Article

TCM syndrome types and the related factors in 145 cases of renal cell carcinoma

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Highlights：

The study analyzed the distribution of traditional Chinese medicine (TCM) syndromes in 145 patients with renal cell carcinoma after surgery. Multivariate logistic regression was also used to analyze the correlation between different TCM syndromes and risk factors. The results showed that spleen-kidney Qi deficiency syndrome, liver-kidney Yin deficiency syndrome, spleen-kidney Yang deficiency syndrome, dampness and heat injection syndrome were the common TCM syndrome types in patients with renal cell carcinoma after surgery. There was a correlation between the TCM syndromes of renal cell carcinoma and the risk factors such as drinking history, overweight and obesity, smoking history and drinking history. The distribution of TCM syndromes and the related factors in renal cell carcinoma patients after surgery can provide ideas for clinical treatment and prognosis.

Abstract

Background: To analyze the distribution of traditional Chinese medicine (TCM) syndromes and the related factors in patients with renal cell carcinoma, and to provide further guidance for the relapse prevention and combination of traditional Chinese and Western medicine in postoperative renal cancer patients. **Methods:** A retrospective survey was conducted to establish a postoperative clinical symptom assessment scale for patients with renal cell carcinoma. The distribution of TCM syndromes in 145 patients with renal cell carcinoma was analyzed statistically. Multivariate logistic regression was used to analyze the correlation between different TCM syndromes and risk factors. **Results:** The postoperative TCM syndromes of patients with cell carcinoma were mainly spleen-kidney deficiency (38.6%), liver-kidney Yin deficiency (15.9%), spleen-kidney Yang deficiency (13.1%), and damp-heat pouring downward (9.7%). The incidence of severe spleen-kidney Qi deficiency syndrome and spleen- kidney Yang deficiency syndrome was statistically different from that of liver-kidney Yin deficiency syndrome ($P < 0.05$). The history of drinking and body mass index ≥ 24 kg/m^2 were risk factors for spleen-kidney Qi deficiency syndrome; the history of hypertension was a protective factor for liver-kidney Yin deficiency syndrome after renal cancer surgery; male was a protective factor for patients with renal cancer who had damp-heat pouring downward syndrome; smoking history and drinking history were risk factors for damp-heat pouring downward; age was a protective factor for spleen-kidney Yang deficiency after renal cancer surgery. **Conclusion:** This study found that spleen-kidney Qi deficiency syndrome, liver-kidney Yin deficiency syndrome, spleen-kidney Yang deficiency syndrome, dampness and heat injection syndrome were the common TCM syndrome types after renal cell carcinoma patients. There was a correlation between the TCM syndromes of renal cell carcinoma and the risk factors such as drinking history, overweight and obesity, smoking history and drinking history. The distribution of TCM syndromes and its correlation with risk factors in renal cell carcinoma patients after surgery can provide ideas for clinical treatment and prognosis.
Key words: Renal cell carcinoma, TCM syndrome, Constitution, Risk factors, Correlation study.

Introduction

Renal cell carcinoma is known as the most deadly urinary tract tumor, and its mortality accounts for about 2% of global cancer deaths [1, 3]. The 5-year survival rate of patients with locally advanced renal cell carcinoma is 40% to 60%. Surgery is still the main treatment for patients with renal cell carcinoma, but 20%–40% of patients will have local recurrence or metastasis after surgery [4, 5]. Some research have found that common risk factors are closely related to the occurrence and development of kidney cancer [6, 7]. The main risk factors for kidney cancer are advanced age, male, family history of kidney cancer, smoking, overweight and high blood pressure [8, 9].

Previous studies have shown that Chinese medicine can improve the quality of life of postoperative patients with renal cell carcinoma. The characteristics of traditional Chinese medicine (TCM) syndromes are closely related to the prognosis of postoperative patients with renal cell carcinoma. Therefore, this study will initially explore the effects of TCM on the patients with renal cell carcinoma, and to approach objective index of TCM syndrome differentiation in renal cell carcinoma.

Materials and Methods

145 patients with renal cell carcinoma after surgery from January 2016 to January 2019 in the Department of Oncology, Shanxi Provincial Hospital of Traditional Chinese Medicine were included. According to ethical requirements, we obtained informed consent from patients before clinical study, and patients signed informed consent. The Ethics Committee of the Shanxi Provincial Hospital of Traditional Chinese Medicine reviewed the scientific and ethical rationality of the research project and approved the study.

Inclusion criteria
Patients diagnosed as renal cancer by postoperative pathology after clinical radical nephrectomy or nephron sparing surgery, were included in the study.

Exclusion criteria
All consecutive patients who met the inclusion criteria were included unless they had any of the following conditions: (1) patients who combined with one or more other malignant tumors; (2) patients who had multiple basic diseases; (3) patients who were confused and could not be clearly expressed; (4) patients who were older than 85 years old or younger than 18 years old.

Shedding standard
The inclusion criteria for the study population were as follows: (1) patients incomplete data or error information; (2) patients who had serious complications or deterioration of the disease occurred during the investigation, and failed to complete the statistician.

TCM constitution classification and syndrome differentiation criteria
TCM constitution classification was based on the TCM Constitution Classification Standards issued by the Chinese Medicine Association in 2009 [10]. The TCM syndrome differentiation standard refers to the "clinical diagnosis and treatment of oncology" in the third edition of the clinical diagnosis and treatment of TCM tumor diseases edited by Wu Wanzhen and Liu Weisheng [11]. To compare the differences of TCM syndrome types in patients with postoperative renal cell carcinoma, a TCM symptom survey form with a total of 74 entries containing the basic information was used.

Statistical methods
The measurement data were expressed as mean ± standard deviation, in which descriptive statistical analysis was expressed by frequency and composition ratio, and the count data was analyzed by chi-square test. Kaplan-Meier analysis was conducted to plot survival curves. $P < 0.05$ was considered statistically signifcant. Statistical analyses were carried out by SPSS 22.0.

Results

Patient characteristics and survival analysis
The majority of patients were mainly middle-aged and elderly patients, with 45.54% (51 cases) for 40-59 years old, 46.43% (52 cases) for 60–79 years old. The average age of the 145 patients was 58.72 ± 9.71 years (range, 29–79 years). There were 115 males with an average age of 57.96 ± 9.38 years and 30 females with an average age of 61.67 ± 10.46 years. The pathological types of patients were mainly renal clear cell carcinoma, papillary carcinoma, mixed renal cell carcinoma, transitional cell carcinoma, spindle cell carcinoma and undefined cell carcinoma. Among them, 73.21% (82 cases) of patients are clear cell carcinoma in renal cell carcinoma and 26.79% (30 cases) of patients are non-transparent cell carcinoma.

Among 145 patients with renal cell carcinoma, the postoperative TCM syndromes of renal cell carcinoma patients were mainly spleen-kidney Qi deficiency type (38.6%), liver-kidney Yin

deficiency type (15.9%), spleen-kidney Yang deficiency type (13.1%), and damp-heat under injection type (9.7%). The mean overall survival of the 145 patients was 38.19 ± 2.47 months (95% confidence interval (CI) 33.35–43.03). Kaplan-Meier analysis indicated that patients with different postoperative TCM syndromes had different survival time ($P = 0.001$), as shown in Figure 1. Therefore, it was necessary to accurately analyze these symptoms for the normalization and standardization of syndrome differentiation and treatment administration.

The relationship between different symptoms and syndrome types
The top 20 four-diagnosis entries for patients with postoperative renal cell carcinoma are showed in Figure 2. Among the top 20 symptoms, heavy legs, pale tongue, thin white tongue, etc., were the main symptoms of spleen-kidney Qi deficiency. Backache, bad mood, dizziness, red tongue, fine pulse, etc., suggested liver-kidney Yin deficiency type. There were also some indicators that suggest spleen-kidney Yang deficiency syndrome, pattern of damp-heat pouring downward, such as heavy limbs, chills, poor appetite, lower extremity edema, dysuria, slippery pulse, yellow greasy moss and so on. According to the frequency distribution of the main symptoms, the pathological basis of patients with renal cell carcinoma was most prominent in Qi deficiency and Yin deficiency.

Comparing the clinically relevant symptoms of major syndromes in patients with renal cell carcinoma, the incidence of leg sinking and waist sleep were the highest, and the spleen-kidney Yang deficiency syndrome was the second. Among them, the incidence of leg depression of liver-kidney Yin deficiency syndrome and spleen-kidney Qi deficiency syndrome were statistically different from that of spleen-kidney Yang deficiency syndrome ($P < 0.05$). There were no significant differences in emotions, low back pain, hematuria, dizziness, edema, weak waist and knees, cough and chest pain, and bone pain between the other syndrome types ($P > 0.05$). The results are shown in Figure 3.

The relationship between patient characteristics and TCM syndrome types
The effects of age, gender, pathological type, survival time, karnofsky performance status (KPS) score, smoking, drinking history, family history, body mass index (BMI) > 24, hypertension history, etc. on postoperative syndromes in patients with renal cell carcinoma were investigated.
Gender and TCM syndrome types. Distribution of TCM syndromes in patients with renal cancer of different genders is shown in Table 1. The main clinical syndromes in women with renal cell carcinoma were spleen-kidney Qi deficiency, spleen-kidney Yang deficiency, liver stagnation and kidney deficiency, and pattern of damp-heat pouring downward. There was a statistically significant difference in TCM syndromes between them in patients with renal cell carcinoma ($P < 0.05$). The distribution of male patients' syndromes was mainly spleen-kidney Qi deficiency type and liver-kidney Yin deficiency type. The distribution of female kidney cancer syndrome type was mainly spleen-kidney Qi deficiency type and spleen-kid Yang deficiency type.
Age and TCM syndrome distribution. Due to the small number of partial groupings, Fisher's exact test was used, $\chi^2 = 18.717$, $P = 0.008$, indicating that the distribution of TCM syndromes in different age groups was statistically different. Distribution of age and TCM syndromes in 145 patients with renal cell carcinoma is shown in Table 2.
Family history and TCM syndrome types. According to statistics, 145 patients with renal cell carcinoma had 23.21% (26 cases) of family history of cancer, and 76.79% (86 cases) without family history of tumors. Due to the small number of partial groupings, Fisher's exact test was used. $\chi^2 = 2.942$, $P = 0.396$, without statistical significance, indicating that there is no statistical difference in the distribution of TCM syndromes in family history. Family history and TCM syndrome distribution of 145 patients with renal cell carcinoma after surgery was shown in Table 3.
Pathological classification and TCM syndrome types. According to statistics, among 145 patients with renal cell carcinoma, clear cell carcinoma accounted for 73.21% (82 cases), and non-transparent cell carcinoma patients accounted for 26.79% (30 cases). Due to the small number of grouping cases, Fisher's exact test was used, $\chi^2 = 3.618$, $P = 0.961$, indicating that there was no statistical difference in TCM syndrome distribution between patients with clear cell carcinoma and non-transparent cell carcinoma. Pathological classification and TCM syndrome distribution of 145 patients with renal cell carcinoma after operation was shown in Table 4.
KPS score and TCM syndrome types. According to statistics, among 145 patients with renal cell carcinoma, KPS > 90 accounted for 62.5% (70 cases), 80 < KPS < 90 accounted for 20.54% (23 cases). Due to the small number of partial groupings, Fisher's exact test was used, $\chi^2 = 2.88$, $P = 0.987$, indicating that there was no statistical difference between KPS score and TCM syndrome type distribution. KPS score and TCM syndrome distribution of 145 patients with renal cell carcinoma after operation is shown in Table 5.

The relationship between different risk factors and syndrome types

The exposure rates of drinking factor in spleen-kidney Qi deficiency, spleen-kidney Yang deficiency patients and spleen-kidney Yin deficiency patients were statistically different ($P <$ 0.05). There were significant differences between patients with kidney deficiency and spleen-kidney Yin deficiency in the exposure rates of smoking status and hypertension ($P <$ 0.05). There was no significant difference between the syndrome types and different risk factors ($P >$ 0.05). The exposure rate distribution of five syndrome types of risk factors in patients with renal cell carcinoma were shown in Figure 4. The highest exposure rate of smoking and drinking was observed in patients with liver-kidney Yin deficiency type. The exposure rate of hypertension and BMI > 24 was lowest in patients with hot-humid injections.

Logistic regression analysis of risk factors and common four syndromes in patients with renal cell carcinoma

The common risk factors for kidney cancer patients were gender, smoking, history of hypertension, age, BMI index, and drinking history. The assignments are shown in Table 6.

Major risk factors of spleen-kidney Qi deficiency syndrome. Through the Logistic regression analysis, we found that the statistical significance of the partial regression coefficients was BMI $\geq$ 24 kg/m^2 (X5) and drinking history (X6), and their odds ratio(OR) (95% CI) were 1.102 (0.218, 5.571) and 2.508 (0.478, 13.147) respectively. It could be considered that BMI $\geq$ 24 kg/m^2 in patients with renal cancer was a risk factor for spleen-kidney Qi deficiency syndrome. BMI $\geq$ 24kg/m^2 was 1.102 times of normal weight patients, and drinking history was 2.508 times than that of non-drinking history. There was no statistically significant difference in the partial regression coefficient of the other risk factors, which was considered to be unrelated to the spleen-kidney Qi deficiency syndrome.

Major factors of liver-kidney Yin deficiency syndrome. After logistic regression analysis, it was found that the statistical significance of the partial regression coefficient was history of hypertension (X4), and its OR (95% CI) was 0.374 (0.063, 2.231). It can be considered that the history of hypertension was a protective factor for liver-kidney Yin deficiency syndrome in patients with renal cancer. There was no statistically significant difference in the partial regression coefficient of the other risk factors, which was considered to be unrelated to liver-kidney Yin deficiency syndrome.

Major factors of spleen-kidney Yang deficiency
syndrome. After logistic regression analysis, we found that the statistical significance of the partial regression coefficient was age (X2), and its OR (95% CI) is 0.483 (0.076, 3.047). It can be considered that age was a protective factor for spleen-kidney Yang deficiency in patients with kidney cancer. There was no statistically significant difference in the partial regression coefficient of the other risk factors, which was considered to be unrelated to the spleen-kidney Yang deficiency syndrome.

The logistic regression equation for the damp-heat pouring downward. Logistic regression analysis found that the statistical significance of the partial regression coefficients was gender (X1), the history of smoking (X3) and drinking history (X6), and their OR (95% CI) were 0.505 (0.029, 8.932), 3.048 (0.339, 27.420), and 5.049 (0.656, 38.843) respectively. Men could be considered as a protective factor for dampness and fever in patients with kidney cancer. The history of smoking and drinking history in patients with renal cancer were risk factors for hot-humid injection. Patients with a history of smoking were 3.048 times more likely to have a history of no smoking, and those with a history of drinking were 5.049 times more likely to have no history of drinking. There was no statistically significant difference in the partial regression coefficients of the remaining risk factor variables, which was considered to be unrelated to the hot-humid injection.

Discussion

Renal cancer is a malignant tumor of the urinary system with high morbidity and mortality. Radical surgical resection is still the main clinical treatment for renal cancer, but the problems of renal insufficiency and high recurrence rate after surgery can not to be ignored. Studies have shown that Chinese medicine can improve the symptoms of postoperative patients with renal cancer, prolong survival, and reduce long-term recurrence rate [11,12]. However, the current TCM syndrome differentiation of patients with renal cell carcinoma is complicated, and the relevant TCM research is also the words of each family. There is no specific evidence-based basis and uniform standards. Therefore, it is particularly important to clarify the distribution pattern of syndromes in patients with postoperative renal cancer, accurate syndrome differentiation and rational prescription addition and subtraction. This study found that 145 cases of renal cell carcinoma patients with postoperative TCM syndrome distribution mainly for spleen and kidney Qi deficiency, liver and kidney Yin deficiency, spleen and kidney Yang deficiency, damp heat bet, accompanied by heavy
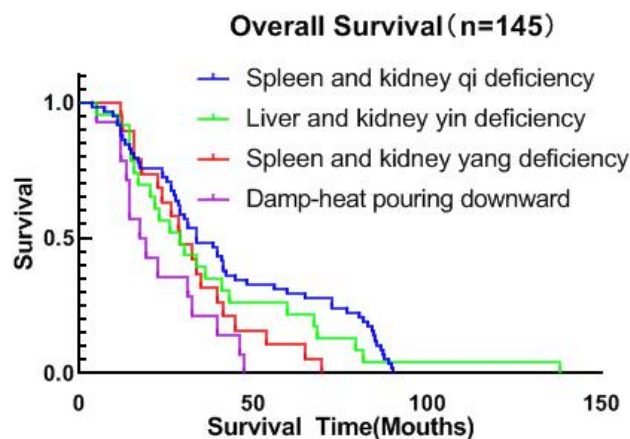
Figure 1 Kaplan-Meier curves for overall survival of four different syndrome types in patients with renal cell carcinoma
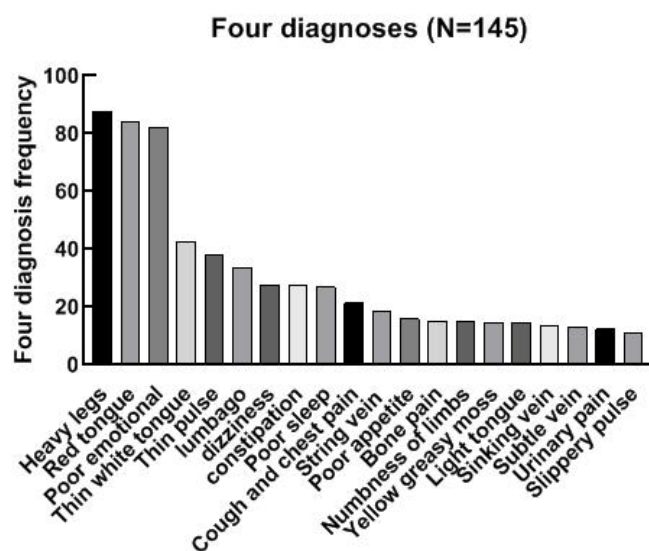

Figure 2 The frequency of occurrence of major four-diagnosis items in patients with renal cell carcinoma
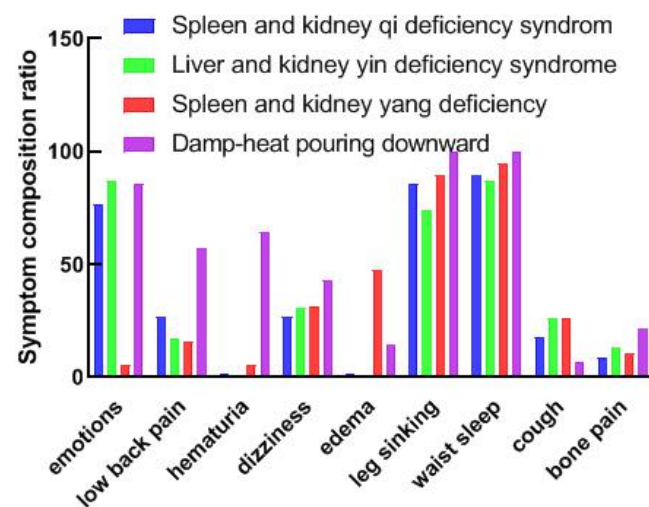

Figure 3 Relationship between different symptoms and four syndrome types
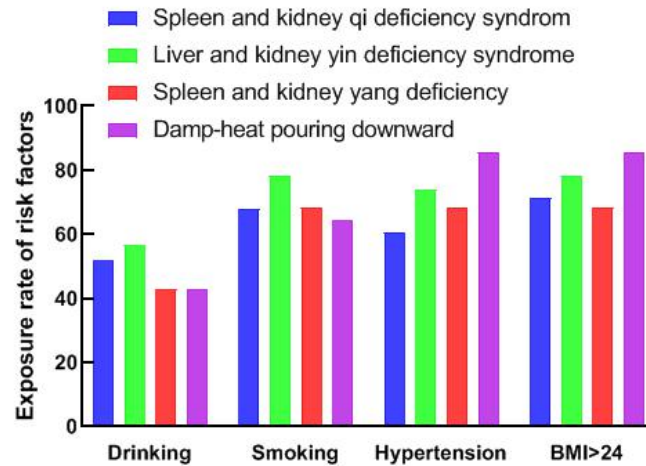
Figure 4 Distribution of exposure rates of five syndrome types of risk factors in patients with renal cell carcinoma

Table 1 Distribution and composition ratio of TCM syndromes in patients with different genders of renal cell carcinoma (example (%))

Syndromes	Male	Female
Spleen-kidney Qi deficiency syndrome	46 (40.00)	10 (33.33)
Liver-kidney Yin deficiency syndrome	19 (16.50)	4 (13.33)
Spleen-kidney Yang deficiency syndrome	13 (11.30)	6 (20.00)
Pattern of damp-heat pouring downward	10 (8.70)	4 (13.33)

Table 2 Distribution of age and TCM syndromes in 145 patients with renal cell carcinoma (example (%))

Age	Spleen-kidney Qi deficiency	Liver-kidney Yin deficiency	Spleen-kidney Yang deficiency	Pattern of damp-heat pouring downward
0–39 yeasr	2 (50)	0 (0)	1 (25)	1 (25)
40–59years	29 (56.86)	10 (19.61)	10 (19.61)	2 (3.92)
60–79years	25 (48.08)	12 (23.08)	8 (15.38)	7 (13.46)
> 80years	0 (0)	1 (20)	0 (0)	4 (80)

Table 3 Family history and TCM syndrome distribution of 145 patients with renal cell carcinoma after surgery (example (%))

Family history	Spleen-kidney Qi deficiency	Liver-kidney Yin deficiency	Spleen-kidney Yang deficiency	Pattern of damp-heat pouring downward
Family history	11 (42.31)	8 (30.77)	3 (11.54)	4 (15.38)
No family history	45 (52.33)	15 (17.44)	16 (18.6)	10 (11.63)

Table 4 Pathological classification and TCM syndrome distribution of 145 patients with renal cell carcinoma after operation (Example (%))

Pathological typing	Spleen-kidney Qi deficiency	Liver-kidney Yin deficiency	Spleen-kidney Yang deficiency	Pattern of damp-heat pouring downward
Renal clear cell carcinoma	42 (51.22)	16 (19.51)	14 (17.07)	10 (12.2)
Papillary carcinoma	5 (41.67)	4 (33.33)	2 (16.67)	1 (8.33)
Hybrid	6 (46.15)	3 (23.08)	2 (15.38)	2 (15.38)
Other	3 (60)	0 (0)	1 (20)	1 (20)

Note: Clear cell carcinoma: including granulosa cell carcinoma. Mixed type: contains two or more pathological types at the same time. Others: including transitional cell carcinoma, spindle cell carcinoma, and undefined cell carcinoma.

Table 5 KPS score and TCM syndrome distribution of 145 patients with renal cell carcinoma after operation (Example (%))

KPS	Spleen-kidney Yang deficiency	Spleen-kidney Yang deficiency	Spleen-kidney Yang deficiency	Spleen-kidney Yang deficiency
> 90	36 (51.43)	14 (20)	12 (17.14)	8 (11.43)
80–89	10 (43.48)	6 (26.09)	4 (17.39)	3 (13.04)
70–79	7 (50)	2 (14.29)	2 (14.29)	3 (21.43)
< 70	3 (60)	1 (20)	1 (20)	0(0)

NOTE: KPS, karnofsky performance status.

Table 6 Different risk factors and assignments

Relevant risk factors	Variable name	Assignment description
Gender	X1	Male = 1, female = 2
Age	X2	$\leq$ 59 years old = 1, $\geq$ 60 years old = 2
History of smoking	X3	No smoking = 0, smoking = 1
History of hypertension	X4	No history of hypertension = 0, history of hypertension = 1
BMI index	X5	BMI $\geq$ 24kg/m^2 = 1, BMI < 24kg/m^2 = 2
Drinking history	X6	No drinking history = 0, there is a history of drinking = 1
Family genetic history	X7	No family genetic history = 0, family genetic history = 1

NOTE: BMI, body mass index.

legs, backache and other major clinical symptoms. It can be seen the TCM syndrome type of patients with renal cell carcinoma was mainly spleen and kidney deficiency syndrome. This may be related to the impaired function of the "kidney" of the innate and the "spleen" of the acquired nature [13, 15].

Modern epidemiological studies have found that gender, age, family history, pathological type, duration of disease, KPS score and other factors are related to the occurrence and development of renal cancer [16,17]. This study analyzed the correlation between gender, age, family history, pathological type, survival time, KPS score and other four major TCM syndromes in patients with renal cell carcinoma, in order to more accurately distinguish disease from syndrome differentiation. Among the 145 patients with postoperative renal cell carcinoma, more patients with liver-stagnation and kidney-deficiency syndrome than women with damp-heat pouring downward, which may be related to women's unique physiological characteristics, that is, easy to cause liver depression. Unstable liver Qi, further aggravating kidney deficiency, leading to the occurrence of liver Qi and kidney deficiency syndrome [18]. Among the patients with renal cell carcinoma of different age groups, most of them were middle-aged and elderly patients, 45.54% (51 cases) of patients were 40–59 years old, and 46.43% of patients were 60–79 years old (52 cases), the main syndrome type was spleen. In kidney deficiency, this may be related to the "Scorpio failure" of middle-aged and elderly patients [19]. This study found that patients with spleen-kidney Qi deficiency have the longest survival period. This may be caused by generalized fatigue, poor mental health, unpleasant diet, weak waist and knees, and other symptoms of spleen and kidney Qi deficiency. Early detection and active treatment may help to prolong survival. Liu Chang's research on the influencing factors of the progression of chronic kidney disease in stage 4 was basically the same [20].

Understanding and avoiding risk factors has far-reaching implications for the prevention and prognosis of patients with kidney cancer. Smoking, drinking, high blood pressure, and obesity are all risk factors for malignant tumors [21, 23]. The results of this study found that patients with liver and kidney Yin deficiency had the highest exposure rate for smoking and drinking. This may be caused by long-term drinking and smoking, which may cause damage to the liver and kidneys, leading to weakening of liver function and kidney function. The study of smoking significantly increased the incidence of renal cancer patients consistently [24]. Dampness and high blood pressure in patients with high blood pressure, BMI > 24 exposure rate was the highest, which may be associated with obesity or obesity patients wet dampness, wet evil for a long time in the human body, easy to form a damp heat evil, damp heat evil may lead to elevated blood pressure Hidayat K and other studies found that for every 10 mm Hg increase in systolic and diastolic blood pressure, the risk of kidney cancer increased by 10% and 22%, respectively, which is consistent with the conclusion of this study [25]. Multivariate logistic regression analysis showed that BMI $\geq$ 24kg/m^2, drinking history was a risk factor for spleen and kidney Qi deficiency syndrome. The spleen-kidney Qi deficiency syndrome in patients with renal cell carcinoma may be caused by long-term consumption of gas, or even damage caused by Qi and Yin or postoperative vitality. Chinese medicine believes that "obese people are more likely to gather wet evil", spleen like dryness and dampness, and wet evil will inhibit the function of the spleen. Alcohol is a spicy and irritating substance that belongs to the poison of Chinese medicine. Liquor poisoning for a long time in the human body, will burn the Yin fluid, long-term consumption of gas, resulting in spleen and kidney Qi deficiency [26]. Among kidney cancer patients, male patients were significantly more than kidney patients, which is roughly the same as male/female kidney cancer patients in the previous literature [27]. Therefore, risk factors such as smoking, drinking, high blood pressure, BMI and even obesity were related to the distribution of major syndromes after renal cancer surgery. They were a common risk factor for clinical kidney cancer attacks and deserve caution.

Conclusion

This study found that spleen-kidney Qi deficiency syndrome, liver-kidney Yin deficiency syndrome, spleen-kidney Yang deficiency syndrome, dampness and heat injection syndrome are the common TCM syndrome types after renal cell carcinoma patients. There is a correlation between the TCM syndromes of renal cell carcinoma and the risk factors such as drinking history, overweight and obesity, smoking history and drinking history. Therefore, to determine the correlation between the distribution of TCM syndromes and risk factors after renal cell carcinoma surgery can provide ideas for clinical treatment and prognosis.

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