Validation of the World Health Organization/International Society of Urological Pathology grading for Chinese patients with clear cell renal cell carcinoma

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Background: This study aimed to compare the World Health Organization/International Society of Urological Pathology (WHO/ISUP) grading system and the Fuhrman grading system and to verify the WHO/ISUP grade as a prognostic parameter of clear cell renal cell carcinoma (ccRCC) in a Chinese population.

Methods: The study consisted of 753 ccRCC patients treated with curative surgery between 2010 and 2018 at Xiangya Hospital Central South University (Changsha, China). All pathologic data were retrospectively reviewed by two pathologists. Cancer-specific survival (CSS) and recurrence-free survival (RFS) were examined as clinical outcomes.

Results: According to the WHO/ISUP grading system (ISUP group), nephrectomy type, pT stage and WHO/ISUP grade were independent risk factors for CSS (P<0.0001, P=0.0127 and P<0.0001, respectively) and RFS (P<0.0001, P=0.0077, and P<0.0001, respectively). In the Fuhrman group, nephrectomy type, pT stage and Fuhrman grade were independent risk factors for CSS (P<0.0001, P=0.0004, and P<0.0001, respectively) and RFS (P<0.0001, P=0.0001, and P<0.0001, respectively). The C-index for CSS and RFS using the Fuhrman grading system was 0.6323 and 0.6342, respectively, and that using the WHO/ISUP grading system was 0.6983 and 0.7005, respectively, both higher than the former (P=0.0185, and P=0.0172, respectively). In addition, upgrading from Fuhrman grade 2 to ISUP grade 3 resulted in worse CSS and RFS for ccRCC patients (P=0.0033 and P =0.0003, respectively).

Conclusions: We first verified correlations between the postoperative prognosis and WHO/ISUP grade of ccRCC in a Chinese population and confirmed that the ability to predict clinical outcomes with the WHO/ISUP grading system was superior to that with the Fuhrman grading system.

Keywords: Renal cell carcinoma (RCC); clear cell renal cell carcinoma (ccRCC); International Society of Urological Pathology (ISUP); grading; prognosis

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Introduction

Renal cell carcinoma (RCC) is the most common solid lesion within the kidney and accounts for approximately 3% of all malignancies in humans. During the last 2 decades, the incidence of RCC has increased annually by 2% both worldwide and in Europe, leading to approximately 19.45/100,000 new RCC cases and 7.67/100,100 kidney cancer-related deaths within the European Union in 2018 (1,2). In China, according to the China Cancer Registration Annual Report, the incidence of RCC was 3.96/100,000 and 4.99/100,000 in 2005 and 2014, respectively (3). The most predominant pathological type is clear cell renal cell carcinoma (ccRCC), which accounts for 70–80% of all RCCs (3,4). Compared with other subtypes of RCC, such as papillary RCC (pRCC) and chromophobe RCC (cRCC), ccRCC is thought to be associated with a more aggressive clinical course and a significantly poorer prognosis, and patients are reported to have a 5-year disease-free survival (DFS) rate of 70% and a cancer-specific survival (CSS) rate of 24% (4-6). Tumour grade has been considered an independent prognostic factor for RCC (7,8). While numerous grading systems have been proposed for RCC, the Fuhrman grading system has been the most widely accepted and endorsed for routine clinical use (9,10). Despite its widespread use, it has become increasingly obvious that the system has a number of inherent problems, in particular those relating to poor interpretability and consequently poor inter-observer reproducibility, which resulted from the Fuhrman grading system requiring the simultaneous assessment of 3 nuclear parameters (i.e., nuclear size, nuclear irregularity, and nucleolar prominence); however, there are no guidelines that can be used to assign a weight to achieve a final grade when the features of any of the parameters appear to be discordant (11,12). To address these inherent difficulties, the International Society of Urological Pathology (ISUP) 2012 Consensus Conference recommended the use of the ISUP grading system, which proposed that for ccRCC, nucleolar prominence alone should be used to identify grade 1 to 3 tumours and extreme nuclear pleomorphism and/or sarcomatoid and/or rhabdoid morphology and/or giant size be used to identify grade 4 tumours (13) (*Tables 1,2*).

In 2015, the ISUP grading system was adopted by the WHO and redesignated as the WHO/ISUP grading system (14,15). The WHO/ISUP grading system has replaced the Fuhrman grading system and has achieved widespread use in contemporary pathology practice worldwide (16).

The pathological grading system is proposed because of its association with the outcome of RCC, and it is constantly updated in order to achieve a better predictive value (10,17,18). Therefore, designed to promote the application of WHO/ISUP grading system, it is extremely necessary to evaluate its predictability. However, there have been few reports citing the verification of the WHO/ISUP grading system in Western countries; these reports showed that the WHO/ISUP grading system reduces the rating parameters but provides better grade separation and increases the predictive value. However, there are no reports on the Chinese population (19-21). As the Chinese are a heterogeneous population, it is necessary to verify the predictive value of the WHO/ISUP grading system in a Chinese cohort.

In this study, we assessed the value of the WHO/ISUP grade and the Fuhrman grade in predicting the prognosis of ccRCC in a Chinese population and compared the excellent predictive accuracy of these two systems. To the best of our knowledge, our study is the first to verify the predictive value of the WHO/ISUP grading system in a Chinese population. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tau-20-799).

Methods

Patients

The Clinical Research Ethics Committee of Xiangya Hospital, Central South University approved the study (No. 2017121011), and informed consent was waived due to the retrospective nature of the research. The authors confirm the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). A computerized search of the pathology database at our institution revealed 1,333 patients with ccRCC that had undergone radical nephrectomy or nephron-sparing surgery between July 2010 and May 2018. One hundred and twelve patients which identified as other subtypes of RCC or mixed with other subtypes of RCC were excluded because the biological aggressiveness is different. Patients who lacked prognosis information (N=143) and who followed-up less than 2 years (N=293) were excluded from our study. Furthermore, 15 patients treated by neoadjuvant therapy and 17 patients died for other reasons were also excluded. Therefore, 753 patients were eventually included in our study.

Table 1 The WHO/ISUP grading system

Grade 1: nucleoli absent or inconspicuous and basophilic at ×400 magnification

Grade 2: nucleoli conspicuous and eosinophilic at ×400 magnification and visible but not prominent at ×100 magnification

Grade 3: nucleoli conspicuous and eosinophilic at ×100 magnification

Grade 4: extreme nuclear pleomorphism and/or sarcomatoid and/or rhabdoid differentiation and/or tumour giant cells

WHO/ISUP, World Health Organization/International Society of Urological Pathology.

Table 2 The Fuhrman grading system

Grade	Nucleoli	Nuclear shape	Nuclear size
Grade 1	Inconspicuous or absent	Small, round, uniform, Irregular	~10 μM
Grade 2	Visible at ×400 magnification	Irregular in outline at ×400 magnification, variable in size	~15 μM
Grade 3	Prominent/large even at ×100 magnification	Obvious irregular outline, large, hyperchromasia, marked variability in size and shape	~20 μM
Grade 4	Cells large, pleomorphic with bizarre multilobed giant cells and heavy chromatic clumps, extreme irregular outlines		

Pathological review

All pathologic data of the 1,333 patients were retrospectively reviewed by two pathologists (H Yin and G Gong, with 25 years and 6 years of experience, respectively, in uropathology). Evaluation of the histological subtype and pathological T stage of all patients was based on the 2016 WHO classification. All lesions were regraded using the criteria of Fuhrman *et al.*, and those regraded using the WHO/ISUP grading system were assessed in line with the 2012 ISUP Consensus Conference recommendations (10,13) (*Tables 1,2*). Tumour grade was based on the highest grade present on any slide, even if focal. When there was a different opinion on a pathological slice, two pathologists re-evaluated the slices together and finally reached a consensus. The reviewers were blinded to the prognostic information.

Statistical analysis

The data were descriptively summarized using frequency counts and percentages for categorical variables and medians and ranges for measured variables. Survival curves were estimated using the Kaplan-Meier method and compared between groups using log-rank tests. The CSS interval was measured from the date of surgery to the date of death from RCC. The RFS interval was measured from the date of surgery until the detection of recurrence or metastasis.

Multivariate analyses were undertaken utilising multivariate Cox proportional hazards models. We separately assessed the clinical outcomes in the Fuhrman group and the ISUP group and evaluated the predictive accuracy for clinical outcomes between the Fuhrman and ISUP groups with the concordance index (C-index), and evaluated the difference in C-index between the two grading systems with Z-test. The C-index refers to the area under the receiver operating characteristic curve. A C-index of 1.0 indicates a perfect predictive model, whereas a value of 0.5 indicates that the feature contains prognostic information equal to that obtained by chance alone. All tests were two-sided, and P values <0.05 were considered statistically significant.

Results

Of the 753 patients that provided adequate pathology information and follow-up data, there were 511 (67.86%) males and 242 (32.14%) females, with a median age of 55 years (range, 5–87 years). A total of 533 patients underwent radical nephrectomy, and 220 underwent partial nephrectomy. The median postoperative follow-up period was 62 months (range, 27–114 months). The clinical characteristics of the patients are summarized in *Table 3*.

All pathologic data of the 753 patients were retrospectively reviewed on the basis of the 2016 WHO/ISUP classification and the Fuhrman grading system (*Tables 1,2*). The group

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Table 3 Clinical characteristics of the 753 patients with ccRCC

Characteristics	No.
Median age, years [range]	55 [5–87]
Gender	
Male	511
Female	242
Side	
Left	375
Right	378
Nephrectomy type	
Radical	533
Partial	220
Median postoperative follow-up, months [range]	62 [27–114]
Pathological T stage	
pT1a	345
pT1b	243
pT2a	114
pT2b	22
pT3a	25
pT3b	1
pT4	3

ccRCC, clear cell renal cell carcinoma.

Table 4 Comparison of 753 ccRCC graded according to the WHO/ISUP and Fuhrman grading systems

ISUP grade	Fuhrman grade				
	1	2	3	4	Total
1	97	40	0	0	137
2	83	375	9	0	467
3	4	85	44	2	135
4	1	1	6	6	14
Total	185	501	59	8	753

ccRCC, clear cell renal cell carcinoma; WHO/ISUP, World Health Organization/International Society of Urological Pathology.

that was reclassified by the 2016 WHO/ISUP grading system was named the ISUP group, and the group that was reclassified by the Fuhrman grading system was named the Fuhrman group. The distribution of the WHO/ISUP

grades and the Fuhrman grade s for the 753 patients was detailed in *Table 4*.

During the follow-up period, 95 patients had died due to ccRCC, and 124 patients had developed recurrence or metastasis. The distribution of the end events in the ISUP and Fuhrman groups is detailed in *Table 5*. The impact of clinicopathological factors on CSS and RFS for all 753 patients with ccRCC was estimated by the Kaplan-Meier method. Through the log-rank test, age (≥55 years), nephrectomy type (radical), pT stage (≥ pT2b), WHO/ISUP grade (3/4), and Fuhrman grade (3/4) were all correlated with CSS and RFS on the univariate analysis (*Figure 1*). In the multivariate analysis, nephrectomy type, pT stage and WHO/ISUP grade were significantly associated with CSS (P<0.0001, P=0.0127 and P<0.0001, respectively) and RFS (P<0.0001, P=0.0077, and P<0.0001, respectively) in the ISUP group (*Table 6*). In addition, nephrectomy type, pT stage and Fuhrman grade were also significantly associated with CSS (P<0.0001, P=0.0004, and P<0.0001, respectively) and RFS (P<0.0001, P=0.0001, and P<0.0001, respectively) in the Fuhrman group (*Table 7*). The C-index for CSS and RFS using the Fuhrman grading system was 0.6323 and 0.6342, respectively; nevertheless, using the WHO/ISUP grading system, the C-index was 0.6983 and 0.7005, respectively (both higher than the former), and the difference is statistically significant (P=0.0185, and P=0.0172, respectively).

A comparison of the WHO/ISUP grade and Fuhrman grade indicated significant upgrading of many tumours after the WHO/ISUP grade was determined. Since 501 tumours were determined to be Fuhrman grade 2, which accounted for 66.53% of the total tumours in our study, we mainly focused on the cases of Fuhrman grade 2. When reviewing the 501 patients with Fuhrman grade 2 tumours using the WHO/ISUP grading system, 375 were classified as having WHO/ISUP grade 2 tumours (non-upgraded group), of whom 43 (11.47%) died from ccRCC, while 85 were upgraded to WHO/ISUP grade 3/4 (upgraded group), of whom 23 (27.06%) died from ccRCC. Univariate and multivariate analyses demonstrated that upgrading from Fuhrman grade 2 to WHO/ISUP grade 3 was a significant factor for the prediction of CSS and RFS in ccRCC patients (P=0.0033 and P=0.0003, respectively) (*Table 8* and *Figure 1*).

Discussion

ccRCC is the most common subtype of RCC, accounting for 70–80% of all RCCs, followed by pRCC and cRCC,

Table 5 The distribution of the ending events according to the WHO/ISUP grading and Fuhrman grading system

System	No. of cases	Cancer-specific survivors			Recurrence-free survivors		
		N (%)	Mean survival (months)	95% confidence interval	N (%)	Mean survival (months)	95% confidence interval
WHO/ISUP grade							
Grade 1	137	137 (100.0)	114	–	134 (97.8)	111.10	107.94–114.26
Grade 2	467	415 (88.9)	104.34	101.79–106.90	401 (85.9)	101.48	98.61–104.36
Grade 3	135	95 (70.4)	85.86	78.70–93.02	85 (63.0)	78.43	70.75–86.11
Fuhrman grade							
Grade 1	185	176 (95.1)	109.55	106.54–112.57	170 (91.9)	106.35	102.50–110.20
Grade 2	501	435 (86.8)	101.64	99.01–104.26	417 (83.2)	98.14	95.18–101.10
Grade 3	59	43 (72.9)	82.84	72.32–93.38	40 (67.8)	72.68	62.30–83.06

WHO/ISUP, World Health Organization/International Society of Urological Pathology.

and its prognosis is significantly poorer than that of the other subtypes (4-6,22). Cheville *et al.* reported that Fuhrman grade lacked prognostic significance for cRCC (23,24). In addition, the WHO/ISUP grading system has replaced the Fuhrman grading system, and it can provide better grade separation, especially in grade 2 and 3 tumours (a drawback to the Fuhrman system), and this new system has exhibited a stronger association with patient outcomes. However, only a few studies have reported that the grading system relying solely on WHO/ISUP grade has shown a stronger association with patient outcomes compared with those relying on Fuhrman grade for ccRCC, and there is no similar study in the Chinese population (19). However, the Chinese are a heterogeneous population, with different obesity rates and smoking rates than others, which are precisely the pathogenic factors of RCC (25,26). For these reasons, our study focused on whether the WHO/ISUP grading system is superior to the Fuhrman grading system and more likely to indicate the prognosis of patients with ccRCC in the Chinese population. Therefore, we reviewed all pathological slides and reassigned pT stage and nuclear grade on the basis of the 2016 WHO/ISUP classification and the Fuhrman grading system. All potential clinicopathological factors for CSS and RFS were estimated by the Kaplan-Meier method; independent associations with CSS and RFS were calculated with Cox proportional hazards regression models.

Our study showed that in the ISUP group, grade 1 tumours were associated with an excellent prognosis, with none of the 137 patients dying due to ccRCC. There was also a significant difference in clinical outcomes between WHO/ISUP grade 1, 2, and 3 tumours; however, the prognosis of grade 3 and 4 tumours classified according to the Fuhrman grading system or the ISUP grading system was not significantly different, which may result from the relatively small number of patients with grade 4 tumours. Previous research has indicated that the modified grading system grouped into either three tiers (grades 1+2, 3, and 4) or two tiers (grades 1+2 and 3+4) exhibited superior predictive accuracy compared with the Fuhrman grading system (27). However, the modified grading system exhibited an obvious reduction in specificity, and our study demonstrated significant differences in the outcomes of grade 1 and 2 tumours classified by the Fuhrman grading system. On the multivariate analysis, nuclear grade was an independent prognostic factor for both CSS and RFS in both groups (ISUP and Fuhrman). However, the predictive accuracy for CSS and RFS using the WHO/ISUP grading system (C-index: 0.6983 and 0.7005, respectively) demonstrated that its predictive ability was superior to that of the Fuhrman grading system (C-index: 0.6323 and 0.6342, respectively and P=0.0185, and P=0.0172, respectively). Delahunt *et al.* reported that nucleolar prominence (in the WHO/ISUP grading system) showed a stronger association with the prognosis of patients with ccRCC than did the Fuhrman grading system (28). In addition, compared with those who were not upgraded, patients who were upgraded to WHO/ISUP grade 3 from Fuhrman grade 2 showed a significantly worse prognosis, which also indicated that the WHO/ISUP grading system was superior to the Fuhrman grading system. Previous research has clarified that nucleolar prominence is often
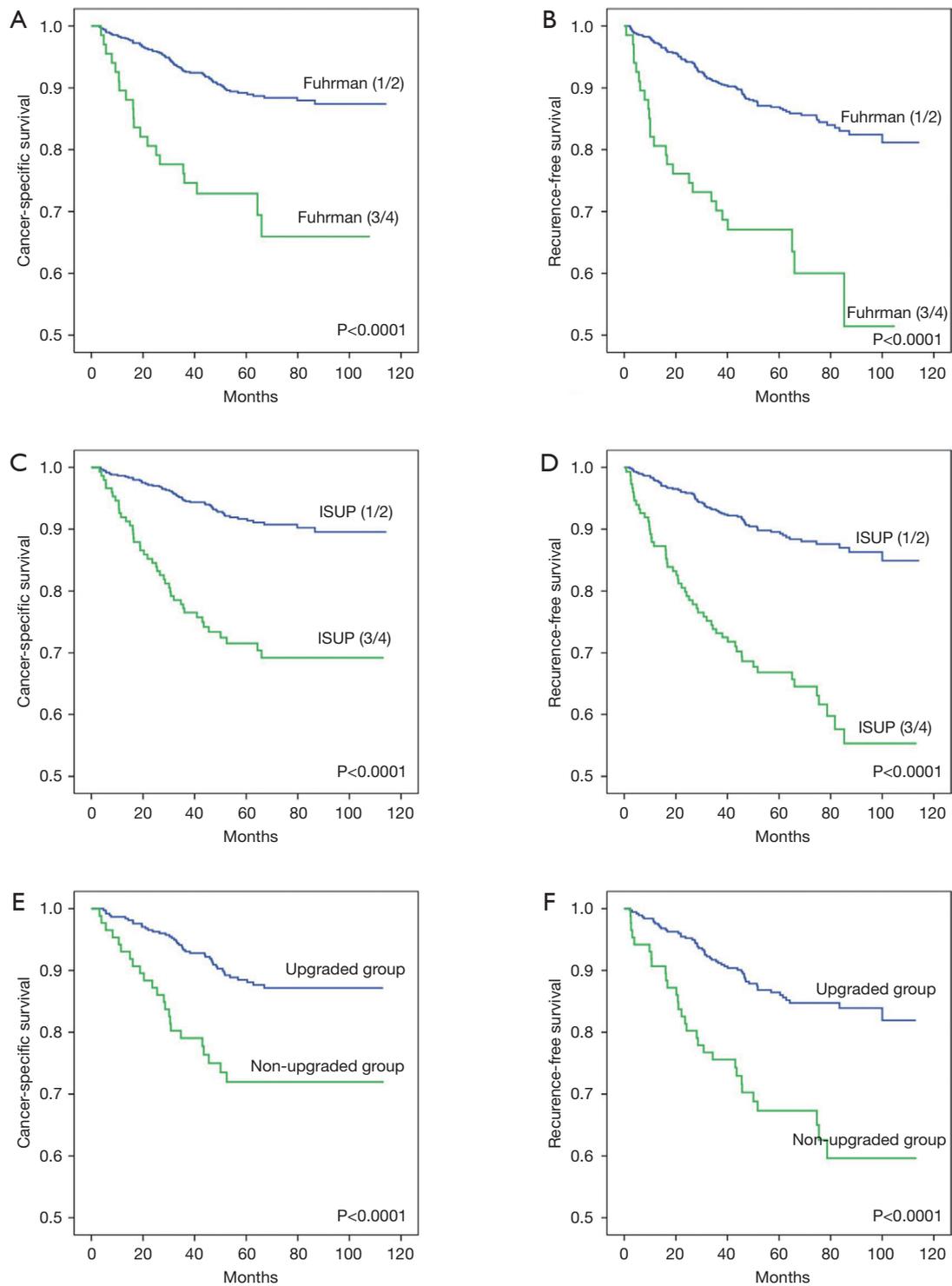
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Figure 1 Survival curve. (A,B) CSS (A) and RFS (B) for 753 ccRCC classified as Fuhrman grade 1/2 (blue line) *vs.* Fuhrman grade 3/4 (green line); (C,D) CSS (C) and RFS (D) for 753 ccRCC classified as ISUP grade 1/2 (blue line) *vs.* ISUP grade 3/4 (green line); (E,F) CSS (E) and RFS (F) for 375 ccRCC classified from Fuhrman grade 2 to ISUP grade 2 (blue line) *vs.* 85 ccRCC upgraded from Fuhrman grade 2 to ISUP grade 3 (green line). ccRCC, clear cell renal cell carcinoma; RFS, recurrence-free survival; CSS, cancer-specific survival; ISUP, International Society of Urological Pathology.

Table 6 Risk factors for predicting postoperative cancer-specific survival and recurrence-free survival in ccRCC using the WHO/ISUP grading system

Factors	Cancer-specific survival			Recurrence-free survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P value	HR (95% CI)	P value	P value	HR (95% CI)	P value
Sex	0.3304	–	–	0.0749	–	–
Age (≥55 years)	0.0355	1.30 (0.85–1.99)	0.2265	0.0492	1.17 (0.81–1.69)	0.4189
Nephrectomy type (radical)	<0.0001	5.93 (2.39–14.70)	<0.0001	<0.0001	4.31 (2.17–8.56)	<0.0001
pT stage (≥ pT2b)	<0.0001	1.99 (1.16–3.43)	0.0127	<0.0001	1.94 (1.19–3.17)	0.0077
ISUP grade (3/4)	<0.0001	3.15 (2.06–4.82)	<0.0001	<0.0001	3.12 (2.14–4.55)	<0.0001

ccRCC, clear cell renal cell carcinoma; HR, hazard ratio; CI, confidence interval; WHO/ISUP, World Health Organization/International Society of Urological Pathology.

Table 7 Risk factors for predicting postoperative cancer-specific survival and recurrence-free survival in ccRCC using the Fuhrman grading system

Factors	Cancer-specific survival			Recurrence-free survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P value	HR (95% CI)	P value	P value	HR (95% CI)	P value
Sex	0.3304	–	–	0.0749	–	–
Age (≥55 years)	0.0355	1.37 (0.90–2.09)	0.1477	0.0492	1.25 (0.86–1.80)	0.2403
Nephrectomy type (radical)	<0.0001	6.42 (2.59–25.91)	<0.0001	<0.0001	4.67 (2.35–9.26)	<0.0001
pT stage (≥ pT2b)	<0.0001	2.61 (1.53–4.23)	0.0004	<0.0001	2.54 (1.58–4.09)	0.0001
Fuhrman grade (3/4)	<0.0001	3.11 (1.83–5.27)	<0.0001	<0.0001	3.20 (1.99–5.15)	<0.0001

ccRCC, clear cell renal cell carcinoma; HR, hazard ratio; CI, confidence interval.

Table 8 Risk factors for predicting postoperative cancer-specific survival and recurrence-free survival in ccRCC with Fuhrman grade 2

Factors	Cancer-specific survival			Recurrence-free survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P value	HR (95% CI)	P value	P value	HR (95% CI)	P value
Sex	0.8155	–	–	0.3959	–	–
Age (≥55 years)	0.2808	–	–	0.1519	–	–
Nephrectomy type (radical)	<0.0001	4.10 (1.48–11.38)	0.0067	<0.0001	4.18 (1.68–10.39)	0.0021
pT stage (≥ pT2b)	0.0016	1.79 (0.92–3.48)	0.0879	<0.0001	1.79 (0.99–3.25)	0.0538
Fuhrman grade 2 (upgraded to ISUP grade 3)	<0.0001	2.18 (1.30–3.68)	0.0033	<0.0001	2.32 (1.46–3.67)	0.0003

ccRCC, clear cell renal cell carcinoma; HR, hazard ratio; CI, confidence interval; ISUP, International Society of Urological Pathology.

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graded at a higher level than nuclear size and nuclear shape. This suggests that if the WHO/ISUP grading system was based upon nucleolar prominence alone, many patients would be over-graded than would be by the Fuhrman grading system (19). RCC is a highly heterogeneous tumor, showing various pathological morphology in different slices, and the areas with high pathological grade are sometimes very subtle and require repeated observation to be clear, which results in a wide upgrading when reassessed, such as 1 patient was classified as Fuhrman grade 1 and ISUP grade 4 (29).

The Fuhrman grading system has been widely adopted worldwide since 1982 (10). However, with its widespread use in contemporary pathology practice, there are many internal problems that are constantly emerging, especially those related to reproducibility (19,30-33). The final determination of Fuhrman classification requires the simultaneous assessment of nuclear size, nuclear shape, and nucleolar prominence, but the Fuhrman grading system does not specify the weight of each parameter, particularly when there is an inconsistency between any of the parameters; no standard exists to allocate a weight to arrive at a final grade. Moreover, there is obvious pathomorphological heterogeneity in RCC and scant defining details relating to some of the grading criteria, which results in the subjectivity of pathologists. Therefore, the Fuhrman grading system shows poor reproducibility (30,33). Furthermore, a previous study reported that of the three defined parameters of the Fuhrman grading system, only nuclear size and nucleolar prominence were associated with the clinical outcome of ccRCC (28). Delahunt *et al.* also noted that although the nuclear long axis was significantly associated with prognosis, the Fuhrman criteria overestimated nuclear size, and nucleolar prominence evaluated individually showed utility for grading purposes (28). Kim *et al.* reported that a high WHO/ISUP grade and a high Fuhrman grade were independent risk factors for CSS but not RFS in ccRCC patients. In addition, both grading systems were significantly associated with the CSS of ccRCC patients, but there was no significant difference in the C-index between the two grading systems (34). However, our study clarified that the two grades were independent prognostic factors for both the CSS and RFS of ccRCC patients and that the predictive ability of the WHO/ISUP grading system was superior to that of the Fuhrman grading system.

There were several limitations to this study. First, because this was a single-institution retrospective study, our results must be verified in larger, prospective multicentre studies. Second, some patients were lost to follow-up or lacked prognostic data. Third, we included only cases pathologically proven to be ccRCC and excluded other primary renal neoplasms. Finally, our study focused only on pathological grades and did not focus on tumour necrosis or vascular invasion.

In summary, to the best of our knowledge, the current study is the first to verify the correlations between postoperative prognosis and the WHO/ISUP grade of ccRCC in a Chinese population. Furthermore, our study confirmed that the WHO/ISUP grading system was superior to the Fuhrman grading system in predicting the clinical outcomes of ccRCC patients. Our study provides a certain clinical value for adopting the WHO/ISUP classification in the Chinese population.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tau-20-799

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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 Clinical Research Ethics Committee of Xiangya Hospital, Central South University approved the study (No. 2017121011), and informed consent was waived due to the retrospective nature of the research. The authors confirm the study conformed to the provisions of the Declaration of Helsinki

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