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Original Article

Risk Factors and Histopathological Features of Renal Cell Carcinoma Subtypes

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HIGHLIGHTS

• Considering the high prevalence of papillary type in recent years in our medical centers, we decided to investigate the types of RCC in recent years.
• We thoroughly investigated the risk factors of kidney cancer according to the type of cancer. inflammatory cells.

ABSTRACT

Introduction
Kidney cancer is currently the 9th most common cancer in men and the 14th most common in women. Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for about 85% of all renal malignancies. It accounts for about 2% of diagnoses and deaths following all cancers. Several risk factors for RCC include smoking, obesity, hypertension, and acquired cystic kidney disease.

Methods
This cross-sectional study was conducted on patients who underwent nephrectomy (partial nephrectomy or radical nephrectomy) due to kidney mass from 2018 to 2021. Patients whose final pathology was RCC remained in the study, and patients with other pathologies were excluded. Risk factors and frequency of RCC pathological subtypes were investigated.

Results
The most common subtype was Clear Cell (60.1%), followed by Papillary (19.7%) and Chromophobe (18.7%). Most patients were men and overweight, with a mean body mass index (BMI) of 27.19±4.68. Hypertension and Diabetes are considered independent and strong risk factors in RCC development. In terms of grading using the Furman grading system, grade 2 was significantly higher than other grades (51%).

Conclusions
Considering the frequency of different sub-types of RCC in our study, it seems different from the global dispersion pattern. Unlike previous studies, blood type did not play a proven role in causing RCC in our research. In contrast, the role of other risk factors, such as a history of Diabetes, hypertension, smoking, and obesity, was proven.

Keywords: Chromophobe Renal Cell Carcinoma; Clear Cell Renal Cell Carcinoma; Nephrectomy; Papillary Renal Cell Carcinoma; Renal Cell Carcinoma

Introduction

The prevalence of kidney cancer has been increasing in the last 3 decades. It is currently the 9th most common cancer in men and the 14th most common in women. It is the 15th among cancers in terms of mortality (1). This cancer is more common in men, and the ratio of males to females is about 1.78:1. The average age of diagnosis for kidney cancer is about 64 years. It is common in black people (2). Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for about 85% of all renal malignancies. It accounts for about 2% of diagnoses and deaths following all cancers (3,4). RCC is the seventh most common cancer in developed countries and is the most lethal urological malignancy, with a 5-year survival rate of 76%. The mortality rate depends on the stage of the disease at the time of diagnosis, with a 5-year relative survival of 93% for stage I, 72.5% for stage II/III, and only 12% for stage IV metastatic disease (5,6).

Several risk factors for RCC include smoking, obesity, hypertension, and acquired cystic kidney disease. Also, RCC is more common among African Americans and is lower among Asian people. Kidney cancer at a younger age can have a genetic background, including Von Hipple-Lindau disease (4). A group of other gene mutations, including Polybromo1 (PBRM1), Breast cancer gene1 (BRCA1)-associated protein 1 (BAP1), SET domain-containing 2 (SETD2), and transcription elongation factor B subunit 1 (TCEB1) plays a role in kidney cancer (7). Several other potential risk factors, including diabetes, alcohol consumption, and occupational exposure to certain substances, including asbestos, have not yet been conclusively proven (8).

There are different types of RCC histopathology, including clear cell, papillary, chromophobe, collecting duct, medullary and unclassified. Approximately 75% of RCCs are clear cell type, the most common subtype. These types can be different regarding tissue origin in the kidney, radiological appearance, associated diseases, and pattern of invasion (9). Nowadays, with the development of radiological diagnostic methods, RCC is often an incidental finding in imaging. Imaging can be helpful in treatment planning and staging. About 30% of patients have metastases at the time of diagnosis, and this rate is decreasing with the advancement of imaging techniques. (10,11). Due to the importance of the subject, we decided to study the risk factors and histopathological features of RCCs in a study.

Methods

This cross-sectional study was conducted on the patients who underwent nephrectomy (partial nephrectomy or radical nephrectomy) due to kidney mass from 2018 to 2021, of which there were 208 cases. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH. REC.1399.1121). Patients whose final pathology was RCC remained in the study, and patients with other pathologies were excluded. Finally, 208 patients participated in the study. Before surgery, all patients underwent an intravenous (IV) contrast-enhanced abdominopelvic CT scan. The study was conducted in Shohada-e Tajrish hospital and Shahid Labbafinejad hospital referral centers.

Risk factors such as obesity, smoking, history of hypertension, and positive family history were assessed. Demographic and histopathological features such as tumors' grade, location of mass in the kidney, and tumor size were also measured. The statistical analysis was done via SPSS-21 software. The T-test examined quantitative data, and the chi-square test examined qualitative variables.

Results

A total of 208 patients were included in the study with a previous history of RCC. The mean age was 55.49±13.66 years. The youngest patient was 21 years old, and the oldest patient was 86 years old. Most underwent radical nephrectomy (53.8%), and the rest underwent partial nephrectomy (46.2%). According to the results, the most common subtype was Clear Cell (60.1%), followed by Papillary (19.7%) and Chromophobe (18.7%). The majority of patients were male, accounting for 64.9% of patients. The lowest sex difference was in the chromophobic group. Even though smoking is one of the risk factors for RCC, most patients were non-smokers (76.4%). Most patients were overweight, with a mean body mass index (BMI) of 27.19±4.68. The lowest BMI was 17.58, while the highest was 45.91. Thirty-nine patients had diabetes mellitus (18.8%), and 79 also had high blood pressure (38%). The most common blood group of patients was O (37%), followed by blood groups A (29.8%) and B (23.1%). Most patients were RH-positive (85.1%). Most patients had no history of kidney mass in their first-degree relatives (94.7%). Table 1 shows the patient's characteristics.

In terms of the site of involvement in the kidney, the most common site was the middle pole of the kidney (29.8%), followed by the upper pole (20.1%) and lower pole (19.7%), respectively. In terms of grading, using the Furman grading system, grade 2 was significantly higher than other grades (51%). Then there were grades 3 (31.2%), 4 (9.1%), and 1 (8.7%), respectively (P-value=0.006).

The overall mean size of the masses was 66.58±59.59 millimeters (mm), with the most significant means belonging to the papillary group (71.11±46.28). The smallest mass size was 13 mm, and the enormous mass was 200mm. Due to the marginal involvement of the pathology sample, 183 samples had a negative margin (88%), while 25 cases had a positive margin (12%). Table

Table 1. Patients characteristics. BMI : Body Mass Index

Patient Characteristics	Clear Cell (n=125)	Papillary (n=41)	Chromophobe (n=39)	Others (n=3)	Total (n=208)	P-value
Mean age, years	55.97 ± 14.17	56.73 ± 12.31	52.38 ± 13.59	59.00 ± 9.54	55.49 ± 13.66	0.242
Sex						
Male	80 (64%)	31 (75.6%)	22 (56.4%)	2 (66.7%)	135 (64.9%)	0.341
Female	45 (36%)	10 (24.4%)	17 (43.6%)	1 (33.3%)	73 (35.1%)	
Smoking						
Yes	30 (24%)	14 (34.1%)	4 (10.2%)	1 (33.3%)	49 (23.6%)	0.087
No	95 (76%)	27 (65.9%)	35 (89.8%)	2 (66.7%)	159 (76.4%)	
BMI	27.76 ± 4.52	25.96 ± 5.0	26.78 ± 4.82	25.72 ± 2.79	27.19 ± 4.68	0.144
DM						
Yes	19 (15.2%)	13 (31.7%)	6 (15.4%)	1 (33.3%)	39 (18.8%)	0.100
No	106 (84.8%)	28 (68.3%)	33 (84.6%)	2 (66.7%)	169 (81.2%)	
HTN						
Yes	42 (33.6%)	19 (46.3%)	16 (41%)	2 (66.7%)	79 (38%)	0.329
No	83 (66.4%)	22 (53.7%)	23 (59%)	1 (33.3%)	129 (62%)	
Blood Group						
A	36 (28.8%)	13 (31.7%)	12 (30.8%)	1 (33.33%)	62 (29.8%)	
B	27 (21.6%)	9 (22%)	12 (30.8%)	0 (0%)	48 (23.1%)	0.726
AB	12 (9.6%)	6 (14.6%)	2 (5.1%)	1 (33.33%)	21 (10.1%)	
O	50 (40%)	13 (31.7%)	13 (33.3%)	1 (33.33%)	77 (37%)	
RH						
Positive	104 (83.2%)	35 (85.4%)	36 (92.3%)	2 (66.7%)	177 (85.1%)	0.430
Negative	21 (16.8%)	6 (14.6%)	3 (7.7%)	1 (33.3%)	31 (14.9%)	
Family History						
Yes	5 (4%)	2 (4.9%)	4 (10.3%)	0 (0%)	11 (5.3%)	0.472
No	120 (96%)	39 (95.1%)	35 (89.7%)	3 (100%)	197 (94.7%)	
Surgery Type						
Radical	65 (52%)	25 (61%)	21 (53.8%)	1 (33.3%)	112 (53.8%)	0.662
Partial	60 (48%)	16 (39%)	18 (46.2%)	2 (66.7%)	96 (46.2%)	

DM: Diabetes Mellitus, HTN: Hyper Tension, RH: Rhesus

2 shows the tumor characteristics.

Discussion

According to the results of our study, which was performed on 208 patients with RCC, the prevalence of this cancer in men was about twice that of women. In a 2020 study, Mancini et al., reported a ratio of 1.85, a similar study (12). RCC is more common in black people, who survive less than other races. (13) Given that this study was conducted in a country with limited racial diversity, no precise judgment can be made. A 2010 study by Leibovic BC and colleagues on 3,062 RCC patients found that the most common subtype was clear cell (80.5%), followed by papillary(14.3%) and chromophobe (5.2%), respectively. This ratio differed slightly in our study, with

60.1% of patients being clear cells and the papillary and chromophobe rates being approximately equal. Smoking can increase the rate of RCC by 35% (14). In our study, there were 49 smokers, 23.6% of the total patients. The number of smokers in the chromophobe group was very low (10.2%). Obesity is not a definite risk factor for RCC, but it is still one of the possible risk factors for this disease (15). In our study, patients had an average BMI higher than normal and were overweight. According to the results, obesity can be associated with a higher chance of developing RCC.

Limited studies have been performed on the relationship between blood groups and RCC development. A study by Hee-Kyung Joh and colleagues found that blood groups other than O had a higher chance of

Table 2. Tumor characteristics.

Tumor Characteristics	Clear Cell (n=125)	Papillary (n=41)	Chromophobe (n=39)	Others (n=3)	Total (n=208)	P-value
Mass Location in CT						
Upper	24 (19.2%)	11 (26.8%)	6 (15.4%)	1 (33.3%)	42 (20.1%)	
Middle	41 (32.8%)	6 (14.6%)	13 (33.3%)	2 (66.7%)	62 (29.8%)	
Inferior	25 (20%)	9 (22%)	7 (18%)	0 (0%)	41 (19.7%)	
Total	1 (0.8%)	1 (2.4%)	0 (0%)	0 (0%)	2 (1%)	0.552
Upper + Middle	13 (10.4%)	4 (9.8%)	5 (12.8%)	0 (0%)	22 (10.6%)	
Middle + Inferior	9 (7.2%)	7 (17.1%)	7 (17.9%)	0 (0%)	23 (11.1%)	
Pelvis	12 (9.6%)	3 (7.3%)	1 (2.6%)	0 (0%)	16 (7.7%)	
Furman Grade						
1	6 (4.8%)	6 (14.6%)	5 (12.8%)	1 (33.3%)	18 (8.7%)	
2	74 (59.2%)	21 (51.2%)	9 (23.1%)	2 (66.7%)	106 (51%)	0.006
3	35 (28%)	12 (29.3%)	18 (46.2%)	0 (0%)	65 (31.2%)	
4	10 (8%)	2 (4.9%)	7 (17.9%)	0 (0%)	19 (9.1%)	
Size	66.46 ± 68.75	71.11 ± 46.28	63.36 ± 39.09	52.33 ± 59.59	66.58 ± 59.59	0.572
Margin						
Positive	15 (12%)	5 (12.2%)	5 (12.8%)	0 (0%)	25 (12%)	0.933
Negative	110 (88%)	36 (87.8%)	34 (87.2%)	3 (100%)	183 (88%)	

CT: Computed Tomography

developing RCC, especially in women (16). In our study, 37% of patients had an O blood type, and 63% had other blood types. Our study refutes this hypothesis because the percentage of blood group O in the world is about 37.12%. Hypertension is considered an independent and strong risk factor in developing RCC, so RCC is eight times more common in those with systolic blood pressure above 160 mm Hg than those with systolic blood pressure below 120 mm Hg (17). In our study, 38% of patients had systolic blood pressure above 140 mm Hg, a significant percentage proving the risk of developing RCC in people with high blood pressure. Diabetes is a risk factor for RCC, especially the clear cell type. In our study, 18.8% of patients had diabetes, which had the highest rate of papillary RCC, contrary to previous results. Also, the role of this risk factor in women is more than in men (18).

Performing partial nephrectomy surgery can prevent kidney failure and high blood pressure in the future. Performing partial nephrectomy surgery depends on the surgeon's skill, the location of the tumor in the kidney, and the size of the tumor. Partial nephrectomy is preferred in the upper and lower pole masses less than 4 cm. Radical nephrectomy surgery is preferred in larger masses, although this choice also depends on the surgeon's skill and the patient's condition (19). The mean mass size of our patients was 66.58±59.59 mm, and 46.2% of patients underwent partial nephrectomy. The most common site of the tumor was the middle bridge of the kidney.

Because the primary treatment of RCC is surgical and resistant to chemotherapy and radiotherapy, early diagnosis and surgery are essential. Patient survival was highly dependent on the pathology grade of patients at the time of diagnosis. If the patient has grade 1 pathology, 5-year survival will be about 93% (5,6). In our study, most patients had Forman Grade 2 pathology, with a 5-year survival of 72.5%. Nineteen patients had grade 4, with a very low 5-year survival of about 12%. Improving imaging techniques and the availability of paraclinical such as ultrasound can lead to early diagnosis and increase patient survival.

Among the limitations of this study is the limited sample size. Indeed, the larger statistical community can help identify the risk factors for RCC and its dispersion better and more accurately.

Conclusions

Considering the frequency of different sub-types of RCC in our study, it seems different from the global dispersion pattern. Regarding RCC risk factors, unlike previous studies, blood type did not play a proven role in causing RCC in our study. In contrast, the role of other risk factors, such as a history of diabetes, hypertension, smoking, and obesity, was proven. More studies with a larger sample size will be needed.

Ethics statement
This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR. SBMU.RETECH.REC.1399.1121).

Data availability
Data will be provided on request.

Abbreviations
BMI   Body mass index
IV   Intravenous
RCC   Renal cell carcinoma
TCEB1   Transcription elongation factor B subunit 1

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