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ORIGINAL RESEARCH

Metabolic Syndrome is an Independent Risk Factor for Fuhrman Grade and TNM Stage of Renal Clear Cell Carcinoma

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Background: More and more evidences show that metabolic syndrome (MS) is closely related to clear cell renal cell carcinoma (ccRCC), but the impact of MS on Fuhrman grade and TNM stage of ccRCC is rarely reported.

Purpose: To explore the relationship between MS and its components of Fuhrman grade and TNM stage in ccRCC.

Objective: The clinical data of 247 patients with ccRCC diagnosed in our hospital from January 2016 to November 2020 were retrospectively collected and analyzed. Based on diagnostic criteria of MS, the patients were divided into MS and non-MS group. Logistic regression analysis was used to analyze the independent risk factors of ccRCC.

Results: The incidence of MS was 32.79% (81/247). There was no significant difference in age, gender, smoking and drinking between MS group and non-MS group ($P > 0.05$). In MS group, BMI $\geq 25 kg/m^2$, hypertension, diabetes, hyperlipidemia, tumor diameter, poorly differentiated renal cancer, high-stage renal cancer, triglyceride, fasting blood glucose, glycated hemoglobin, fasting insulin and homeostasis model assessment index were significantly higher than those in non-MS group ($P < 0.001$), while in high density lipoprotein cholesterol ($p < 0.005$), islet beta cell secretory index ($P < 0.001$), well-differentiated renal cell carcinoma ($P= 0.009$), and low-stage renal cell carcinoma ($P = 0.019$) were significantly lower than that of non-MS group. Logistic regression analysis showed that hypertension ($P = 0.005$), diabetes ($P = 0.012$), hyperlipidemia ($P = 0.021$) are independent risk factors for Fuhrman grade of ccRCC, while diabetes ($P = 0.002$), hyperlipidemia ($P = 0.007$) are independent risk factors for TNM staging of ccRCC.

Conclusion: The patients with ccRCC and MS had higher Fuhrman grade and TNM stage. MS is an independent risk factor for Fuhrman grade and TNM stage of ccRCC.

Keywords: metabolic syndrome, clear cell renal cell carcinoma, diabetes, hypertension, hyperlipidemia, risk factors, Fuhrman grade, TNM stage

Introduction

Metabolic syndrome (MS) is a group of diseases with central obesity, hyperglycemia (diabetes or impaired glucose regulation), dyslipidemia and hypertension as its main characteristics, and insulin resistance as the common pathophysiological basis Clinical syndrome.[1,2] In recent years, the incidence rate of MS has increased significantly. It has become one of the public health problems which seriously threaten human health.[3] A large number of epidemiological studies have shown that MS is related to the occurrence of a variety of malignant tumors, such as

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pancreatic cancer, breast cancer, colorectal cancer, liver cancer, gastric cancer, cervical cancer and prostate cancer, etc.[4,5] The mechanism of MS inducing malignant tumor is very complex. MS patients have multiple metabolic disorders and insulin resistance. MS can participate in the occurrence and development of malignant tumor through hyperglycemia, abnormal lipid deposition, oxidative stress, inflammatory factors, insulin/insulin-like growth factor signal transduction and other pathways.[4–6]

Clear cell renal cell carcinoma (ccRCC) is a malignant tumor originating from the urinary tubule epithelial system of the renal parenchyma. Its occurrence and development are thought to be related to a variety of metabolic factors.[7,34] In Western countries, ccRCC accounts for 3% of adult malignant tumors. Compared with other malignant tumors, the incidence of ccRCC is relatively low. However, in recent years, the global incidence and mortality have been on the rise. This trend is particularly obvious.[8–10] The results of epidemiology and basic research suggest that metabolic factors such as obesity, hypertension, diabetes and dyslipidemia may have certain effects on the occurrence and development of ccRCC.[10,11] Haggstrom et al found that in men, obesity, high blood pressure, high blood sugar and high blood lipids are risk factors for kidney cancer.[12,13] More and more evidences show that MS is closely related to ccRCC, but the impact of MS on Fuhrman grade and TNM stage of ccRCC is rarely reported.[8–13] Based on this, the clinical data of 219 patients with ccRCC were collected retrospectively to analyze the relationship between MS and Fuhrman grade and TNM stage.

Materials and Methods

Inclusion and Exclusion Criteria

Methods the clinical data of 247 patients with ccRCC diagnosed in our hospital from January 2016 to November 2020 were retrospectively analyzed. Inclusion criteria: ① ccRCC was confirmed by postoperative pathology; ② no anti-tumor treatment was received before operation; ③ complete clinical data of the patient; ④ the age of the patient was more than 18 years old. Exclusion criteria: ① postoperative pathological diagnosis was not clear cell renal cell carcinoma; ② relevant data of patients were missing. ③ Patients who had received anti-tumor therapy before operation; ④ bilateral renal cell carcinoma or family history of renal cell carcinoma; ⑤ patients with other malignant tumors at the same time. The clinical data including gender, age, increase, weight, blood pressure, blood glucose, blood lipid, insulin level, glycosylated hemoglobin A1c (HbA1c), homeostasis model assessment of insulin resistance index (HOMA-IR=fasting blood glucose×FINS/22.5), islet beta cell function index [HOMA-β=fasting insulin×20/(fasting blood glucose-3.5)], tumor diameter, pathological type, Fuhrman grade and TNM stage were collected. Patients with renal clear cell carcinoma were divided into MS group and non-MS group according to the presence or absence of MS. This study was reviewed and approved by the Ethics Committee of General Hospital of Northern Theater Command PLA and was carried out in accordance with the Declaration of Helsinki. The subjects agreed to the study, and all subjects signed the informed consent form.

Metabolic Syndrome Diagnostic Criteria

The diagnostic criteria for metabolic syndrome are based on the criteria proposed by the International Diabetes Federation.[14,15] Patients with any 3 or all of the following 4 items are diagnosed as MS: ① BMI of ≥ 25 kg/m^2 or Waist circumference ≥ 0.90 for men and ≥ 0.85 for women; ② raised TG level: ≥1.7 mmol/L (150 mg/dL) or reduced HDL-cholesterol: <1.03 mmol/L (40 mg/dL) in males and <1.29 mmol/L (50 mg/dL) in females or specific treatment for these lipid abnormalities; ③ raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension. ④Fasting plasma glucose ≥5.6 mmol/L (100 mg/dL) or previously diagnosed Type 2 diabetes.

Renal Cell Carcinoma Fuhrman Classification and TNM Staging Criteria

The TNM staging of renal cell carcinoma adopts the 2010 American Joint Committee on Cancer (AJCC) Standards.[16,17] Since there are fewer patients in the T3 and T4 stages in the enrolled patients, the T1a and T1b stages are regarded as the low stage, and the T2a, T2b, T3, and T4 stages are regarded as the high stage in this study. The histological grading standard of renal cell carcinoma was evaluated according to the Fuhrman grading standard recommended by the World Health Organization in 1997. Fuhrman grade I and II are low-grade tumors, and Fuhrman grade III and IV are high-grade tumors.[18,19]

Statistical Analysis

SPSS20.0 software was used for data statistical analysis. K-S single sample test was used to evaluate whether the data conform to the normal distribution. The measurement data conforming to the normal distribution is expressed as x ± s, the measurement data not conforming to the normal

distribution is expressed as the median (minimum, maximum), and the counting data is expressed as (percentage). Normally distributed continuous variables were analyzed by *t* test, non-normally distributed continuous variables were analyzed by Mann–Whitney *U*-test, and categorical variables were analyzed by chi-square test. Logistic regression was used to analyze the influence of metabolic syndrome related components on the grading and staging of renal cell carcinoma. P <0.05 is considered statistically significant.

Result

Baseline Characteristics of Patients Included in the Study

As shown in Table 1, t 247 patients with renal clear cell carcinoma were involved in current investigation, consist of 164 males and 83 females, with an medium age of 55 (45~80) years. There were 174 (70.44%) cases with Fuhrman grade I and II, and 73 (29.55%) cases with Fuhrman grade III and IV. Two hundred (80.97%) patients with low and 47 (19.03%) patients with high TNM stage were analyzed. One hundred fifteen (46.56%) cases of BMI≥25kg/m^2, 67 (27.12%) cases of diabetes, 89 (36.03%) cases of hypertension, 103 (41.70%) cases of hyperlipidemia were enrolled. Among the patients, 81 (32.79%) patients met with diagnosis of MS.

Table 1 Baseline Characteristics of Patients

Parameters	Case (%)
Number of included cases	247 (100%)
Male	164 (66.39%)
Female	83 (33.61%)
Age (year)	55 (45~80)
Fuhrman grading	
Grade I and II	174 (70.44%)
Grade III and IV	73 (29.55%)
TNM staging	
T1	200 (80.97%)
T2	40 (16.19%)
T3	5 (2.02%)
T4	2 (0.81%)
BMI≥25kg/m^2	115(46.56%)
Diabetes	67 (27.12%)
Hyperlipidemia	103 (41.70%)
Hypertension	89(36.03%)
Metabolic syndrome	81(32.79%)

Comparison of Clinical Characteristics Between MS Group and Non-MS Group

As shown in Table 2, there was no significant difference in age (P = 0.513), gender (P = 0.416), smoking (P = 0.873), and drinking (P = 0.540) between MS group and non-MS group. Patients with BMI≥25kg/m^2 (66.67% vs 36.75%, P < 0.001), hypertension (62.96% vs 17.47%, P < 0.001), diabetes (56.75% vs 13.25%, P < 0.001), hyperlipidemia (76.54% vs 24.69%, P < 0.001), tumor diameter (54.17 ±24.16 vs 38.67±20.28, P < 0.001), poorly differentiated renal cell carcinoma (43.21% vs 22.89%, P = 0.009), high-stage renal cell carcinoma (30.86) % vs 13.25%, P = 0.019), triglycerides (1.91±0.34 vs 1.24±0.28, P < 0.001), fasting blood glucose (7.47±1.26 vs 4.87±1.45, p = 0.019), HbA1c (8.26±1.01 vs 4.38±0.73, P < 0.001), fasting insulin (8.01±2.17 vs 4.44±1.96, P < 0.001), HOMA-IR (2.94 ±0.57 vs 1.52±0.36, P < 0.001) in the MS group were significantly higher than that in non-MS group. But with HDL Cholesterol (Male = 0.71±0.33 vs 1.42±0.57, p < 0.001; Female = 0.93±0.34 vs 1.58±0.52, p = 0.038), HOMA-β (45.47±6.24 vs 80.24±5.04, P < 0.001), well-differentiated renal cell carcinoma (56.79% vs 77.11%, P = 0.009), and low-stage renal cancer (69.14% vs 86.75%, P = 0.019) in the MS group were significantly lower than those in the non-MS group.

Analysis of the Relationship Between the Components of Metabolic Syndrome and the Fuhrman Pathological Grade of ccRCC

As shown in Table 3, hypertension (23.56% vs 65.75%, P < 0.001), diabetes (18.39% vs 65.75%, P < 0.001), hyperlipidemia (35.05% vs 57.53%, P = 0.004) were closely related to the Fuhrman pathological grade of ccRCC, but BMI (48.28% vs 42.47%, P = 0.495) was not significantly related to the Fuhrman pathological grade of ccRCC.

Analysis of the Relationship Between Metabolic Syndrome Related Components and TNM Staging of ccRCC

As shown in Table 4, hypertension (32.00% vs 55.32%, P = 0.012), diabetes (22.00% vs 48.93%, P < 0.001), hyperlipidemia (34.00% vs 74.47%, P < 0.001) were closely related to TNM stage of ccRCC, but BMI (45.00% vs 53.19%, P = 0.409) was not significantly related to Fuhrman pathological grade of ccRCC.

Table 2 Comparison of Clinical Characteristics Between MS Group and Non-MS Group

Parameters	MS Group (n=81)	Non-MS Group (n=166)	P value
Age (year)	54 (45–72)	55 (48–80)	0.513
Gender (%)			0.416
Male	55 (67.91%)	104 (62.65%)	
Female	26 (32.09%)	62 (37.35%)	
Smoking (%)	43(53.09%)	97(58.44%)	0.540
Drinking (%)	17 (20.99%)	41(34.69%)	0.518
BMI (%)			
≥25kg/m^2	54 (66.67%)	61 (36.75%)	
<25kg/m^2	27 (33.33%)	105 (63.25%)	<0.001*
Hyperlipidemia(%)	62 (76.54%)	41 (24.69%)	<0.001*
Hypertension(%)	60 (62.96%)	29 (17.47%)	<0.001*
TG (mmol/L)	1.91±0.34	1.24±0.28	<0.001*
HDL-C (male, mmol/L)	0.71±0.33	1.42±0.57	<0.001*
HDL-C (female, mmol/L)	0.93±0.34	1.58±0.52	0.038*
Diabetes(%)	45 (56.75%)	22 (13.25%)	<0.001*
Tumor diameter(mm)	54.17±24.16	38.67±20.28	<0.001*
HbA1c(%)	8.26±1.01	4.38±0.73	<0.001*
FPG (mmol/L)	7.47±1.26	4.87±1.45	0.019*
FINS (mU/L)	8.01±2.17	4.44±1.96	<0.001*
HOMA-IR	2.94±0.57	1.52±0.36	<0.001*
HOMA-β	45.47±6.24	80.24±5.04	<0.001*
Fuhrman grading(%)			
Well differentiated	46(56.79%)	128 (77.11%)	
Poorly differentiated	35 (43.21%)	38 (22.89%)	<0.001*
TNM staging(%)			
Low staging	56 (69.14%)	144 (86.75%)	
High staging	25 (30.86%)	22 (13.25%)	0.019*

Note: *After correction, P < 0.05.

Abbreviations: BMI, body mass index; HDL-C, High-density lipoprotein-cholesterol; FINS, fasting insulin, HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-β, homeostasis modelassessment for β-cell function.

Univariate and Multivariate Logistic Regression Analysis of the Influence of Metabolic Syndrome Related Components on the Fuhrman Grading of ccRCC

As shown in Table 5, logistic regression analysis found that hypertension (OR = 2.037, 95% CI = 1.765–11.472, P = 0.005), diabetes (OR = 3.579, 95% CI = 1.034–8.037, P = 0.012), hyperlipidemia (OR = 4.347, 95% CI = 1.357–9.671, P = 0.021) can increase the risk of Fuhrman grading in patients with ccRCC whether in univariate or multivariate logistical analysis. Hypertension, diabetes mellitus and hyperlipidemia were independent risk factors for Fuhrman grade of ccRCC, but BMI ≥ 25kg/m^2 was not (P = 0.387).

Univariate and Multivariate Logistic Regression Analysis of the Effect of Metabolic Syndrome Related Components on TNM Staging of ccRCC

As shown in Table 6, logistic regression analysis showed that diabetes mellitus (or = 4.028, 95% CI = 2.071–9.281, P = 0.002) and hyperlipidemia (or = 3.247, 95% CI = 1.557–6.343, P = 0.007) increased the risk of TNM staging in patients with ccRCC whether in univariate or multivariate logistical analysis. Diabetes mellitus and hyperlipidemia were independent risk factors for TNM stage of ccRCC, while BMI ≥ 25kg/m^2 (P = 0.231) and hypertension (P = 0.125) were not independent risk factors for TNM stage of ccRCC.

Table 3 The Influence of Metabolic Syndrome Related Components on the Fuhrman Grading of ccRCC

Parameters	Well Differentiated (n=174)	Poorly Differentiated (n=73)	P value
BMI (%)			0.495
≥25kg/m^2	84 (48.28%)	31 (42.47%)	
<25kg/m^2	94 (51.72%)	42 (57.53%)	
Hypertension (%)			<0.001*
Yes	41 (23.56%)	48 (65.75%)	
No	133 (76.44%)	25 (34.25%)	
Diabetes (%)			<0.001*
Yes	32 (18.39%)	35 (47.95%)	
No	142 (81.61%)	38 (52.05%)	
Hyperlipidemia (%)			0.004*
Yes	61 (35.05%)	42 (57.53%)	
No	113 (64.95%)	31 (42.46%)	

Note: *P<0.05.

Discussion

Many studies have shown that MS is related to the occurrence and development of many diseases and is an important risk factor for the occurrence of many diseases.[20] Recent studies have found that MS increases the risk of colon cancer, pancreatic cancer and liver cancer.[4] In addition, MS is associated with high risk of recurrence and poor prognosis after bladder cancer and prostate cancer surgery.[21,22] At present, some clinical evidences indicate that MS can increase the risk of renal cell carcinoma.[23,24] However, it is rarely reported whether the MS is related to the malignant degree of renal cancer. In this study, we found that hypertension, diabetes and hyperlipidemia are independent risk factors for the Fuhrman grading of ccRCC, while BMI≥25kg/m^2 is not an independent risk factor for the Fuhrman grading of ccRCC (P = 0.387). In addition, diabetes and hyperlipidemia are independent risk factors for ccRCC TNM staging, while BMI≥25kg/m^2 (P = 0.231) and hypertension (P = 0.125) are not independent risk factors for ccRCC TNM staging.

Table 4 Analysis of the Relationship Between Metabolic Syndrome Related Components and TNM Staging of ccRCC

Parameters	low Staging (n=200)	high Staging (n=47)	P value
BMI (%)			0.409
≥25kg/m^2	90 (45.00%)	25 (53.19%)	
<25kg/m^2	110 (55.00%)	22 (46.81%)	
Hypertension (%)			0.012*
Yes	64 (32.00%)	26 (55.32%)	
No	136 (58.00%)	21 (44.68%)	
Diabetes (%)			<0.001*
Yes	44 (22.00%)	23 (48.93%)	
No	156 (78.00%)	24 (51.07%)	
Hyperlipidemia (%)			<0.001*
Yes	68 (34.00%)	35 (74.47%)	
No	132 (66.00%)	12 (25.53%)	

Note: *P<0.05.

Existing epidemiological studies suggest that BMI is positively correlated with the incidence of ccRCC.[25] In a prospective epidemiological study involving more than 900,000 American adults, researchers found that obesity can increase the risk of renal cell carcinoma, with a relative risk of 1.70 in men and 4.75 in women.[26] Interestingly, although a higher BMI can increase the risk of renal cell carcinoma. However, Parker et al suggest that renal cell carcinoma patients with higher BMI have a lower degree of tumor malignancy.[27] This contradictory result suggests that the relationship between obesity and renal cancer is more complicated, and further research is needed. In this research, we found that the proportion of obesity in MS group was significantly higher than that in non MS group, but logistic regression analysis showed that there was no significant difference between obesity and ccRCC in terms of Fuhrman grading and TNM staging. The reason for this situation may be that the population included in this study is an Asian population, and the populations in other studies are European and American populations. In addition, it may be due to the increased consumption of the body by tumor progression, which leads to a decrease in BMI level. On the other hand, it may be due to malnutrition in patients with low BMI and poor immunity of the body, resulting in accelerated tumor progression.

Both epidemiological studies and basic research results suggest that hypertension is related to renal cell carcinoma.[28–32] Hypertension is one of the independent risk factors of renal cancer, and the risk of renal cancer in patients with hypertension is 40% higher than that in patients with normal blood pressure.[29] Another prospective study showed that there was a positive correlation between blood pressure level and mortality of renal cell carcinoma, but the correlation between blood pressure level and risk of renal cell carcinoma was only found in men.[30] Basic research results suggest that renin,

Table 5 Univariate and Multivariate Logistic Regression Analysis of the Influence of Metabolic Syndrome Related Components on the Fuhrman Grading of ccRCC

Variables	Univariate Analysis				Multivariate Analysis			
	β value	OR value	95% CI	p value	β value	OR value	95% CI	p value
BMI≥25kg/m^2	0.425	1.024	0.74–1.32	0.265	0.315	1.578	0.435–2.973	0.387
Diabetes (%)	1.954	4.21	2.34–8.57	0.003*	2.037	6.327	1.765–11.472	0.005*
Hypertension (%)	1.286	2.87	1.904–3.83	0.04*	1.354	3.579	1.034–8.037	0.012*
Hyperlipidemia (%)	2.01	2.93	0.86–3.29	0.038*	1.839	4.347	1.357–9.671	0.021*

Note: *Statistically significant (p<0.05).

Table 6 Univariate and Logistic Regression Analysis of the Effect of Metabolic Syndrome Related Components on TNM Staging of ccRCC

Variables	Univariate Analysis				Multivariate Analysis			
	β value	OR value	95% CI	p value	β value	OR value	95% CI	p value
BMI≥25kg/m^2	−0.53	0.842	0.64–1.45	0.365	−0.429	0.793	0.367–1.839	0.231
Hypertension (%)	1.046	1.265	0.89–1.465	0.24	1.003	1.327	0.665–3.072	0.125
Diabetes (%)	1.72	3.67	2.90–4.85	0.012*	1.607	4.028	2.071 −9.281	0.002*
Hyperlipidemia (%)	1.263	2.63	0.96–3.57	0.003*	1.148	3.247	1.557–6.343	0.007*

Note: *Statistically significant (p<0.05).

endothelin-1 and angiotensin II secreted by renal cell carcinoma may be the cause of increased blood pressure in patients with renal cell carcinoma.[31] In this study, we found that hypertension is an independent risk factor for the Fuhrman grading of ccRCC, while hypertension is not an independent risk factor for the TNM staging of ccRCC. The possible reason for this result is that due to the limitation of sample size, there are not many patients with T3 and T4 stages in this study. Therefore, subdivision of TNM staging on the basis of large sample in the future will help to further clarify the relationship between hypertension and tumor TNM staging.

At present, it is believed that the central link of MS is insulin resistance. The increase of serum insulin level can stimulate tumor cells to absorb energy, thus stimulating cell proliferation and promoting tumor growth.[32,33] In this study, we found that the incidence of diabetes, FPG, FINS and HOMA-IR in ccRCC patients with MS were significantly higher than those in non MS group, while HOMA - β was significantly lower than that in non MS group. These results suggest that there are obvious abnormal glucose metabolism and insulin resistance in ccRCC patients with MS, which can promote tumor discovery to a certain extent. Most studies have shown that type 2 diabetes is an independent risk factor for renal cell carcinoma. The incidence rate and mortality of type 2 diabetic patients are significantly higher than those of non-diabetic patients.[34] Studies by stocks and Otunctemur et al found that patients with invasive renal cell carcinoma complicated with MS or diabetes had larger tumors and lower grades.[35,36] Also in this study, we found that MS patients with ccRCC had higher pathological stage, lower grade and larger tumor diameter than non MS patients with ccRCC. In Logistic regression analysis, we further found that type 2 diabetes is an independent risk factor for the Fuhrman grade and TNM staging of ccRCC.

Current research suggests that lipid metabolism disorders are closely related to the occurrence and development of tumors.[37] Babayan et al found through animals that the blood TG concentration of mice was increased by 20 times after the kidney cancer cells were planted. When the planted tumor was removed, the blood TG concentration returned to normal. This shows that there is a close relationship between TG and kidney cancer.[38] Van Hemelrijck et al also found that TG and hypercholesterolemia is significantly positively correlated with the risk of renal cell carcinoma.[39,40] In this study, we found that the incidence of hyperlipidemia and TG concentration in ccRCC with MS group were significantly higher than those in non-MS group. Logistic regression analysis further found that hyperlipidemia was positively correlated with the grade and stage of ccRCC, and

hyperlipidemia was an independent risk factor for the Fuhrman grade and TNM stage of ccRCC. The mechanism closely related to hyperlipidemia and renal cell carcinoma may be that patients with hyperlipidemia are often accompanied by increased expression of fatty acid synthase, thereby accelerating fatty acid metabolism, and fatty acid metabolites such as arachidonic acid can promote the proliferation, invasion and migration of renal cell carcinoma.[41]

The limitations of this study are as follows: ① This study is a retrospective study, which has inherent deficiencies. ② The sample size included in this study is relatively limited, large sample, multi center study needs to further explain the relationship between MS and renal cell carcinoma grade and stage. ③ Although BMI can replace obesity, it cannot effectively display body fat distribution. Therefore, the results of this study on obesity and renal cancer grading and staging require further research. ④ The number of T3 and T4 patients included in this study is less, and the conclusion has certain limitations.

Conclusion

Hypertension, diabetes and hyperlipidemia are independent risk factors for the Fuhrman grading of ccRCC. Diabetes and hyperlipidemia are independent risk factors for ccRCC TNM staging, while BMI≥25kg/m^2 are not independent risk factors for ccRCC Fuhrman grading and TNM staging.

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Disclosure

The authors declare that there is no conflict of interest in this article.

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