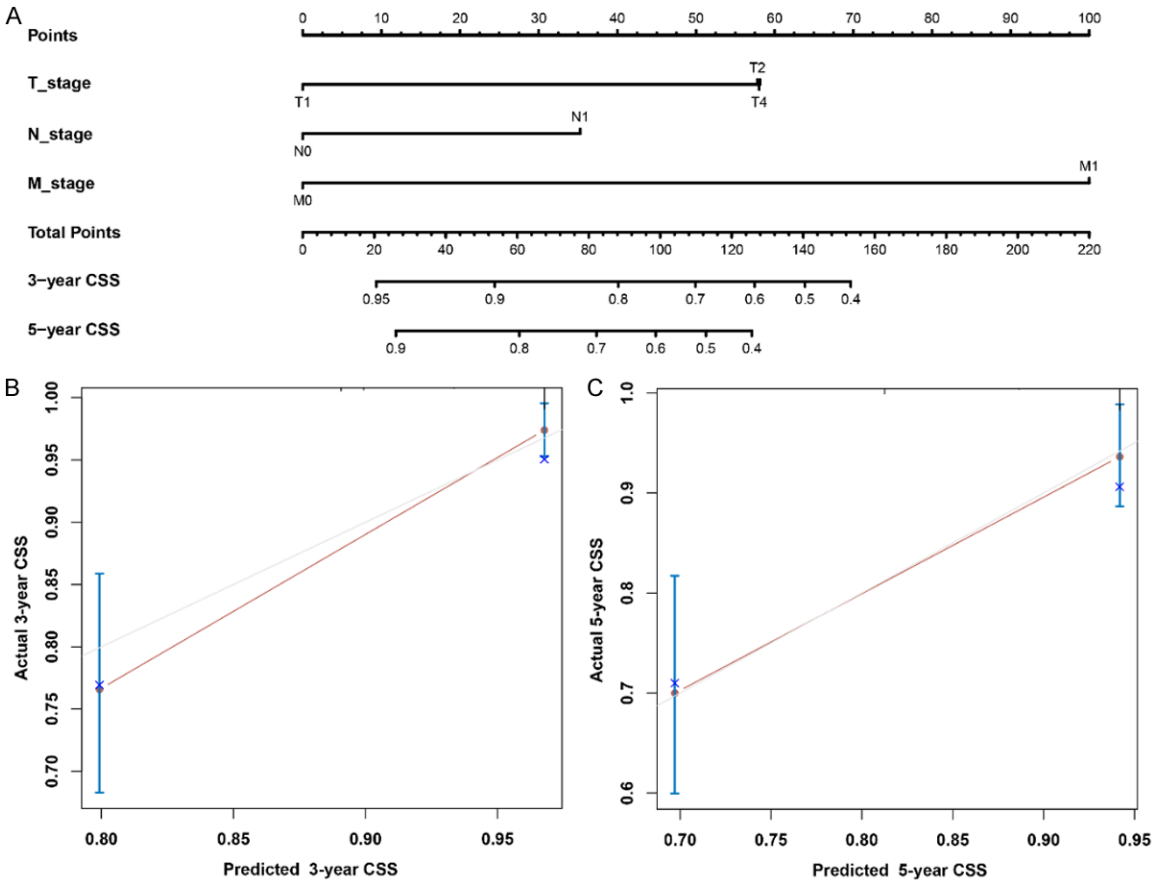

Figure S3. A nomogram of the traditional TNM staging system without the F-NLR score for predicting the 3-year and 5-year cancer-specific survival (CSS) in patients with renal cell carcinoma (RCC) after laparoscopic nephrectomy (A). Calibration curves for 3-year (B) and 5-year (C) CSS for internal validation.