



Effects of BAP1, Ki-67 index, and Id-1 in patients with clear cell renal carcinoma and their correlation with clinical features and prognosis

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Background: Clear cell renal carcinoma (CCRCC) is a multigene-related tumor. The aim of the present study was to analyze the expression of breast cancer 1-associated protein 1 (BAP1), Ki-67, and inhibitor of differentiation-1 (Id-1) in CCRCC patients and their correlation with clinical features and prognosis.

Methods: A total of 45 CCRCC patients who were diagnosed and treated at our hospital from January 2016 to January 2018 were included in the present study. BAP1, Ki-67, and Id-1 protein expression in the CCRCC tissue group and adjacent mucosa group was compared. The correlation between BAP1, Ki-67, and Id-1 proteins, and the clinical characteristics and the prognosis of CCRCC patients, were analyzed. Multiple logistic regression was used to analyze the risk factors that affect the prognosis of CCRCC patients.

Results: The negative rate of BAP1 in the CCRCC group was higher than that in the adjacent mucosa group. There were more patients with a Ki-67 index >10 and a higher Id-1-positive rate in the CCRCC tissue group. BAP-1, Ki-67 index, and Id-1 protein expression were not correlated with age, sex, surgical method, microscopic necrosis, and degree of sarcomatoid characteristics of CCRCC patients ($P>0.05$), but were related to tumor diameter, pathological stage, TNM stage, and World Health Organization (WHO)/Internal Society of Urologic Pathology (ISUP) grade. The Kaplan-Meier survival curve showed that the average survival time of the BAP1-negative group, Ki-67 index >10 group, and Id-1 protein-positive group was shorter than that of the BAP1-positive group, Ki-67 index ≤ 10 group, and Id-1 protein-negative group, respectively. Pathological staging, WHO/ISUP classification, negative BAP1, Ki-67 index >10, and positive Id-1 protein were independent risk factors affecting CCRCC patients ($P<0.05$).

Conclusions: The expression of BAP1 in CCRCC patients decreased, and the expression of Ki-67 and Id-1 protein increased. Abnormal expression levels of BAP1, Ki-67, and Id-1 proteins were involved in the occurrence and development of CCRCC, and closely related to the prognosis of patients. These can be used as molecular markers for predicting the prognosis of CCRCC patients and as potential targets for tumor treatment.

Keywords: Breast cancer 1-associated protein 1; Ki-67 index; inhibitor of differentiation-1 protein; clear cell renal carcinoma (CCRCC); prognosis

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Introduction

Renal cell carcinoma (RCC) is the most common renal malignant tumor, and clear cell renal carcinoma (CCRCC) is the most common histopathological type of renal cancer (1). As a multigene-related tumor, the molecular biologic mechanism of CCRCC occurrence and development has not yet been elucidated. Although treatments, such as radical nephrectomy or nephron-preservation therapies, have achieved satisfactory results among CCRCC patients, some patients still suffer from recurrence, metastasis, and even death after surgery. Therefore, it is important to find effective monitoring biomarkers and interventions to improve the prognosis of CCRCC patients (2).

Breast cancer 1 (coded by *BRCA1* gene) is a tumor suppressor, with mutations or deletions in various tumor tissues. BRCA1-associated protein 1 (BAP1) is the translation product of BRCA1 and belongs to the family of deubiquitinating enzymes. The target proteins of BAP1 participate in the occurrence and development of cancer through various pathways; therefore, the expression and function of CCRCC has attracted wide attention (3). Ki-67 is a nuclear protein involved in the transcription of ribosomal RNA, and is currently often used as a sensitive indicator of cell proliferation activity (2). The Ki-67 index is widely used, and it has been noted that the expression of Ki-67 can predict the biologic behavior and prognosis of RCC (4). Inhibitor of differentiation-1 (Id-1) is involved in cell cycle regulation and plays an important role in the process of cell differentiation. Id-1 has been the focus of study for the prognosis of cancer (5). In the present study, the expression of BAP1, Ki-67, and Id-1 protein in CCRCC patients and their relationship with clinical characteristics and prognosis were studied, with the aim of developing treatment modalities for CCRCC. We present the following article in accordance with the REMARK reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-1258>).

Methods

General information

A total of 45 CCRCC patients who were diagnosed and treated at our hospital from January 2016 to January 2018 were included in the present study. Of these patients, 23 were male and 22 were female. The patients were aged 27–70 years, with an average age of 46.75 ± 5.16 years. A total of 36 cases involved the renal capsule, and 9 involved the renal pelvis; the tumor diameter was 1.63–13 cm, with an average

diameter of 5.79 ± 1.53 cm. Based on the TNM staging standard of RCC established by the International Anti-Cancer Association, 12 cases were pT1 stage, 13 cases were pT2 stage, 13 cases were pT3 stage, and 7 cases were pT4 stage. Tumor tissue and normal renal mucosa tissue adjacent to the tumor (>3 cm away from the CCRCC tissue) were collected, and defined as the CCRCC group (n=45) and the adjacent tissue group (n=45), respectively. There were no differences in general data, such as sex or age, between the two groups ($P > 0.05$).

The inclusion criteria were as follows: (I) all patients had clear evidence of pathological diagnosis and were diagnosed with CCRCC; (II) patients did not undergo radiotherapy or chemotherapy before enrollment; and (III) all patients agreed with the study protocols, provided signed informed consent, and were approved by the medical ethics committee of West China Hospital. The exclusion criteria were as follows: (I) patients with hematological diseases; (II) patients who did not agree with the study protocols; (III) patients with severe mental illness or dementia who were unable to participate; (IV) patients with other primary malignant tumors other than CCRCC; and (V) patients with rheumatic immunity or connective tissue disease. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Research methods

The clinical data of all patients were collected, and the expression of BAP1, Ki-67, and Id-1 protein were compared in CCRCC and adjacent tissues. Survival and death for all patients were recorded during the follow-up period. The correlation between BAP1, Ki-67 index, and Id-1 protein level, and the various clinical characteristics of the CCRCC patients, were then analyzed. The Kaplan-Meier survival curve was drawn to study the effect of BAP1, Ki-67 index, and Id-1 protein on the prognosis of patients, and multiple logistic regression analysis was used to analyze the risk factors affecting the prognosis of CCRCC patients.

Main reagents and instruments

Anti-BAP1 polyclonal antibody, horseradish peroxidase-conjugated secondary antibody of goat anti-rabbit immunoglobulin antibody, and ready-to-use rapid immunohistochemistry Max Vision kit were purchased from Fuzhou Maixin Biotechnology Development Company

(China). Primary antibody for Id-1 was purchased from Sigma (USA); the ready-to-use EnVision kit was purchased from Dako Biological Products (Denmark) and used at a dilution of 1:200, and sections for positive control were also provided in this company. All the sections were observed under an optical microscope (Olympus, Japan). The human adult skin keratinocyte (HaCaT) cell line was purchased from the American Standard Biological Collection (USA).

BAP1, Ki-67 index, Id-1 protein detection

The collected tissues were cut into 4 μm -thick slices, and immunohistochemical staining was performed according to the instructions of the detection kits. Slices incubated with phosphate-buffered saline (PBS) instead of the primary antibody was used as negative control, and the positive control was the known positive sections of the corresponding antibody.

Ki-67 index detection

The area with high-staining cell density was magnified at 400 \times to count a total of 600 positive cells, and patients were divided into two groups according to a Ki-67 index of ≤ 10 or > 10 . The Ki-67 index was defined as the result of the number of positive cells/600 tumor cells.

BAP1 and Id-1 protein detection

The presence of clearly located brown or tan particles in the tumor cells was defined as positive expression. Ten randomly selected images were analyzed under high power field, and scored according to staining depth and the proportion of positive cells in the field: 0 score, no coloring; 1, $< 25\%$ light; 2, 25–50% brown; and 3, $> 50\%$ brown. The score of immune response was multiplied by the 2 scores; scores of 0–3 points were negative (–), and scores of > 3 were positive (+). Histochemical staining results were independently read and scored by at least two senior pathologists.

Polymerase chain reaction (PCR)

The DNA of the patients was extracted from the resected specimens. After purity detection and quantitative analysis, the DNA was modified with sodium bisulfite, purified and recovered, and stored at $-20\text{ }^{\circ}\text{C}$ for later use. The primers for the promoter region of BAP1, Ki-67 and Id-1 genes were from the published literature (6), and synthesized by Dalian Bao Biological Company. And the methylation primers: (forward) 5'-TCGTGGTAACGGAAAAGCGC-3'

and (reverse) 5'-AACGAACTCACGCCGCGCAA-3'; Non-methylated primers: (forward) 5'-TTGAGAGGTTGTTGTTGTTTAGTGG-3' and (reverse) 5'-AACAAACTCACAC-CACACAA-3'. The total reaction system is 25 μL , and the reaction conditions were as follows: pre-denaturation at $95\text{ }^{\circ}\text{C}$ for 10 min, denaturation at $95\text{ }^{\circ}\text{C}$ for 30 s, annealing at $62\text{ }^{\circ}\text{C}$ for 30 s for methylated primer; annealing at $55\text{ }^{\circ}\text{C}$ for 30 s for non-methylated primer, then extension at $72\text{ }^{\circ}\text{C}$ for 30 s, for a total of 40 cycles, and final extension at $72\text{ }^{\circ}\text{C}$ for 10 min. The take 5 μL reaction product to run the 1.8% agarose gel electrophoresis with EB staining and finally analyzing the gel imaging.

Follow-up methods

In the present study, follow up commenced following the operation until January 2020 or death. The average follow-up time for all patients was 20.31 ± 2.66 months. Patients were followed up mainly by patients coming to the hospital for reexamination (telephone follow-up was used in special cases). In the present study, overall survival (OS) was defined as the length of time that CCRCC patients were alive after diagnosis.

Statistical methods

Data were analyzed using SPSS version 18.0 (IBM, USA), and the measurement data were expressed as the mean \pm standard deviation ($\bar{x} \pm s$), and analyzed by χ^2 -test. A receiver-operating characteristic (ROC) curve was drawn, and the Kaplan-Meier method was used for the prognostic analysis of patients among different groups. Multiple logistic regression was used to analyze the risk factors that affect the prognosis and survival of CCRCC patients. Results with $P < 0.05$ was considered to be statistically significant.

Results

Expression of BAP1, Ki-67, and Id-1 protein in CCRCC and adjacent tissues

The negative rate of BAP1 in the CCRCC group was significantly higher than that in the adjacent tissue group ($P < 0.05$). There were more patients in the CCRCC group with a Ki-67 index > 10 than in the adjacent tissue group, and the Id-1-positive rate in the CCRCC group was higher than that in the adjacent tissue group ($P < 0.05$) (Table 1, Figure 1).

Table 1 Expression of breast cancer 1-associated protein 1 (BAP1), Ki-67 index, and inhibitor of differentiation-1 (Id-1) protein in clear cell renal carcinoma (CCRCC) and adjacent mucosa tissues

Indicator	CCRCC tissue group (n=45)	Adjacent mucosa group (n=45)	χ^2	P value
BAP1, n (%)			16.172	<0.001
Negative	34 (75.56)	15 (33.33)		
Positive	11 (24.44)	30 (66.67)		
Ki-67 index, n (%)			37.675	<0.001
≤10	10 (22.22)	39 (86.67)		
>10	35 (77.78)	6 (13.33)		
Id-1 protein, n (%)			17.787	<0.001
Negative	12 (26.67)	32 (71.11)		
Positive	33 (73.33)	13 (28.89)		

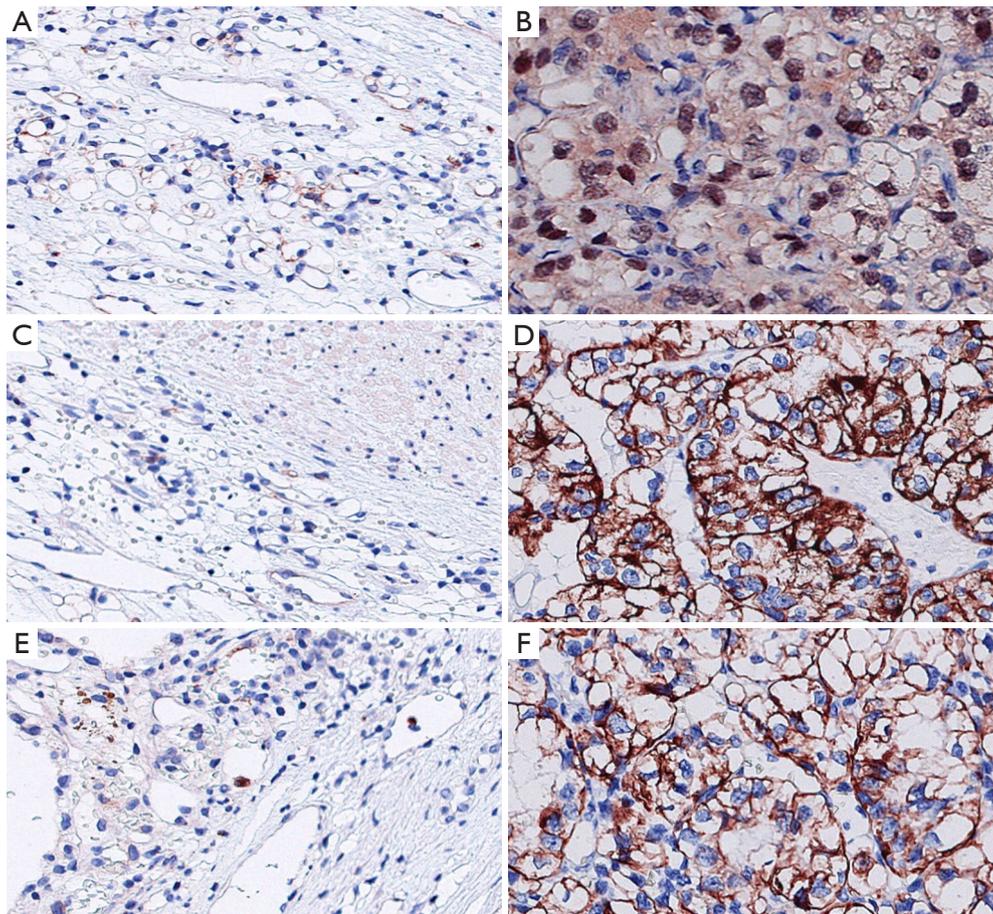


Figure 1 BAP1, Ki-67 index and Id-1 protein expression under immunohistochemical staining (×200). (A,B) Respectively BAP1 protein expression in carcinoma adjacent tissues and CCRCC organizations; (C,D) expression of KI-67 index in adjacent tissues and CCRCC cancer tissues, respectively; (E,F) expression of Id-1 protein in adjacent tissue and CCRCC cancer tissue, respectively.

Table 2 Correlation between breast cancer 1-associated protein 1 (BAP1), Ki-67 index, and inhibitor of differentiation-1 (Id-1) protein and clinical characteristics of clear cell renal carcinoma (CCRCC) patients

Pathological parameters	Cases (n=45)	BAP1		χ^2	P	Ki-67 index		χ^2	P	Id-1 protein		χ^2	P
		Negative (n=34)	Positive (n=11)			≤ 10 (n=10)	>10 (n=35)			Negative (n=12)	Positive (n=33)		
Age (years)				0.602	0.438							0.187	0.666
>60	20	14	6			4	16			5	15		
≤ 60	25	20	5			6	20	0.103	0.748	7	28		
Sex				0.186	0.666							0.008	0.828
Male	23	18	5			6	17			6	17		
Female	22	16	6			4	18	0.407	0.524	6	16		
Surgical type				0.012	0.911							0.105	0.746
Nephron preservation	17	13	4			3	14			5	12		
Radical nephrectomy	28	21	7			7	21	0.331	0.565	7	21		
Maximum tumor diameter (cm)				4.450	0.035							5.292	0.021
≤ 4	29	19	10			10	19			11	18		
> 4	16	15	1			0	16	7.094	0.008	1	15		
Pathological staging				7.370	0.007							5.114	0.024
pT1–2	25	15	10			9	16			10	15		
pT3–4	20	19	1			1	19	6.178	0.013	2	18		
TNM stage				7.228	0.007							13.314	<0.001
I–II	21	12	9			8	13			11	10		
III–IV	24	22	2			2	22	5.740	0.017	1	23		
WHO/ISUP grade				6.497	0.011							12.803	<0.001
1–2	18	10	8			8	10			10	8		
3–4	27	24	3			2	25	8.571	0.003	2	25		
Microscopic necrosis				1.120	0.290							2.628	0.105
Yes	11	7	4			4	7			5	6		
No	34	27	7			6	28	1.684	0.194	7	27		
Sarcomatoid characteristics				1.684	0.194							1.169	0.280
Yes	10	6	4			4	6			4	6		
No	35	28	7			6	29	2.351	0.125	8	27		

ISUP, Internal Society of Urologic Pathology; WHO, World Health Organization.

Correlation between BAP1, Ki-67 index, and Id-1 protein and the clinical characteristics of CCRCC patients

The findings indicated that the expression of BAP-1, Ki-67, and Id-1 protein were not correlated with age, sex, surgical

method, microscopic features of necrosis, and sarcomatoid characteristics of CCRCC patients ($P>0.05$), but was correlated to tumor diameter, pathological stage, TNM stage, and WHO/ISUP classification ($P<0.05$) (Table 2).

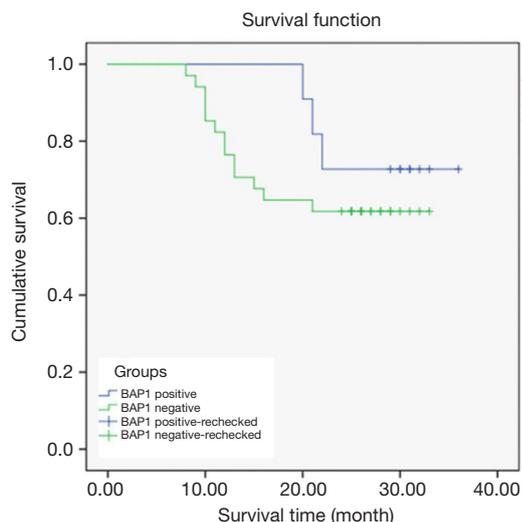


Figure 2 Relationship between breast cancer 1-associated protein 1 (BAP1) and overall survival of clear cell renal carcinoma patients.

Prognosis of the 45 CCRCC patients

By the last follow up, 17 of 45 CCRCC patients had died, with a mortality rate of 37.78% and a survival rate of 62.22%.

Relationship between BAP1 and prognostic survival of CCRCC patients

A total of 20 patients survived in the BAP1-negative group and 14 died. In the BAP1-positive group, 8 patients survived and 3 died.

Kaplan-Meier survival curves differed according to BAP1 expression level. The survival time of the BAP1-negative group was, on average, 25.09 ± 1.76 months, and was 31.91 ± 2.02 months in the BAP1-positive group, indicating that the average OS of patients in the BAP1-negative group was shorter than that in the positive group ($P < 0.05$) (Figure 2).

Relationship between Ki-67 index and prognostic survival of CCRCC patients

In the Ki-67 index ≤ 10 group, 9 patients survived and 1 died; in the Ki-67 index > 10 group, 19 patients survived and 16 died.

The Kaplan-Meier survival curves differed according to Ki-67 index expression level. The average survival time of patients in the Ki-67 index ≤ 10 group was

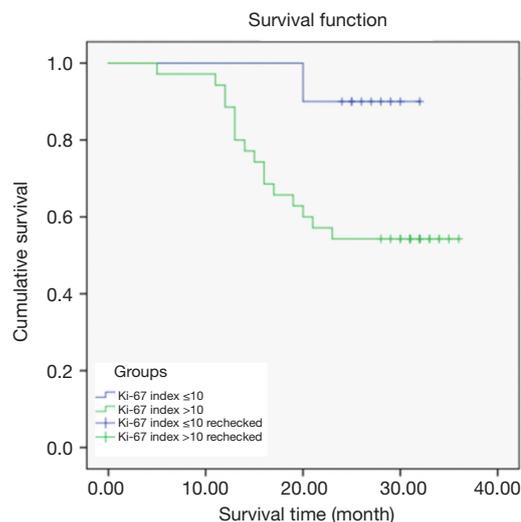


Figure 3 Relationship between Ki-67 index and overall survival of clear cell renal carcinoma patients.

30.80 ± 1.14 months, and 26.40 ± 1.84 months in the Ki-67 index > 10 group, indicating that the average survival time of CCRCC patients was significantly shorter in the Ki-67 index > 10 group than the Ki-67 index ≤ 10 group ($P < 0.05$) (Figure 3).

Relationship between Id-1 protein and prognostic survival of CCRCC patients

In the Id-1-negative group, 10 of 12 patients survived; in the Id-1-positive group 18 of 33 patients survived.

The Kaplan-Meier survival curves significantly differed depending on Id-1 protein expression level. The average survival time of patients in the Id-1-negative group was 37.00 ± 2.61 months, and 25.55 ± 1.60 months in the Id-1 protein-positive group, indicating that the average survival time of patients in the Id-1-negative group was significantly longer than that in the Id-1-positive group ($P < 0.05$) (Figure 4).

Univariate and multivariate analyses of the prognostic survival of CCRCC patients

The results of the univariate and multivariate analyses showed that factors, such as pathological staging, WHO/ISUP classification, BAP1 negativity, Ki-67 index > 10 , and Id-1 protein positivity, were independent risk factors affecting the prognosis of CCRCC patients ($P < 0.05$) (Table 3).

Discussion

CCRCC is the most common histopathological type of renal cancer. Related studies have found that the survival rate of CCRCC patients is mainly affected by pathological staging and tumor cell grading. In addition, molecular indicators and their prognostic significance are still the focus of current research.

BAP1 is a deubiquitinating enzyme, which contains an 80.4-kDa nuclear localization protein and ubiquitin carboxy-terminal hydrolase domain (7). BAP1 appears to be a tumor suppressor in cultured cells *in vitro*, and its

deubiquitinating enzyme domain and nuclear localization sequence are the main pathways of BAP1 in inhibiting cell growth. Shankar *et al.* found that 47% of uveal melanomas are inactivated by BAP1 protein mutations (8). They reported that BAP1 regulates a variety of cellular pathways related to tumorigenesis and closely related to tumor metastasis. The results of previous sequencing studies have shown that there are base substitutions at the BAP1 mRNA site, and the mutation of BAP1 gene occurs in 15% of the CCRCC cases, and the mutation of BAP1 gene was considered as a pathogenic factor of CCRCC (9). The findings of the present study indicate that the BAP1 protein in cancer tissues of CCRCC patients was mainly negatively expressed, and the expression of BAP1 and Ki-67 was related to the tumor diameter, pathological stage, TNM stage, and WHO/ISUP grade of the CCRCC patients ($P < 0.05$), indicating that the BAP1 protein can inhibit cell proliferation and the metastasis of cancer cells. The Kaplan–Meier survival curve was further used to analyze its impact on the prognosis of patients. The average OS of patients in the BAP1-negative group was shorter than that in the BAP1-positive group ($P < 0.05$), indicating that BAP1-negative expression is also an independent risk factor affecting CCRCC patients ($P < 0.05$). This indicates that the overexpression of BAP1 may be an important way to promote the progression and deterioration of CCRCC patients, and it is expected to be a good biologic target for controlling CCRCC progression.

Immortal proliferation is one of the hallmarks of malignant tumors. Ki-67 is a proliferation-related nuclear antigen involved in the transcription of ribosomal RNA that can reflect cell proliferation activity (10). In normal

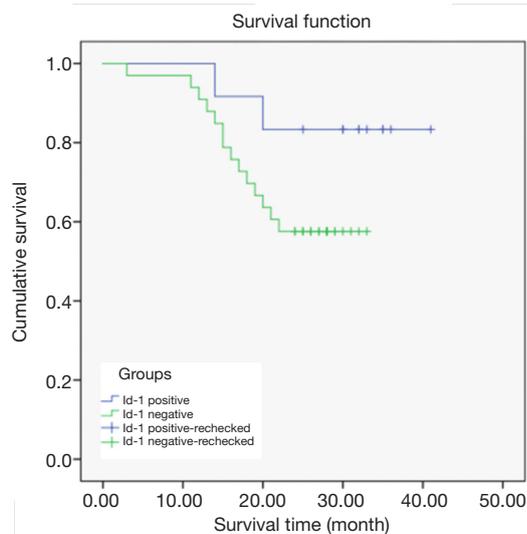


Figure 4 Relationship between inhibitor of differentiation-1 (Id-1) and overall survival of clear cell renal carcinoma patients.

Table 3 Univariate and multivariate analyses of the prognostic survival of clear cell renal carcinoma (CCRCC) patients

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (>60 vs. ≤60 years)	1.996	0.945–4.195	0.792	–	–	–
Surgical type (nephron preservation vs. radical nephrectomy)	1.842	0.894–3.797	0.851	–	–	–
Pathological staging (pT1–2. vs. pT3–4)	2.130	1.584–2.863	0.017	1.291	1.091–2.942	<0.001
WHO/ISUP grade (grade 1–2 vs. grade 3–4)	2.206	1.699–3.286	0.004	2.147	1.572–2.932	<0.001
BAP1 (negative vs. positive)	1.831	1.791–2.268	0.021	1.970	1.579–2.458	<0.001
Ki-67 index (>10 vs. ≤10)	2.659	1.943–3.610	0.001	1.546	1.338–2.617	<0.001
Id-1 protein (positive vs. negative)	2.396	1.758–3.266	0.003	1.578	1.235–2.174	<0.001

BAP1, breast cancer 1-associated protein 1; CI, confidence interval; Id-1, inhibitor of differentiation-1; ISUP, Internal Society of Urologic Pathology; OR, odds ratio. WHO, World Health Organization.

cells, Ki-67 is a sign of the late-stage cell cycle. The mRNA level of Ki-67 is highest around the G2 phase, while its protein level increases throughout the cell cycle and reaches a peak during mitosis (11). At the same time, ki-67 was found to play a key role in mitosis by regulating recombinant chromatin, promoting epithelial mesenchymal transformation and thus inducing the occurrence and development of CCRCC. The relationship between its expression and prognostic factors and pathological stage has also been confirmed by several studies. The Id-1 protein belongs to the helix-loop-helix protein family and has the same characteristics as oncogenes, which inhibit cell differentiation and promote cell proliferation, thereby playing a role in tumor occurrence and invasion (12). At present, the well-defined mechanisms of the Id-1 protein in promoting tumor progression include downregulating the downstream MAPK signals of thrombotic constrictor gene (*tsp-1*), upregulating phosphorylation levels of Raf and mitogen-activated protein kinase (MEK1/2), thereby promoting the expression of genes on early growth response. In recent years, Ki-67 and Id-1 have been used as sensitive indicators to assess prognosis in a variety of malignant tumors (13,14). However, there are few studies on the expression of Ki-67 index and Id-1 protein in patients with different clinical characteristics and prognoses (15). Therefore, in the present study, we studied the expression of the Ki-67 index and Id-1 protein in CCRCC patients and their correlation with clinical features and prognosis. The results showed that the majority of CCRCC patients were those with Ki-67 index >10 and a high expression of Id-1 positivity in cancer tissues ($P < 0.05$). The average OS of patients in the Ki-67 index >10 group and the Id-1-positive group was shorter than those in the Ki-67 index ≤ 10 group and the Id-1-negative group ($P < 0.05$), respectively, indicating that Ki-67 index and Id-1 protein are closely related to the development and prognosis of CCRCC. These results suggest that Ki-67 and Id-1 may be potential biomarkers for clinical prognoses.

Risk factors affecting the prognosis of CCRCC patients are very complex, and differ among regions (16). The results of the present study showed that pathological staging, WHO/ISUP grade, negative expression of BAP1, Ki-67 index >10, and positive expression of Id-1 protein were all independent risk factors affecting the prognosis of CCRCC patients ($P < 0.05$). These findings indicate that patients with adverse prognostic factors should be treated differently to those without. Effective measures and comprehensive treatment should be adopted for patients with unfavorable

prognoses to further improve the survival rate of patients.

In CCRCC patients in the present study, the BAP1 expression level decreased, and the Ki-67 index and Id-1 protein expression levels increased, indicating that the abnormal expression levels of BAP1, Ki-67, and Id-1 protein are involved in the occurrence and development of CCRCC, and are closely related to the prognosis of CCRCC. These indicators can be used as molecular biomarkers for predicting the prognosis of CCRCC patients, as well as potential targets for tumor treatment.

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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-20-1258>). The 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). All patients agreed with the study protocols, provided signed informed consent, and the study were approved by the medical ethics committee of West China Hospital.

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