Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Immunohistochemical co-expression of PAX2 and CAIX predicts better prognosis in clear cell renal cell carcinoma after nephrectomy: A retrospective observational study

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Article Info

Article history:

Received: January 22, 2024
Accepted: April 14, 2024
Published: June 30, 2024

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Abstract

Clear cell renal cell carcinoma (ccRCC) is a lethal malignancy with high metastatic probability. Paired box 2 gene product (PAX2) carbonic anhydrase IX were biomolecules closely linked with ccRCC development and outcomes of multiple malignancies. We aim to explore the role of immunohistochemical staining of PAX2 and CAIX to predict ccRCC prognosis after nephrectomy. Surgical specimens of patients who were pathologically diagnosed as ccRCC were reviewed. Expression levels of PAX2 and CAIX were assessed via immunohistochemical staining. Recurrence-free survival (RFS) and overall survival were compared among different phenotypes. Inverse probability of treatment weighting (IPTW) was used for adjustment of confounding factors. 56 patients were included. Patients with PAX2 and CAIX high-expression (the two-high group, n=8) had significantly longer RFS and OS than those of simultaneously down-expression (the two-low group, n=31). Median RFS was 38.4 (95% CI: 32.3-NA) for the two-high group and 14.8 (95% CI: 13.4-39.0) months for the two-low group (P=0.043). IPTW confirmed PAX2 and CAIX co-expression is associated with less recurrence risk HR: 0.39, 95% CI: 0.17-0.92, P=0.031). Co-expression of PAX2 and CAIX is associated better prognosis of ccRCC. We are looking for validation by large cohort studies.

Keywords: Clear cell renal cell carcinoma, Paired box 2 gene product, Carbonic anhydrase IX, Nephrectomy, Prognosis.

1. Introduction

Renal cell carcinoma (RCC) is the most common and lethal kidney malignancy of which the major cases are the clear cell subtype (ccRCC) [1]. To date, radical or partial nephrectomy remains the standard curative therapy for locally advanced ccRCC [2]. However, tumor metastases still occur in approximately 20–40% of cases after surgery, which brings big challenges for patient recovery and long-term treatment [3]. Conventional risk stratification systems including the UCLA integrated staging system (UISS) and the Mayo Clinic stage, size, grade, and necrosis (SSIGN) tend to be based on clinicopathological features to guide postoperative surveillance [4,5]. However, given the extreme heterogeneity of genomic expression profile and microenvironment of ccRCC [6], predicting efficiency of tumor relapses through these models is inevitably limited. Therefore, increasing researches attempted to identify novel biomarkers from blood and pathological samples to aid prognostic prediction [7].

Paired box 2 gene product (PAX2) is a transcription factor that is expressed in both primary tumors and tumor-derived cell lines [8]. As early as 1990s, researches has already identified its role in regulating renal epithelium development and proliferation of RCC cells [9]. In 2006, Hueber and his team revealed that PAX2 inhibition would facilitate cisplatin-caused apoptosis of RCC cells in elephant kidney models [10]. Recently, Li et al innovatively proved expression of PAX cluster 2 or 8 of RCC tissues was associated with better clinical outcomes through TCGA data analyses [11]. Besides, a clinical study conducted in breast indicated that PAX2 up-expression was associated with tamoxifen efficiency and better survival [12]. Taken together, we speculated that PAX2 is likely to serve as a novel biomarker for ccRCC.

Carbonic anhydrase IX (CAIX) is a specific biomarker of RCC and is useful in assistance of ccRCC diagnosis [13]. Priorly, Patard, Zhao and Büscheck et al successively revealed that CAIX up-expression was linked with good clinicopathological phenotype and superior survival of ccRCC patients [14-16]. However, other studies conducted in large cohorts and TACG data put forward a contradictory conclusion that prognostic power of CAIX is unsatisfying [17,18]. Researchers explained that inference of frequent somatic mutation of the von Hippel-Lindau (VHL) gene in ccRCC might account for this [19]. Notably, previously study found VHL gene loss would apparently drive PAX2

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Doi: http://dx.doi.org/10.14715/cmb/2024.70.6.20

reactivation. Therefore, we speculated that a comprehensive analysis of both PAX2 and CAIX expression could possibly improve prognostic accuracy of ccRCC.

In this prospective observational study, we aim to assess whether PAX2 and CAIX up-expression indicate better outcomes of ccRCC patients after nephrectomy.

2. Materials and Methods

2.1. Research oversight

This prospective observational study was approved by Ethical Committee of Mian Yang Central Hospital (approval number: No. 201456) Patients were enrolled adhering to the guidelines for Helsinki Declaration and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [20]. Written consents were signed after adequate information. We reported this work in accordance to in line with the STROCSS criteria [21].

2.2. Patients and study design

From January 1st, 2017 to December 31st, 2020, patients who received nephrectomy and were pathologically diagnosed as ccRCC at Mian Yang Central Hospital were prospectively enrolled in this study (Figure 1). The inclusion criteria were as follows: (1) pathologically diagnosed as ccRCC; (2) AJCC stage I to III (retroperitoneal lymph nodes ≤1 cm were considered as N0); (3) receiving radical or partial nephrectomy; (4) no previous anti-tumor therapy; (4) R0 resection according to histopathological outcomes. The exclusion criteria were as follows: (1) combined with other malignancies; (2) patients who received adjuvant anti-tumor therapy; (3) tissue insufficiency or quality fail; (4) inadequate information or follow-up; (5) patients' dissent with this study. Preoperative features (including patient demographics, medical history, symptoms at presentation, laboratory and imaging examinations) and surgical features (approach, time, estimated blood loss and pathological outcomes) were recorded in electronic medical record system of our hospital. Tissue specimens were collected and assessed using hematoxylin-eosin (H&E) staining and immunohistochemistry. After surgery, patients were followed up for at least one year.

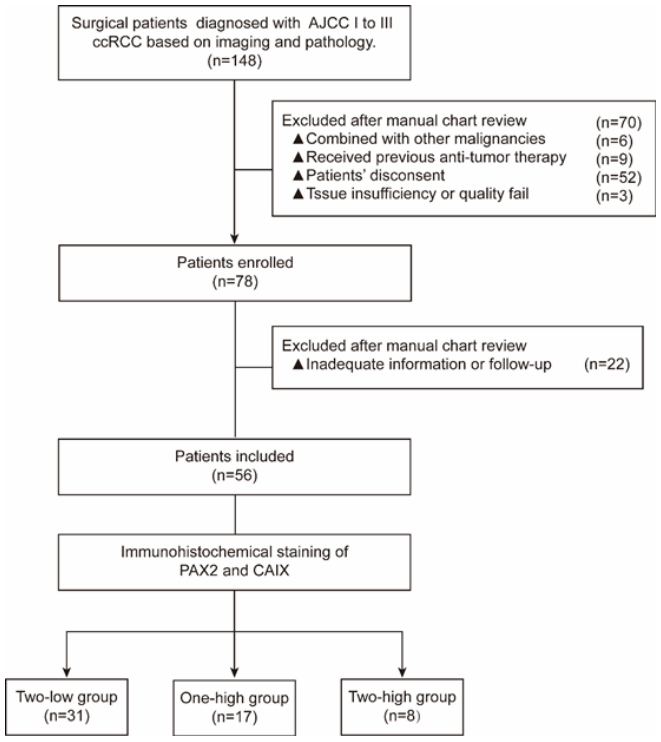

Fig. 1. Patient inclusion.

2.3. Immunohistochemistry

To evaluate PAX2 and CAIX protein expression, representative tissue microarray (TMA) formats were analyzed by immunohistochemical staining. The protocols of PAX2 and CAIX immunohistochemical staining were based on the descriptions by Ozcan's and Leibovich's teams [22,23]. In short, adjacent specimens from the same tumor tissue were stained with either anti-PAX2 antibodies (Invitrogen, Carlsbad, California) or anti-CAIX antibodies (Institute of Molecular Genetics, Prague, Czech Republic). If the staining areas were not homogeneous enough (more than 25% showed a different intensity), a secondary staining would be performed. All tumors were reviewed and assessed blindly by two senior pathologists. For stratification of PAX2 expression, <50% and >50% of the nuclei stained indicated high expression and low expression, respectively [24-26]. For stratification of CAIX expression, <85% and >85% of the nuclei stained indicated high expression and low expression, respectively [23].

2.4. Follow-up and study outcome

Patients were followed up every 6 months for the first 2 years and then annually with enhanced CT. Follow-up data (including physical and imaging examinations) were recorded by electronic medical record system. For patients who took reexaminations at other institutions for a long time, we also followed them up by telephone contact and recorded relevant information in manual format. The date of the final follow-up was June 30, 2023. The primary outcome was recurrence-free survival (RFS), which was defined by occurrence of new lesions or the last negative follow-up or death. Secondary outcome was overall survival, which was defined by the last follow-up or death.

2.5. Statistical analysis

The associations between clinicopathologic factors and PAX2 and CAIX expression were analyzed by the student's t-test and Pearson's chi-square test. Kaplan-Meier methods were used to demonstrate associations of expression patterns of PAX2 and CAIX with RFS and OS. Inverse probability of treatment weighting (IPTW) was employed to adjust for potential confounding factors including age, gender, AJCC stage, existence of constitutional symptoms, ECOG score, surgical extent and differential grade. P-values less than 0.05 were considered as statistically significant. All statistical analyses were performed and visualized using R statistical software (Version 4.1.3, https://www.r-project.org).

3. Results

3.1. Clinicopathological characteristics

56 patients were finally included in this study with a mean age of 56.3 (SD: 8.5) years old (Table 1). 17 (30.4%) patients were diagnosed with AJCC stage III ccRCC according to imaging examination. 10 patients (17.9%) had eastern cooperative oncology group (ECOG) scores of 1. 17 (30.4%) patients were presented with constitutional symptoms at first admission. 14 (25.0%) patients underwent partial nephrectomy. Finally, high expression of PAX2 and CAIX were observed in 17 (30.4%) and 16

(28.6%) patients' specimens. Examples of immunohistochemical staining of PAX2 and CAIX were demonstrated in Figure 2.

PAX2 and CAIX shared high expression in 8 (14.3%) patients (spearman's ρ=0.27, P=0.043). We then divided the patients into three groups: two-low group, one-high group and two-high group. Association between PAX2/CAIX expression and clinicopathological features was demonstrated in Table 2. Patients' characteristics were roughly balanced.

3.2. Association of PAX2 and CAIX expression with patients' survival

Median follow-up period was 45.5 (range: 16.7-84.2)

Table 1. Patients' Clinicopathological Characteristics.

Characteristics		N=56
Age (mean (SD))		56.38 (8.46)
Male Gender (%)		39 (69.6)
BMI (mean (SD))		24.26 (2.31)
Constitutional symptom (%)		17 (30.4)
Right Site (%)		35 (62.5)
AJCC stage (%)	I	15 (26.8)
	II	24 (42.9)
	III	17 (30.4)
ECOG score (%)	0	46 (82.1)
	1	10 (17.9)
Surgical Extent (%)	Partial	42 (75.0)
	Radical	14 (25.0)
Surgical Time (mean (SD))		172.91 (20.22)
Blood loss (mean (SD))		152.68 (78.29)
Grade (mean (SD))	I	6 (10.7)
	II	18 (32.1)
	III	24 (42.9)
	IV	8 (14.3)
High PAX2 expression (%)		17 (30.4)
High CAIX expression (%)		16 (28.6)

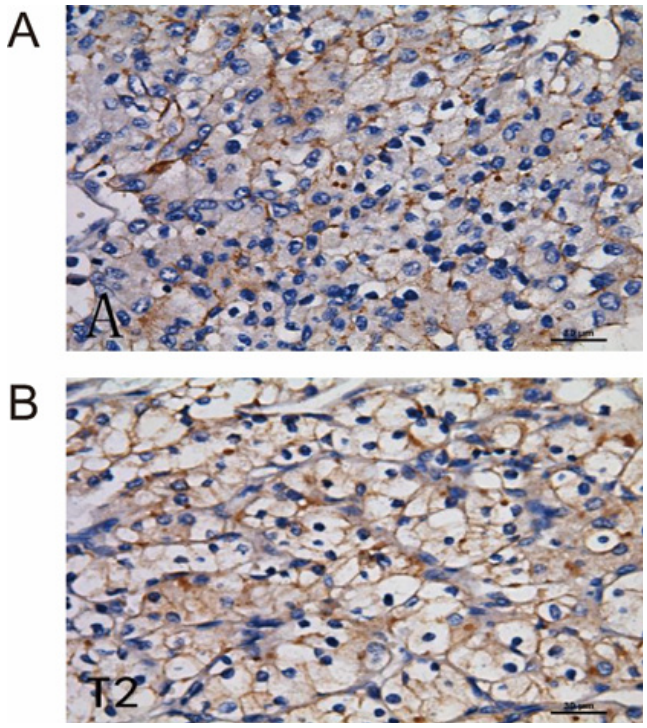

Fig. 2. Examples of immunohistochemical images for PAX2 (A) and CAIX (B) positive expression.

Table 2. Association between PAX2CAIX expression and clinicopathological features.

Characteristics		Two-low	One-high	Two-high	P-value
		(n=31)	(n=17)	(n=8)	
Age (mean (SD))		56.74 (8.27)	57.29 (8.27)	53.00 (9.86)	0.473
Sex (%)	Female	11 (35.5)	3 (17.6)	3 (37.5)	0.391
	Male	20 (64.5)	14 (82.4)	5 (62.5)	
BMI (mean (SD))		24.50 (2.31)	23.71 (2.03)	24.50 (2.94)	0.504
Constitutional symptoms (%)	No	21 (67.7)	11 (64.7)	7 (87.5)	0.483
	Yes	10 (32.3)	6 (35.3)	1 (12.5)	
Site (%)	Right	23 (74.2)	8 (47.1)	4 (50.0)	0.131
	Left	8 (25.8)	9 (52.9)	4 (50.0)	
AJCC staging (%)	I	8 (25.8)	5 (29.4)	2 (25.0)	0.728
	II	15 (48.4)	5 (29.4)	4 (50.0)	
	III	8 (25.8)	7 (41.2)	2 (25.0)	
ECOG (%)	0	26 (83.9)	15 (88.2)	5 (62.5)	0.273
	1	5 (16.1)	2 (11.8)	3 (37.5)	
Extent (%)	Partial	25 (80.6)	11 (64.7)	6 (75.0)	0.475
	Radical	6 (19.4)	6 (35.3)	2 (25.0)	
Surgical Time (mean (SD))		169.45 (20.35)	178.41 (20.34)	174.62 (19.04)	0.335
Blood loss (mean (SD))		154.84 (85.98)	155.88 (63.45)	137.50 (83.45)	0.843
Differential grade (%)	I	2 (6.5)	3 (17.6)	1 (12.5)	0.223
	II	12 (38.7)	2 (11.8)	4 (50.0)	
	III	13 (41.9)	10 (58.8)	1 (12.5)	
	IV	4 (12.9)	2 (11.8)	2 (25.0)	

months. Median RFS was 14.8 (95% CI: 13.4-39.0) months for the two-low group, 23.9 (95% CI: 19.1-NA) for the one-high group, 38.4 (95% CI: 32.3-NA) months for two-high group (P=0.047; Figure 3A). Median OS was 41.5 (95% CI: 33.3-NA) months for the two-low group, not available (95% CI: 44.5-NA) for the one-high group, 78.6 (95% CI: 78.6-NA) months for two-high group (p=0.033; Figure 3B). By employing IPTW (Table 3), we found patients with co-expression of PAX2 and CAIX had better RFS (HR: 0.39, 95% CI: 0.17-0.92, P=0.031) and OS (HR:0.29, 95% CI: 0.10-0.80, P=0.017) compared with those with negative expression. Finally, we investigated predicting ability of combined PAX2 and CAIX staining (proportions, %) for 2-year recurrence (Figure 4), which showed better performance than the AJCC staging system (C-indexes: 0.63 vs. 0.53, P=0.33).

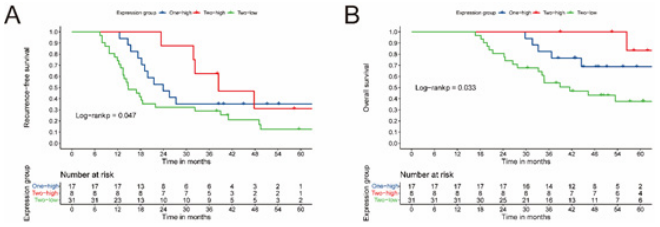

Fig. 3. Comparison of RFS and OS among patients with different PAX2 and CAIX expression levels.

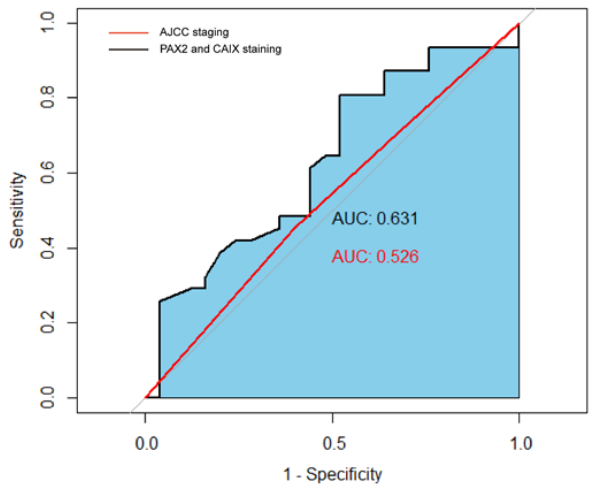

Fig. 4. Receiver operating curves comparing PAX2 and CAIX expression with AJCC stagings system.

4. Discussion

ccRCC represents a special subtype of renal malignancy featured by high relapsing rates. Up to now, there are various predicting models for patients' outcomes in ccRCC [4,27-32]. Generally, these models are derived from conventional clinicopathologic data and are independent of the AJCC staging system. Despite the relatively good performance, those models shared a common deficiency to focus only on clear cell histology. A large cohort study from the Mayo Clinic constructed two models for progression-free survival (c-index: 0.83) and cancer-specific survival (c-index: 0.86) prognostication [33]. The study put abundant clinicopathological features into analyses. However, due to the retrospective nature and lack of external validation, clinicians should still hold a prudential attitude to the results. In a word, it is still helpful to evacuate more clinicopathological biomarkers for ccRCC prognosis.

PAX2 and CAIX are two biomolecules associated with RCC proliferation and prognosis. On one hand, a recent bioinformatics study revealed that expression PAX2 may be associated with better prognosis in RCC patients [11]. On the other hand, prognostic power of CAIX didn't match its diagnostic significance. Some scholars blamed it to the frequent somatic mutation of VHL genes of RCC cells. Intriguingly, we noticed that VHL gene inactivation regulated up-expression of PAX2. Thus, the present study made such an exploration.

In the present study, we found high expression of both PAX2 and CAIX harbored significantly better RFS and OS than the remaining patients. Although PAX2 or CAIX were found to be associated with long-term prognosis of RCC, our study didn't observe a significant difference in RFS or OS between the one-high and the two-low groups. This phenomenon suggests that a single index may not be powerful enough for prognostication of RCC. IPTW confirmed that expression of PAX2 and CAIX was a prognostic factor independent of age, AJCC stage, surgical extent, tumor differentiation, etc. Our study provides novel biomarkers for construction of future prognostic models.

Our study is inevitably affected by some limits. The major deficiency is the small sample size. The number of ccRCC patients admitted to our institution is limited, approximately 30 cases per year. The two-high group comprised only 8 patients, which brought uncertainty to the findings. The small sample size also restricted conduction of the multivariate and subgroup analyses. However, baseline characteristics among the groups were relatively balanced, and employment of IPTW has made up for this deficiency to some degree. Another deficiency is the lack of more serum or histopathological biomarkers included, subject to patients' will.

Table 3. ITPW adjusted COX regression analyses of RFS and OS for PAX2 and CAIX expression.

Survival	N	Non-adjusted	P value	Adjusted#	P value#
RFS					
Two-low	31	Reference		Reference	
One-high	17	0.54 (0.27, 1.09)	0.086	0.59 (0.28, 1.24)	0.162
Two-high	8	0.37 (0.14, 0.97)	0.043	0.39 (0.17, 0.92)	0.031
OS					
Two-low	31	Reference		Reference	
One-high	17	0.41 (0.15, 1.11)	0.079	0.45 (0.16, 1.22)	0.117
Two-high	8	0.23 (0.05, 1.01)	0.052	0.29 (0.10, 0.80)	0.017

5. Conclusion

This study showed simultaneous up-expression of PAX2 and CAIX is associated better prognosis of ccRCC. Validation of the findings by large cohort study is appreciated.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

This study was approved by the ethics committee of Mian Yang Central Hospital (approval number: No. 201456).

Informed consent

Signed written informed consent were obtained from the patients and/or guardians.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Honggang Shao and Yougang Liao designed the study and performed the experiments, Min Xiang and Deng Hu collected the data, Min Xiang, Deng Hu and Sha Liu analyzed the data, Honggang Shao and Yougang Liao prepared the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Sichuan Medical Association youth project (Q15089) [Prospective study of PAX2. CAIX combined with PAx2.CAIX in early diagnosis and recurrence and metastasis of renal cell carcinoma].

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