Original Article

The predictive value of the preoperative fibrinogen-albumin ratio on the postoperative prognosis of renal cell carcinoma

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Background: Urologists urgently need a simple, effective, accurate clinical biomarker to identify renal cell carcinoma (RCC) patients with poor prognosis and those with a high risk of recurrence as early as possible. Therefore, we investigated the prognostic value of the preoperative fibrinogen-albumin ratio (FAR) in patients with RCC.

Methods: We retrospectively analyzed data from 279 cases of renal cancer admitted to the First Hospital of Peking University from 2010 to 2012. The best cutoff value of the FAR was obtained using receiver operating characteristic (ROC) curve analysis, and patients were divided into high- and low-FAR groups. The correlation between the preoperative FAR and clinicopathological features was analyzed by χ^2 test. Log-rank test and Cox proportional hazard regression model were used to evaluate the predictive value of clinicopathological parameters for overall survival (OS).

Results: The best cutoff value for the FAR was 0.116. A FAR >0.116 was associated with higher Fuhrman grade (P<0.0001) and later pathological T stage (P<0.0001). Patients with a high FAR (>0.116) had worse OS [hazard ratio (HR) 10.497, 95% confidence interval (CI): 3.263–33.766, P<0.0001]. In multivariate analysis, the FAR was an independent risk factor for OS (HR 5.047, 95% CI: 2.109–12.076, P=0.003). Moreover, in Fuhrman grade I–II patients, the FAR could distinguish patients with worse prognosis (P<0.0001).

Conclusions: The preoperative FAR is an independent prognostic factor of OS in renal cancer patients. A FAR >0.116 was significantly related to decreased survival in renal cancer patients.

Keywords: Albumins; biomarkers; fibrinogen; renal cell carcinoma (RCC); prognosis

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Introduction

Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urinary system, and it is the 6th most common cancer in men and the 10th in women. RCC accounts for 5% of all tumors in men and 3% of all tumors in women (1). Although most patients are diagnosed at early stages, a considerable proportion of renal cancer is only diagnosed in the local advanced stage, and 17% of patients have distant metastasis at the time of diagnosis (2). In recent years, due to the great progress of anti-angiogenic drugs and immunotherapy (3,4), many patients with advanced renal cancer have achieved good therapeutic effect, which has changed the natural course of renal cancer. Therefore,

urologists urgently need a simple, effective, accurate clinical biomarker to screen out patients with poor prognosis and identify patients with a high risk of recurrence and poor prognosis as early as possible. Identifying such a biomarker can also provide accurate clinical decision-making and active follow-up monitoring.

Fibrinogen is a kind of glycoprotein that is mainly produced in the liver and secreted into the serum. A number of recent epidemiological studies have shown that fibrinogen not only participates in coagulation but also plays a role in the occurrence and development of tumors. Previous studies have shown that an increase in preoperative fibrinogen is associated with the progression and poor prognosis of malignant tumors (5,6). In addition, hypoproteinemia has been found to be associated with poor prognosis in a variety of cancers, including lung cancer, gastric cancer, and colon cancer (7-9). The fibrinogen-albumin ratio (FAR), as well as fibrinogen and albumin as single factors, are related to poor prognosis in esophageal cancer, liver cancer, and other tumors (10,11). Therefore, we assume that the FAR has potential value in evaluating the prognosis of patients with nonmetastatic renal cancer. The purpose of this study was to evaluate the prognostic value of the preoperative FAR in patients with renal cancer after resection and to compare it with established systemic inflammatory immune biomarkers, including the neutrophil-lymphocyte ratio (NLR), prognostic nutrition index (PNI), and controlling nutritional status (CONUT) score.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tau-19-873).

Methods

Patients

From 2010 to 2012, 279 patients with renal cancer who underwent radical nephrectomy or partial nephrectomy were collected from the Urology Department of Peking University First Hospital. All cases were confirmed by postoperative pathology. All patients had no history of other types of malignant tumor, no lymph node metastasis or distant metastasis, no thrombotic disease, and no history of anticoagulation treatment. The clinicopathological data were obtained from the patient's electronic medical record, and the pathological and clinical data of all cases were complete. During the follow-up of this study, the patients or their relatives were informed about the content of this study in detail and got their oral consent. The study was approved by the central ethics committee of our hospital.

Clinical data and peripheral blood biomarkers

In all patients included in the study, serum fibrinogen, albumin, neutrophil count, lymphocyte count, and serum total cholesterol level were measured within 1 week before operation. Other factors were calculated as follows: FAR = total fibrinogen/total albumin, NLR = absolute neutrophil count/absolute lymphocyte count, and PNI = albumin (g/dL) + 5 × absolute lymphocyte count (10^9/L). The CONUT score was calculated as described previously (12,13).

Follow-up

The patients were followed up every 3 months in the first 2 years and every 6 months thereafter. Patients were followed up by blood examination, biochemical tests, chest radiography, and abdominal ultrasound/abdominal CT. The follow-up methods included telephone follow-up and outpatient follow-up.

Statistical analysis

The end point of this study was overall survival (OS). OS was defined as the time from the operation to death from any cause.

SPSS 24.0 software was used to analyze the data. The best cutoff value for the FAR was calculated by receiver operating characteristic (ROC) curve analysis. Patients were divided into two groups based on the best cutoff value (high-FAR and low-FAR), and the clinical and pathological characteristics between the two groups were compared, including age, gender, hypertension, diabetes, Fuhrman grade, tumor classification, pathological T stage, histological subtype, and operation method. χ^2 test was used for the comparison of count data. The Kaplan-Meier method was used to calculate the survival rate and draw survival curves. The log-rank test was used to compare survival differences between groups. Cox hazards regression model was used to analyze the prognostic factors and determine the independent predictors of OS. A bilateral

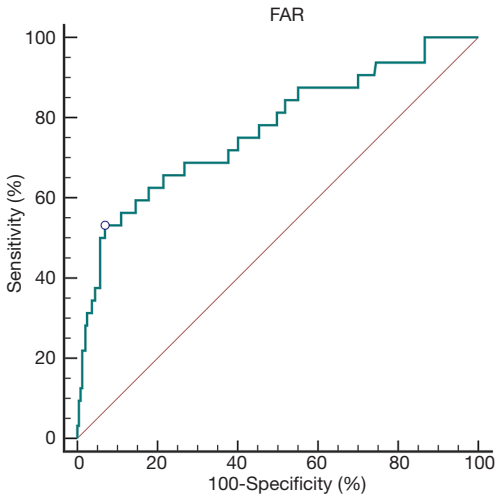

Figure 1 Determination of the cut-off value for the FAR by ROC curve analysis. FAR, fibrinogen-albumin ratio; ROC, receiver operating characteristic.

P<0.05 was considered statistically significant.

Results

Determination of the optimal cutoff value of the FAR

The best cutoff value for the preoperative FAR was determined by ROC curve analysis (*Figure 1*). At a FAR of 0.116, the Youden index of the FAR was highest, at 0.462 (sensitivity =53.13%, specificity =93.12%); therefore, 0.116 was selected as the cutoff value of the FAR (AUC: 0.769, 95% CI: 0.715–0.817, P<0.0001).

The relationship between the preoperative FAR and clinicopathological factors of RCC

Of the 279 patients included in the study, 195 were men and 84 were women. The median follow-up time was 65 months (range, 2–75 months). *Table 1* summarizes the detailed baseline characteristics of the selected patients. According to the best cutoff value of the FAR as determined by ROC curve analysis, the patients were divided into two groups. There were 35 patients in the high-FAR (>0.116) group and 244 patients in the low-FAR (≤0.116) group. A FAR >0.116 was significantly correlated with high Fuhrman grade (P<0.0001) and late pathological T stage (P<0.0001) (*Table 1*). There was no significant correlation between FAR and age, gender, diabetes, hypertension, tumor histology, or operation method.

The relationship between clinicopathological features and prognosis of RCC

Kaplan-Meier survival analysis indicated that a FAR >0.116 was associated with worse OS (*Figure 2*). In order to further determine the predictors of postoperative OS, we evaluated the FAR and other clinicopathological parameters by Cox proportional hazards regression analysis. In univariate regression analysis, higher Fuhrman grade (P<0.0001), higher pathological T stage (P<0.0001), laparoscopy (P=0.021), and a FAR >0.116 (P<0.0001) were associated with shorter OS. Multiple regression analysis indicated that Fuhrman grade and the FAR were independent prognostic factors of OS (*Table 2*).

Comparison of the AUCs for the FAR, NLR, PNI, and CONUT score

We use the AUCs to estimate the accuracy of the FAR for 5-year OS prediction. The AUC scores of the NLR, PNI, and CONUT score were 0.751 (95% CI: 0.696–0.801), 0.697 (95% CI: 0.639–0.750), and 0.728 (95% CI: 0.672–0.780), respectively. The AUC of the FAR was 0.769 (95% CI: 0.715–0.817), which was higher than those of the NLR, PNI, and CONUT score (*Figure 3*). However, there was no statistical difference in the AUCs, indicating that the FAR had the same accuracy in predicting the 5-year OS as the NLR, PNI, and CONUT score (*Table 3*).

Prognostic significance of the FAR based on Fuhrman grade

We further studied the prognostic significance of the FAR in patients with Fuhrman I–II RCC and found that the FAR was significantly correlated with OS (P<0.0001) (*Figure 4A*). However, in Fuhrman III–IV RCC patients, the FAR did not distinguish patients with worse OS (P=0.059) (*Figure 4B*). Further, in Fuhrman I–II RCC, the patients with FAR ≤0.16, have a better OS (P<0.0001), the FAR was a prognostic factor for OS in Fuhrman grade I–II renal cancer patients.

Discussion

The FAR reflects the ratio of fibrinogen to albumin, and it has been shown to have good prognostic value in esophageal cancer (10) and hepatocellular carcinoma (HCC) (11). Inspired by this, we explored the prognostic

Table 1 Comparison of clinicopathological data of different FAR groups

Features	Total	Preoperative FAR		χ^2 value	P value
		≤0.116 (n=244)	>0.116 (n=35)		
Age				2.985	0.084
≤65 years	198 (71.0)	178 (73.0)	20 (57.1)		
>65 years	81 (29.0)	66 (27.0)	15 (42.9)		
Gender				0.598	0.439
Male	195 (69.9)	173 (70.9)	22 (62.9)		
Female	84 (30.1)	71 (29.1)	13 (37.1)		
Diabetes				2.074	0.150
Yes	38 (13.6)	30 (12.3)	8 (22.9)		
No	241 (86.4)	214 (87.7)	27 (77.1)		
Hypertension				0.065	0.799
Yes	118 (42.3)	102 (41.8)	16 (45.7)		
No	161 (57.7)	142 (58.2)	19 (54.3)		
Fuhrman grade				45.698	<0.0001
I–II	245 (87.8)	227 (93.0)	18 (51.4)		
III–IV	34 (12.2)	17 (7.0)	17 (48.6)		
Operation				3.516	0.0607
Open	138 (49.5)	115 (47.1)	23 (65.7)		
Laparoscopy	141 (50.5)	129 (52.9)	12 (34.3)		
Pathological T stage				48.352	<0.0001
pT1–2	239 (85.7)	223 (91.4)	16 (45.7)		
pT3–4	40 (14.3)	21 (8.6)	19 (54.3)		
Histology				0.543	0.461
Clear cell carcinoma	249 (89.2)	216 (88.5)	33 (94.3)		
Non clear cell carcinoma	30 (10.8)	28 (11.5)	2 (5.7)		

Data are presented as n (%). FAR, fibrinogen-albumin ratio.

value of the FAR after radical nephrectomy. To our knowledge, this is the first study to focus on the impact of the FAR on the prognosis of RCC.

In this study, we explored the FAR as a predictor of renal cancer prognosis. We divided the patients into two groups based on the best cutoff value for the FAR as determined by ROC curve analysis. There were 35 patients in the high-FAR (>0.116) group and 244 patients in the low-FAR (≤0.116) group. A high FAR was significantly correlated with high tumor grade (P<0.0001) and late pathological T stage (P<0.0001) (*Table 1*). In addition, multivariate Cox regression analysis showed that Fuhrman grade and the FAR were independent prognostic factors of OS. Both fibrinogen and albumin are routinely measured in the clinic. Therefore, using the FAR to assess prognosis would be cheap, convenient, and repeatable.

The nuclear grade, pathological stage, and pathological type of tumor have commonly been used as indexes to

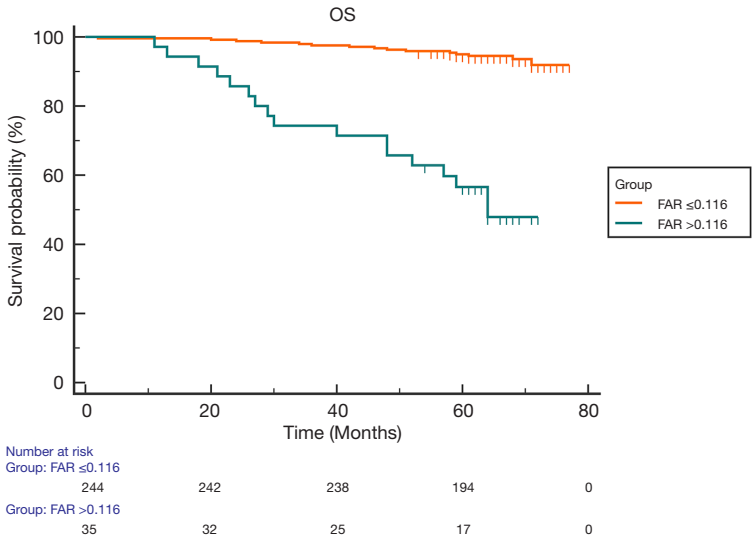

Figure 2 Kaplan-Meier survival curves for RCC patients. The OS of patients with a FAR >0.116 was significantly shorter than that of those with a FAR ≤0.116 (P<0.0001, log-rank test). RCC, renal cell carcinoma; OS, overall survival; FAR, fibrinogen-albumin ratio.

Table 2 Univariate and multivariate analyses of clinicopathological variables to predict OS in patients with RCC

Variables	Overall survival			
	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>65 *vs.* ≤65 years)	2.029 (1.009–4.081)	0.047	–	–
Gender (male *vs.* female)	0.899 (0.416–1.942)	0.786	–	–
Hypertension (yes *vs.* no)	1.107 (0.550–2.226)	0.777	–	–
Diabetes (yes *vs.* no)	2.203 (0.989–4.904)	0.053	–	–
Fuhrman grade (I–II *vs.* III–IV)	9.035 (4.512–18.092)	<0.0001	2.214 (1.031–4.755)	0.042
Histology (non-clear cell *vs.* clear cell)	1.211 (0.425–3.455)	0.721	–	–
Pathological T stage (T3–T4 *vs.* T1–T2)	6.491 (3.236–13.019)	<0.0001	1.401 (0.525–3.738)	0.502
Surgery (open *vs.* laparoscopy)	0.414 (0.196–0.875)	0.021	0.683 (0.306–1.526)	0.355
FAR (>0.116 *vs.* ≤0.116)	10.497 (3.263–33.766)	<0.0001	5.047 (2.109–12.076)	0.003

OS, overall survival; RCC, renal cell carcinoma; HR, hazard ratio; 95% CI, 95% confidence interval; FAR, fibrinogen-albumin ratio.

evaluate the prognosis of patients with RCC (14). However, these indexes are obtained by postoperative pathology, and more accurately identifying patients with poor prognosis before operation and carrying out tumor risk stratification is vital to determine treatment plans and guide postoperative follow-up. Therefore, finding biomarkers that can accurately predict tumor prognosis is of great interest. As early as the 19th century, Professor Rudolf Virchow first showed that there might be a connection between inflammation and cancer by observing the leukocytes in tumors. It is now generally believed that inflammation affects every step of tumor development, from tumorigenesis to metastasis (15).

Fibrinogen is not only an important factor to maintain normal coagulation function but also an acute phase reactive protein that can reflect the systemic inflammatory response. The systemic inflammatory response and coagulation are closely related to tumor development (16). Many recent studies have shown that preoperative peripheral blood

fibrinogen levels are related to survival in a variety of malignant tumors. Further, higher plasma fibrinogen levels are related to poor pathological characteristics and can predict survival in lung cancer, breast cancer, ovarian cancer, colon cancer, prostate cancer, and other tumors (17-21). This may be related to the direct involvement of fibrinogen in the interaction between vascular endothelial growth factor, transforming growth factor-β, platelet-derived growth factor, and fibroblast growth factor to regulate angiogenesis. Fibrinogen also plays a key role in cell proliferation, angiogenesis, and hematogenous metastasis of tumor cells (22-24).

At present, serum albumin levels are the most direct laboratory index to evaluate the nutritional status of patients.

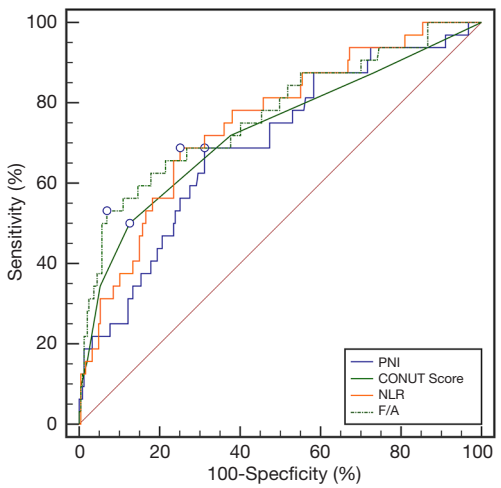

Figure 3 Comparison of the areas under the curves for the FAR, NLR, PNI, and CONUT score. The discrimination abilities of the FAR, NLR, PNI, and CONUT score for OS were compared. FAR, fibrinogen-albumin ratio; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutrition index; CONUT, controlling nutritional status; OS, overall survival.

Studies have shown that the inflammatory response and tumor state also affect serum albumin concentration. Low albumin levels may weaken the immune system, increase the chance of infection, and further accelerate the development of malignant tumors (25). Albumin has been reported to be of prognostic value in a variety of human malignant tumors: the lower the serum albumin level, the worse the prognosis of cancer patients, including in head and neck cancer (26), non-small cell lung cancer (27), ovarian cancer (28), and adenocarcinoma of the gastric cardia (29). In addition, serum albumin is one of the components of the Child-Pugh classification system reflecting liver function. Studies have shown that hypoproteinemia is an independent prognostic factor for poor prognosis in patients with liver cancer (30).

Other preoperative blood indexes based on inflammation and nutritional metabolism, such as the NLR, PNI, and CONUT score, have recently been reported as useful prognostic indexes of renal cancer (12,13,31,32). We compared the FAR to these common indexes in predicting the 5-year OS after surgery and found that the FAR had the same or better accuracy in predicting the 5-year OS.

Clinically, Fuhrman classification is considered to be an important factor influencing the prognosis of renal cancer patients after surgery (14). A higher Fuhrman grade indicates worse prognosis and shorter OS. However, the prognosis is still poor in some Fuhrman grade I–II patients. Therefore, it is of great clinical significance to find a predictor to distinguish high-risk patients in this subgroup. In our study, Fuhrman grade was an independent prognostic factor in patients with RCC, and patients with Fuhrman grade III–IV had worse OS (P<0.0001). After stratifying the patient cohort according to the Fuhrman grade, we found that in Fuhrman III–IV RCC patients, the FAR does not distinguish patients with worse OS (P=0.059), although this may be due to the small sample size in the subgroup. However, in Fuhrman grade I–II RCC patients,

Table 3 Comparison of the areas under the curves for the FAR, NLR, PNI, and CONUT score

Markers	AUC	HR (95% CI)	P value
FAR (dichotomized)	0.769	0.715–0.817	0.140
NLR (dichotomized)	0.751	0.696–0.801	0.534
PNI (dichotomized)	0.697	0.639–0.750	0.271
CONUT score (dichotomized)	0.728	0.672–0.780	0.538

AUC, area under the curve; HR, hazard ratio; 95% CI, 95% confidence interval; FAR, fibrinogen-albumin ratio; NLR, neutrophil-lymphocyte ratio; PNI, prognostic nutrition index; CONUT, controlling nutritional status.

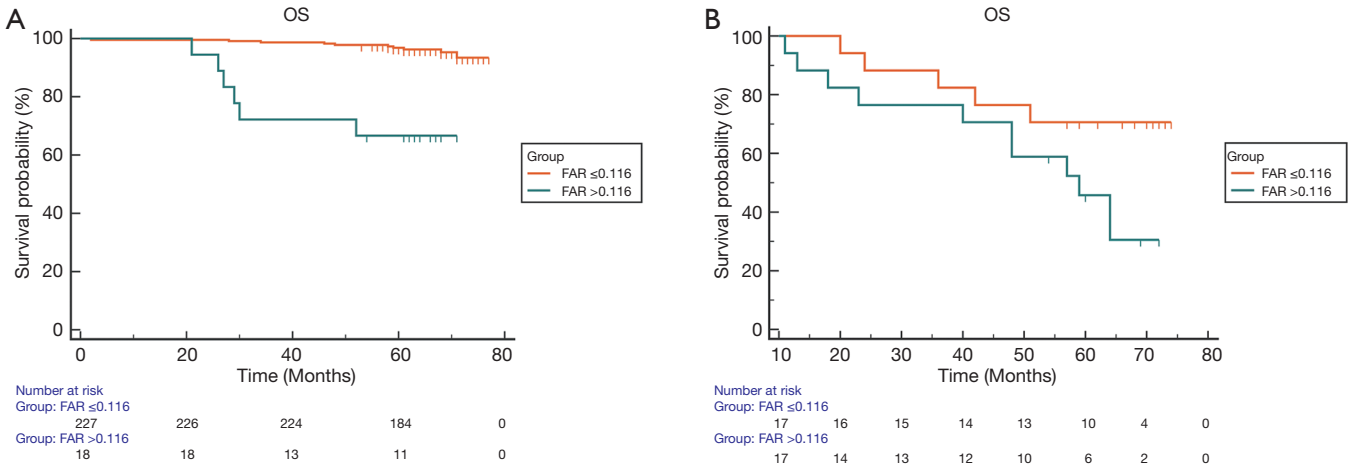

Figure 4 Kaplan-Meier survival curves of RCC patients with Fuhrman grade I–II (A, n=245) and Fuhrman grade III–IV (B, n=34). A FAR >0.116 was significantly correlated with a shorter OS in patients with Fuhrman grade I–II. RCC, renal cell carcinoma; OS, overall survival; FAR, fibrinogen-albumin ratio.

the prognostic significance of the FAR was very strong. Therefore, patients with Fuhrman grade I–II RCC with a high FAR may need to be followed up more closely as soon as possible because they are more likely to have worse OS. If early prediction and timely intervention can be achieved, these patients may achieve better results.

Other predictive biomarkers, such as Glasgow predictive score (GPS), platform to lymphocyte ratio (PLR), C-reactive protein to albumin ratio, in different studies, the results have a certain predictive effect on the prognosis of renal cancer (33-35). In this study, we found that FAR is a new and simple prognostic factor for renal cancer patients after surgery. However, there are some unavoidable limitations in this study. First, this is a single-center retrospective study. The results may be affected by selection bias. Whether our findings are applicable to other centers needs to be verified. Second, many other factors affect the FAR, such as acute and chronic infection and chronic liver disease; this may affect the accuracy of prognosis prediction based on this ratio. In addition, because the study population collected in this study was relatively early, many patients received different treatment measures due to tumor recurrence during follow-up, which affected OS.

In conclusion, despite these limitations, our study is the first to prove that the preoperative FAR is a new and simple prognostic factor for renal cancer patients after surgery, especially for patients with low Fuhrman grade. It is a simple and sensitive method to evaluate the prognosis of renal cancer patients that does not increase the economic burden or physical pain of patients and a promising biomarker.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-19-873). QZ serves as an unpaid editorial board member of *Translational Andrology and Urology* from May 2019 to Apr 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was approved by the Central Ethics Committee of our hospital (No. 2018-386).

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