


Basic Characteristics and Survival Outcomes of Asian-American Patients with Clear Cell Renal Cell Carcinoma and Comparisons with White Patients: A Population-Based Analysis

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Background: To explore the baseline characteristics, pathological and survival outcomes of Asian-American patients with clear cell renal cell carcinoma (ccRCC), and make comparisons with White patients.

Materials and Methods: In this study, patients diagnosed with ccRCC between 2010 and 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Basic characteristics of Asian-American patients were analysed and compared with White patients. Then, proportional mortality ratio (PMR) analyses were performed in Asian population to investigate the proportions of different cause of deaths (CODs), and make comparisons with White patients. Moreover, Kaplan–Meier (KM) analyses were developed to investigate the survival disparities of ccRCC patients between Asian-Americans and White patients. Finally, a competing risk regression model was constructed to identify potential prognostic factors for ccRCC patients in the whole population.

Results: A total of 1586 Asian-American patients were eventually identified, and the median age at diagnosis was 61 years old. In Asian patients, those from South Asian had the youngest age at diagnosis ($P<0.001$) and the earliest stage of diseases (localized: 76.83%, T1: 70.73%, all $P<0.05$) when compared with other ethnicities. No significant differences were detected in tumor characteristics between Asian-Americans and White patients. Older age ($P<0.001$), earlier stage ($P<0.001$) and the administration of surgery ($P=0.050$) were tightly associated with a lower risk of dying of RCC in Asian-American patients. Additionally, Asian-American patients had comparable survival outcomes when compared with White patients. Lastly, competing risk regression model revealed that age at diagnosis ($P<0.001$), tumor grade ($P<0.001$), histological stage ($P<0.001$), median household income ($P<0.001$) and the administration of surgery ($P<0.001$) were prognostic factors for cancer-specific survival (CSS) in ccRCC patients, while died of other causes was regarded as a competing event.

Conclusion: Asian-American patients had similar tumor characteristics and survival outcomes with White patients. In Asian patients, those from South Asian had the youngest age at diagnosis and the earliest stage of diseases. Age, grade, histological stage, household income and surgery were identified to be closely related to CSS in ccRCC patients. In the future, prospective and well-designed studies are needed to verify our findings.

Keywords: ccRCC, Asian-American, SEER, White, prognosis

Introduction

Kidney cancer is the third most common malignant tumor in the genitourinary system, second only to prostate cancer and bladder cancer,¹ accounting for 2.2% of all malignant tumors. The incidence rate of kidney cancer varies substantially worldwide, ranging from 0.1–15.3 per 100,000 person-years.² Early stage RCC patients have better survival outcomes and can be successfully treated by surgery or ablation,³ while up to one third of cases are metastatic at diagnosis or will develop to metastasis.⁴ Generally, the prognosis of metastatic RCC is very poor, and the 5-year survival rate is less than 10%.⁵

Many studies have reported the racial and ethnic disparities of kidney cancer patients in incidence rates, clinical characteristics and prognosis. Compared with Whites, African Americans with ccRCC had lower VHL inactivation frequency, abundant ccB molecular subtypes and reduced up-regulation of HIF-related gene signals. These gene mutations indicated that African American patients with ccRCC were less sensitive to VEGF targeted therapy, and were risk factors for poor prognosis.⁶ Batai et al⁷ found that Hispanic American patients had significant younger age at RCC diagnosis than European American patients. In Hispanic Americans, patients with older age and Spanish native speaking were more likely to experience late stage RCC. Moreover, some other studies have well demonstrated the racial disparities of kidney cancer between White and Black patients.^{8–11} However, there are few studies on ccRCC in Asian populations, and most of these studies are single-center, small sample or retrospective.^{12,13}

In addition, most high-quality references included in the clinical practice guidelines (NCCN, EAU) were from European and American countries, and mainly included White patients. Therefore, we extracted patients diagnosed with ccRCC between 2010 and 2015 from the SEER database to explore the baseline characteristics, pathological and prognosis of Asian American patients with ccRCC, and make comparisons with White patients.

Materials and Methods

Database

All data were collected retrospectively from the SEER database. It is a public, population-based database, which records the incidence, basic information, treatment methods and prognosis of cancer patients in the United States since 1975. So far, it has covered about 34.6% of the US

population (https://surveillance.cancer.gov/statistics/types/race_ethnic.html) and is currently the largest cancer database worldwide. Additionally, approval for this study was obtained from the Ethics Committee of Jiangsu Cancer Hospital. Authors have signed the data-use agreement and got permission from SEER program to use this data.

Patient Identification

The “Case Listing Session” function in SEER*Stat software was applied to screen out patients diagnosed with ccRCC between 2010 and 2015. Inclusion criteria: (1) patients were confirmed as ccRCC with positive histology (C74.9, ICD-O: 8310/3) (2) year of diagnosis was from 2010 to 2015, (3) ccRCC was the only malignancy of each patient, (4) patients with complete dates of survival. Moreover, patients who met any of the following should be excluded: (1) patients with unknown laterality or bilateral tumors, (2) patients with missing or ineligible data in race/ethnicity, TNM stage, marital and insurance status, household income, cause of death (COD), (3) patients were not Asians or Whites, (4) reporting source being autopsy/death certificate only. The selection flowchart is shown in Figure 1.

Clinical Characteristics

We extracted the baseline characteristics and pathological long-term survival outcomes of enrolled patients using the SEER*Stat software, variables including race/ethnicity, age at diagnosis, sex, year of diagnosis, primary site, histologic type, tumor grade, tumor laterality, diagnostic confirmation, SEER histological stage, AJCC 7th ed TNM stage, surgery, vital status, survival time, COD, insurance and marital status, sequence number, household income and so on.

In this study, we only included White patients and Asian patients in the United States. Asian patients were further divided into four groups: Chinese, Japanese, South Asian (Asian Indian, Pakistani and Asian Indian or Pakistani) and other Asian (Filipino, Korean, Laotian, Thai, Hmong, Kampuchean, Vietnamese). Hispanic was not removed from the White patients because we only divided enrolled patients on the basis of race/ethnicity rather than origin recode (including Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian or Pacific Islander, Non-Hispanic American Indian/Alaska Native and Hispanic). Insurance status was defined as insured, uninsured and any Medicaid. Marital status was categorized into never married, married and SDW (including

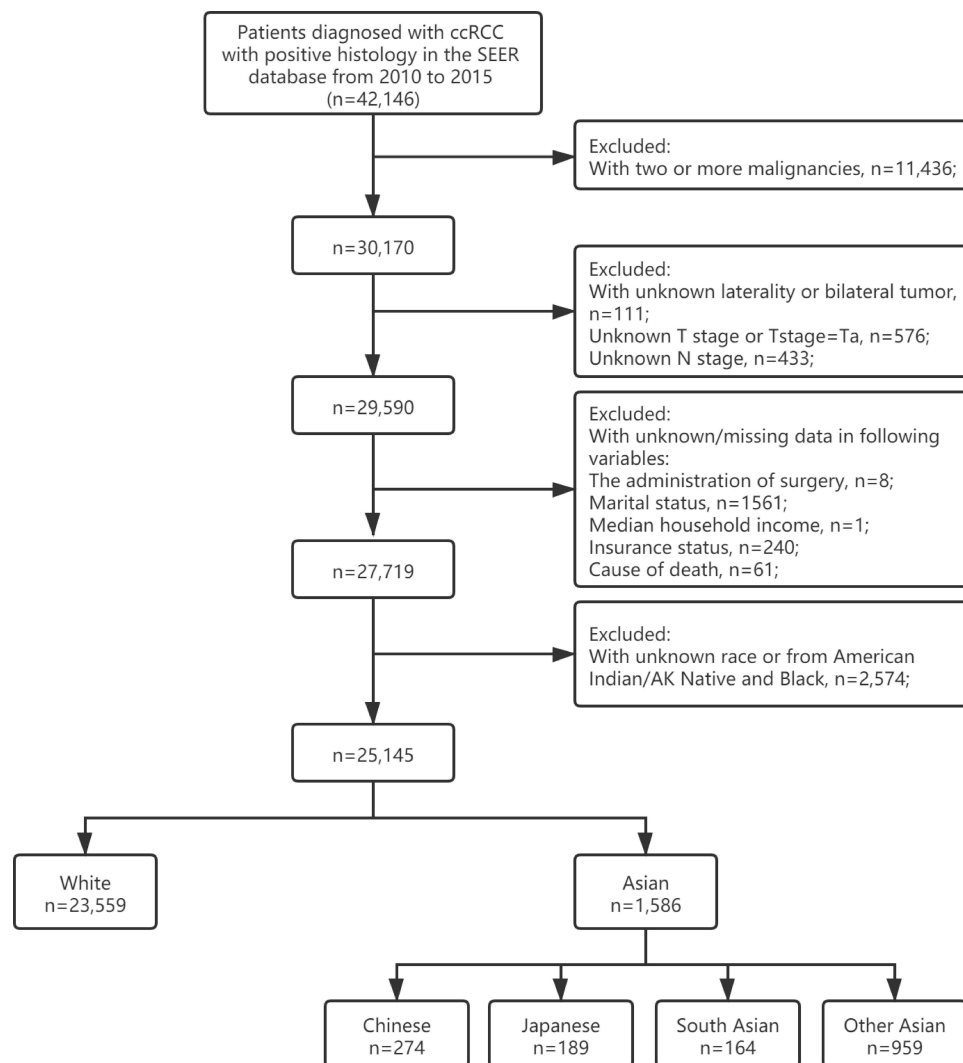


Figure 1 Flowchart of patient selection.

separated, divorced and widowed). In addition, the household income was divided into low and high levels according to the median value.

Previous studies have reported on the association between kidney cancer and risk factors such as smoking,¹⁴ obesity,¹⁵ and hypertension.¹⁶ Moreover, cancer survivors have an increased risk of cardiovascular disease (CVD) due to the shared lifestyles or toxicities of cancer treatment.^{17,18} Therefore, in this study, COD was mainly divided into three categories: died of ccRCC, died of CVD and died of other causes. Moreover, in order to balance the basic characteristics between Asian and White patients, we performed propensity score matching (PSM) analysis with a ratio of 1:3 using the nearest neighbor matching method. Variables utilized for PSM analysis included age at diagnosis, sex, tumor grade, laterality,

histological stage, T stage, N stage, M stage, insurance status, marital status and median household income.

Proportional Mortality Ratio (PMR)

PMR, which could exhibit the proportion of each COD properly, was defined as the number of deaths due to a specific cause divided by the number of total deaths. Variable “COD to site record” in the SEER registry was applied to recognize different CODs. CVD mortality includes: diseases of heart (ICD 10=100–109, 111, 113, 120–151), hypertension without heart disease (ICD 10=110, 112), cerebrovascular diseases (ICD 10=160–169), atherosclerosis (ICD 10=170), aortic aneurysm (ICD 10=171), other diseases of arteries, arterioles and capillaries (ICD 10=172–178). We performed PMR analyses in Asian patients, and further

Table I Basic Characteristics of Patients with ccRCC in the SEER Database (Asian Vs White)

	Total	White	Asian	P
N	25,145	23,559	1586	
Age, year Median (IQR)	60.00 (52.00, 69.00)	60.00 (52.00, 69.00)	61.00 (52.00, 70.00)	0.013
Sex, n (%)				<0.001
Male	15,792 (62.80)	14,703 (62.41)	1089 (68.66)	
Female	9353 (37.20)	8856 (37.59)	497 (31.34)	
Year of diagnosis, n (%)				0.802
2010	3479 (13.84)	3273 (13.89)	206 (12.99)	
2011	3720 (14.79)	3485 (14.79)	235 (14.82)	
2012	4064 (16.16)	3804 (16.15)	260 (16.39)	
2013	4237 (16.85)	3980 (16.89)	257 (16.2)	
2014	4630 (18.41)	4322 (18.35)	308 (19.42)	
2015	5015 (19.94)	4695 (19.93)	320 (20.18)	
Laterality, n (%)				0.057
Left	12,339 (49.07)	11,524 (48.92)	815 (51.39)	
Right	12,806 (50.93)	12,035 (51.08)	771 (48.61)	
Histological stage, n (%)				0.134
Localized	18,042 (71.75)	16,878 (71.64)	1164 (73.39)	
Regional	4612 (18.34)	4351 (18.47)	261 (16.46)	
Distant	2491 (9.91)	2330 (9.89)	161 (10.15)	
Tumor Grade ^a , n (%)				0.369
I–II	14,057	13,173 (55.91)	884 (55.74)	
III–IV	7990	7468 (31.7)	522 (32.91)	
Unknown	3098	2918 (12.39)	180 (11.35)	
T stage, n (%)				0.503
T1	16,351 (65.03)	15,297 (64.93)	1054 (66.46)	
T2	2679 (10.65)	2509 (10.65)	170 (10.72)	
T3	5667 (22.54)	5329 (22.62)	338 (21.31)	
T4	448 (1.78)	424 (1.8)	24 (1.51)	
N stage, n (%)				0.629
N0	24,201 (96.25)	22,671 (96.2307)	1530 (96.47)	
N1	944 (3.75)	888 (3.7693)	56 (3.53)	
M stage, n (%)				0.767
M0	22,678 (90.19)	21,251 (90.2)	1427 (89.97)	
M1	2467 (9.81)	2308 (9.8)	159 (10.03)	
Median household income, n (%)				<0.001
Low	12,832 (51.03)	12,334 (52.35)	498 (31.40)	
High ^b	12,313 (48.97)	11,225 (47.65)	1088 (68.60)	
Marital status, n (%)				<0.001
Never married	3890 (15.47)	3686 (15.65)	204 (12.86)	
Married	16,705 (66.43)	15,529 (65.92)	1176 (74.15)	
SDW	4550 (18.10)	4344 (18.43)	206 (12.99)	
Insurance status, n (%)				<0.001
Any Medicaid	3001 (11.93)	2760 (11.71)	241 (15.2)	
Insured	21,390 (85.07)	20,083 (85.25)	1307 (82.41)	

(Continued)

Table 1 (Continued).

	Total	White	Asian	P
Uninsured	754 (3.00)	716 (3.04)	38 (2.39)	
Surgery, n (%)				0.311
No	1244 (4.95)	1174 (4.98)	70 (4.41)	
Yes	23,901 (95.05)	22,385 (95.02)	1516 (95.59)	

Notes: ^aGrade I: well differentiated; Grade II: moderately differentiated; Grade III: poorly differentiated; Grade IV: undifferentiated. ^bHigh median household income: defined by earnings above the median value in this sample.

Abbreviations: ccRCC, clear cell renal cell carcinoma; SEER, Surveillance Epidemiology and End Results; IQR, interquartile range; SDW, separated, divorced or widowed.

stratified by race ethnicity, age, sex, tumor laterality, histological stage, median household income, marital status, insurance status and surgery. Finally, comparison between Asian and White patients in PMRs was developed.

Survival Outcomes

In Asian patients, Kaplan–Meier (KM) analyses were performed to explore the long-term prognosis. Racial disparities between Asian and White patients were then compared. Furthermore, we developed subgroup analyses stratified by clinical variables. Similarly, KM analyses were performed in the PSM patients. Moreover, the 3- and 5-year OS/ cancer-specific survival (CSS) probabilities were calculated for subsequent comparisons. Lastly, a competing risk regression model was built to explore the prognostic factors of CSS in ccRCC patients, while deaths from other causes were regard as competing events.

Statistical Analyses

Continuous variables were displayed in the form of median (interquartile range, IQR) and compared using Mann–Whitney U or Kruskal–Wallis test. Categorical variables were presented in the form of n (%), and Chi-square test or Fisher's exact test was utilized to explore the statistical significance in proportion differences. PSM analysis was performed to balance the basic characteristics. Racial disparities in survival outcomes were compared utilizing KM analyses. Competing risk regression model was applied to identify prognostic factors for CSS in ccRCC patients. In this study, statistical analyses were produced using SPSS 23.0 software (SPSS Inc, Chicago, IL, USA) and R software (V3.4.1). A two-sided $P < 0.05$ was statistically significant.

Results

Clinical Characteristics

A total of 1586 Asian patients were eventually enrolled in our study. As shown in Table 1, the median (IQR) age at diagnosis was 61 (52–70) years old. Most patients were male (68.66%), older (>45 : 88.52%), married (74.15%), insured (82.41%), with earlier tumor stage (T1: 66.46%), grade (grade I–II: 66.46%) and higher median household income (68.60%). In addition, most diseases were localized (73.39%) without lymph node (N0: 96.47%) or distant metastasis (M0: 89.97%), and surgery was performed in 95.59% of Asian patients.

In Table 2, subsequent analyses based on race/ethnicity in Asian-American patients revealed that patients from South Asian had the youngest age at diagnosis (median: 56 years old), while Japanese patients had the oldest age at diagnosis (median: 65 years old). Moreover, Japanese patients had the highest proportion of insured patients (94.71%) and the lowest proportion of married patients (67.72%) than other populations. In tumor characteristics, patients from South Asian seemed to have the earliest stage of diseases (localized: 76.83%, T1: 70.73%) than other ethnicities.

Compared with White patients (Table 1), Asian patients had a higher proportion of male (68.66% vs 62.41%, $P < 0.001$) and high level of median household income (68.60% vs 47.65%, $P < 0.001$). Moreover, the proportions of insured patients (85.25%) and never married or SDW (34.08%) patients in Whites were significantly higher than Asians.

PMR

A total of 228 (14.38%) Asian patients died up to the last follow-up, including 175 (76.75%) patients died of cancer itself, 28 (12.28%) patients died of CVD and 25 (10.96%) patients died of other causes (Figure 2). Subsequently, we

Table 2 Basic Characteristics of Asian Patients with ccRCC in the SEER Database, Stratified by Race/Ethnicity

	Chinese	Japanese	South Asian	Other Asian	P
N	274	189	164	959	
Age, year or n (%)					
Median (IQR)	64.00 (54.00, 72.75)	65.00 (55.00, 74.00)	56.00 (46.00, 65.00)	61.00 (52.00, 69.00)	<0.0001
<45	24 (8.76)	13 (6.88)	39 (23.78)	106 (11.05)	<0.0001
45–65	119 (43.43)	78 (41.27)	81 (49.39)	487 (50.78)	
>65	131 (47.81)	98 (51.85)	44 (26.83)	366 (38.16)	
Sex, n (%)					0.2506
Male	193 (70.44)	135 (71.43)	120 (73.17)	641 (66.84)	
Female	81 (29.56)	54 (28.57)	44 (26.83)	318 (33.16)	
Year of diagnosis, n (%)					0.2303
2010	33 (12.04)	27 (14.29)	23 (14.02)	123 (12.83)	
2011	41 (14.96)	34 (17.99)	28 (17.07)	132 (13.76)	
2012	51 (18.61)	29 (15.34)	18 (10.98)	162 (16.89)	
2013	35 (12.77)	29 (15.34)	27 (16.46)	166 (17.31)	
2014	53 (19.34)	40 (21.16)	24 (14.63)	191 (19.92)	
2015	61 (22.26)	30 (15.87)	44 (26.83)	185 (19.29)	
Laterality, n (%)					0.4997
Left	136 (49.64)	89 (47.09)	85 (51.83)	505 (52.66)	
Right	138 (50.36)	100 (52.91)	79 (48.17)	454 (47.34)	
Histological stage, n (%)					0.0422
Localized	208 (75.91)	119 (62.96)	126 (76.83)	711 (74.14)	
Regional	41 (14.96)	45 (23.81)	24 (14.63)	151 (15.75)	
Distant	25 (9.12)	25 (13.23)	14 (8.54)	97 (10.11)	
Tumor Grade ^a , n (%)					0.0135
I–II	169 (61.68)	106 (56.08)	85 (51.83)	524 (54.64)	
III–IV	81 (29.56)	73 (38.62)	58 (35.37)	310 (32.33)	
Unknown	24 (8.76)	10 (5.29)	21 (12.80)	125 (13.03)	
T stage, n (%)					0.0447
T1	185 (67.52)	112 (59.26)	116 (70.73)	641 (66.84)	
T2	32 (11.68)	15 (7.94)	14 (8.54)	109 (11.37)	
T3	52 (18.98)	60 (31.75)	33 (20.12)	193 (20.13)	
T4	5 (1.82)	2 (1.06)	1 (0.61)	16 (1.67)	
N stage, n (%)					0.7286
N0	267 (97.45)	181 (95.77)	157 (95.73)	925 (96.45)	
N1	7 (2.55)	8 (4.23)	7 (4.27)	34 (3.55)	
M stage, n (%)					0.3624
M0	249 (90.88)	164 (86.77)	151 (92.07)	863 (89.99)	
M1	25 (9.12)	25 (13.23)	13 (7.93)	96 (10.01)	
Median household income, n (%)					
Low	138 (50.36)	153 (80.95)	66 (40.24)	138 (50.36)	
High ^b	136 (49.64)	36 (19.05)	98 (59.76)	136 (49.64)	
Marital status, n (%)					<0.0001
Never married	21 (7.66)	37 (19.58)	10 (6.10)	136 (14.18)	
Married	208 (75.91)	128 (67.72)	142 (86.59)	698 (72.78)	
SDW	45 (16.42)	24 (12.70)	12 (7.32)	125 (13.03)	

(Continued)

Table 2 (Continued).

	Chinese	Japanese	South Asian	Other Asian	P
Insurance status, n (%)					<0.0001
Any Medicaid	49 (17.88)	7 (3.70)	28 (17.07)	157 (16.37)	
Insured	225 (82.12)	179 (94.71)	128 (78.05)	775 (80.81)	
Uninsured	0 (0.00)	3 (1.59)	8 (4.88)	27 (2.82)	
Surgery, n (%)					0.3485
No	11 (4.01)	9 (4.76)	3 (1.83)	47 (4.90)	
Yes	263 (95.99)	180 (95.24)	161 (98.17)	912 (95.10)	

Notes: ^aGrade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated. ^bHigh median household income: defined by earnings above the median value in this sample.

Abbreviations: ccRCC, clear cell renal cell carcinoma; SEER, Surveillance Epidemiology and End Results; IQR, interquartile range; SDW, separated, divorced or widowed.

performed PMR analyses in Asian patients further stratified by race/ethnicity (Figure 3A), age at diagnosis (Figure 3B), sex (Figure 3C), tumor laterality (Figure 3D), histological stage (Figure 3E), median household income (Figure 3F), marital status (Figure 3G), insurance status (Figure 3H) and the administration of surgery (Figure 3I).

In Asian populations, the PMRs of different CODs were similar in different races, without statistical difference ($P=0.767$, Table 3 and Figure 3). The PMR of ccRCC in patients ≤ 65 years old was significantly higher than that in patients >65 years old (90.11% vs 67.88%), while the PMR of CVD was significantly lower in patients ≤ 65 years old

(3.30% vs 18.25%). Moreover, as the disease progressed, the proportion of patients who died of ccRCC (58.46% vs 70.18% vs 91.51%) increased gradually, while the proportion of patients who died of CVD (21.54% vs 14.04% vs 5.66%) and other causes (20.00% vs 15.79% vs 2.83%) decreased. In addition, the administration of surgery could reduce the risk of dying from ccRCC significantly (89.80% vs 73.18%). However, sex, tumor laterality, median household income, marital status and insurance status seemed to have no significant effect on the PMRs of different CODs.

Similarly, there were 3908 (16.59%) White patients died up to the last follow-up, including 2785 (71.26%) patients died of ccRCC, 521 (13.33%) patients died of CVD and 602

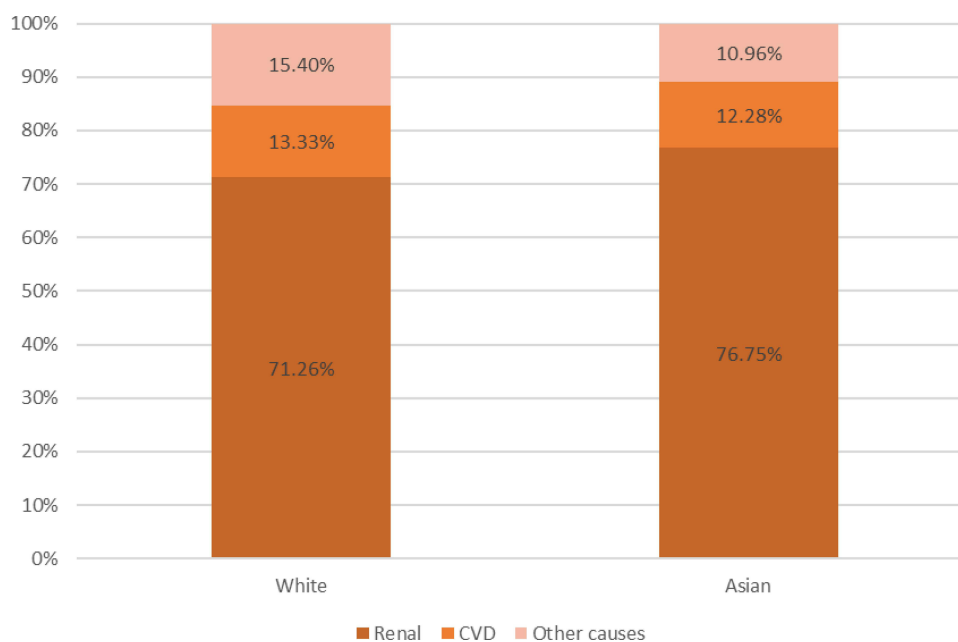


Figure 2 Proportional mortality ratios of different CODs (renal cancer vs CVD vs other causes) in Asian-American and White patients with ccRCC.

Abbreviations: COD, causes of death; CVD, cardiovascular diseases; ccRCC, clear cell renal cell carcinoma.

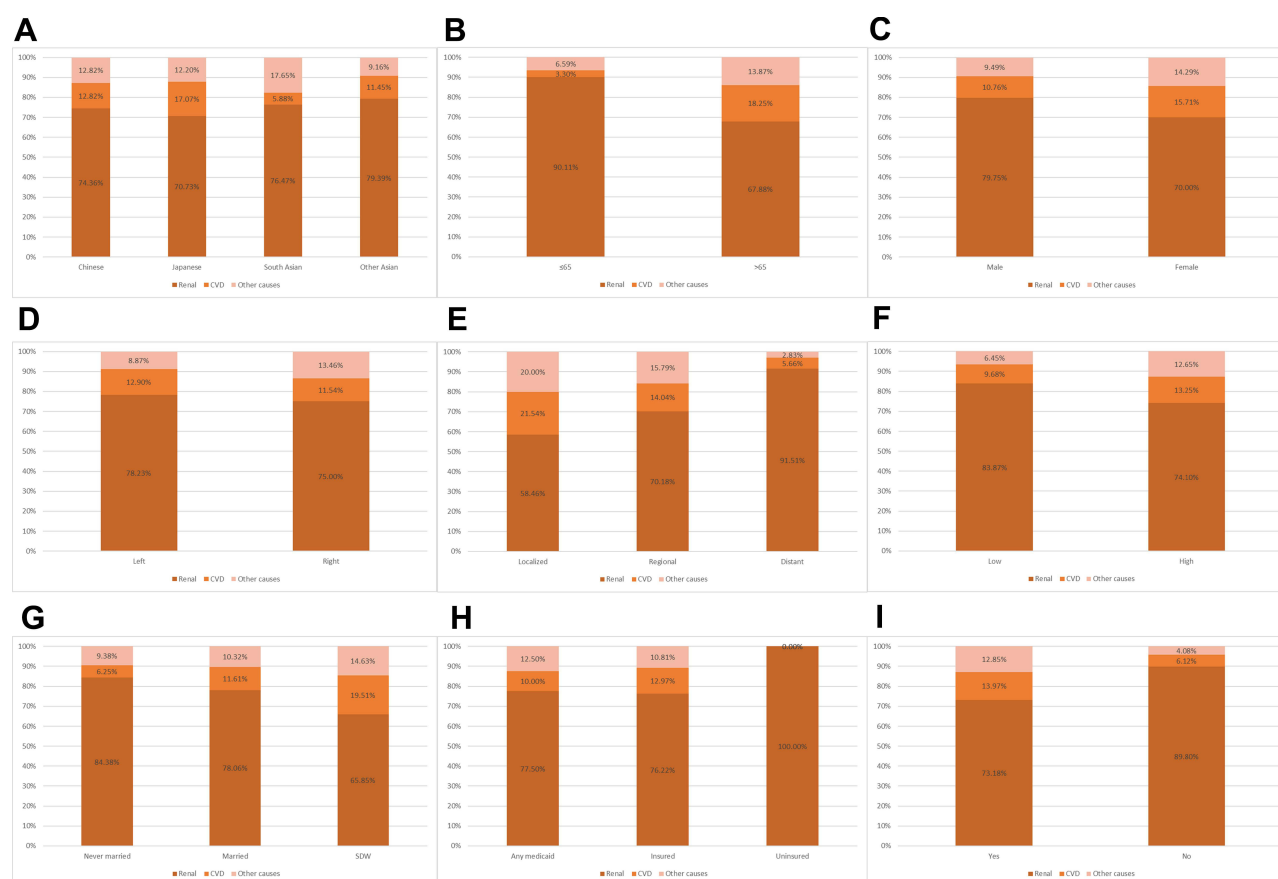


Figure 3 Proportional mortality ratios of different CODs in Asian patients with ccRCC, stratified by race/ethnicity (A), age at diagnosis (B), sex (C), tumor laterality (D), historic stage (E), median household income (F), marital status (G), insurance status (H) and the administration of surgery (I).

Abbreviations: COD, causes of death; ccRCC, clear cell renal cell carcinoma.

(15.04%) patients died of other causes. No significant differences were detected between Asian and White patients in PMRs of different CODs ($P=0.143$, Figure 2).

Survival Outcomes

In the whole population, the last follow-up time was December 31, 2017, and the median follow-up was 35 (IQR: 19–55) months. The 5-year OS and CSS rates of Asian patients were 81.2% and 85.9%, respectively. As shown in Figures 4 and 5, in Asian populations, Japanese patients (5-year OS: 74.0%, 95% CI= 66.9–82.0%) had the worst OS while those from South Asian (5-year OS: 85.5%, 95% CI= 78.6–93.0%) had the best OS (Figure 4A). Moreover, younger age (Figures 4B and 5B), earlier stage of disease [histological stage (Figures 4C and 5C), TNM stage (Figures 4D–F and 5D–F), and surgery (Figures 4G and 5G)] were tightly associated with better OS and CSS in Asian patients. However, tumor laterality (Figures 4H and 5H) and sex (Figures 4I and 5I) were not related to survival outcomes significantly.

Before PSM, no significant differences were detected in OS and CSS between Asian and White patients (Figure 6A and B), and further subgroup analyses stratified by clinical variables revealed the same results (Tables S1 and S2). Furthermore, PSM analyses were conducted to balance the basic characteristics between Asian and White patients (Table S3). In addition, comparable survival outcomes were detected in patients after PSM (Figure 6C and D, Tables S4–S5).

Lastly, competing risk regression model found that age at diagnosis ($P<0.001$), tumor grade ($P<0.001$), histological stage ($P<0.001$), median household income ($P<0.001$) and the administration of surgery ($P<0.001$) were prognostic factors for CSS in ccRCC patients, while died of other causes was regarded as a competing event (Table 4).

Discussion

In our study, we investigated the basic characteristics, PMRs and long-term survival outcomes of Asian-American patients with ccRCC, and made comparisons

Table 3 Proportional Mortality Ratios of Different Causes of Death in Asian Patients with ccRCC

	Total	Renal	CVD	Other Causes	P value
Total	228	175 (76.74)	28 (12.28)	25 (10.96)	
Race					0.767
Chinese	39	29 (74.36)	5 (12.82)	5 (12.82)	
Japanese	41	29 (70.73)	7 (17.07)	5 (12.20)	
South Asian	17	13 (76.47)	1 (5.88)	3 (17.65)	
Other Asian	131	104 (79.39)	15 (11.45)	12 (9.16)	
Age					<0.001
<65	91	82 (90.11)	3 (3.30)	6 (6.59)	
>65	137	93 (67.88)	25 (18.25)	19 (13.87)	
Sex					0.274
Male	158	126 (79.75)	17 (10.76)	15 (9.49)	
Female	70	49 (70.00)	11 (15.71)	10 (14.29)	
Laterality					0.535
Left	124	97 (78.23)	16 (12.9)	11 (8.87)	
Right	104	78 (75.00)	12 (11.54)	14 (13.46)	
Histological stage					<0.001
Localized	65	38 (58.46)	14 (21.54)	13 (20.00)	
Regional	57	40 (70.18)	8 (14.04)	9 (15.79)	
Distant	106	97 (91.51)	6 (5.66)	3 (2.83)	
Median household income					0.271
Low	62	52 (83.87)	6 (9.68)	4 (6.45)	
High ^a	166	123 (74.10)	22 (13.25)	21 (12.65)	
Marital status					0.373
Never married	32	27 (84.38)	2 (6.25)	3 (9.38)	
Married	155	121 (78.06)	18 (11.61)	16 (10.32)	
SDW	41	27 (65.85)	8 (19.51)	6 (14.63)	
Insurance status					0.942
Any Medicaid	40	31 (77.50)	4 (10.00)	5 (12.50)	
Insured	185	141 (76.22)	24 (12.97)	20 (10.81)	
Uninsured	3	3 (100.00)	0 (0.00)	0 (0.00)	
Surgery					0.050
No	49	44 (89.80)	3 (6.12)	2 (4.08)	
Yes	179	131 (73.18)	25 (13.97)	23 (12.85)	

Notes: ^aHigh median household income: defined by earnings above the median value in this sample CVD = cardiovascular disease; SDW = separated, divorced or widowed. CVD mortality includes: diseases of heart (ICD 10 = 100–109, 111, 113, 120–151), hypertension without heart disease (ICD 10 = 110, 112), cerebrovascular diseases (ICD 10 = 160–169), atherosclerosis (ICD 10 = 170), aortic aneurysm (ICD 10 = 171), other diseases of arteries, arterioles and capillaries (ICD 10 = 172–178).

with White patients. There are many histological subtypes of kidney cancer, mainly including ccRCC, collecting duct RCC, papillary RCC, chromophobe RCC, each of which has a unique molecular structure. ccRCC is the most common subtype, accounting for approximately three-fourths of kidney cancer.^{3,19} In addition, different subtypes of RCC have been prove to exhibit different survival outcomes,^{20–22} and there may be a large selection bias in the analysis of mixed tumors of different histological

types. In Asian populations, Japanese patients with ccRCC had the highest proportion of insured patients (94.71%) and lowest proportion of married patients (67.72%) than other populations. In tumor characteristics, patients from South Asian seemed to have the earliest stage diseases than other ethnicities. Older age at diagnosis, earlier stage and surgery were tightly associated with a lower risk of dying of RCC. Asian patients had higher age at diagnosis and comparable tumor characteristics

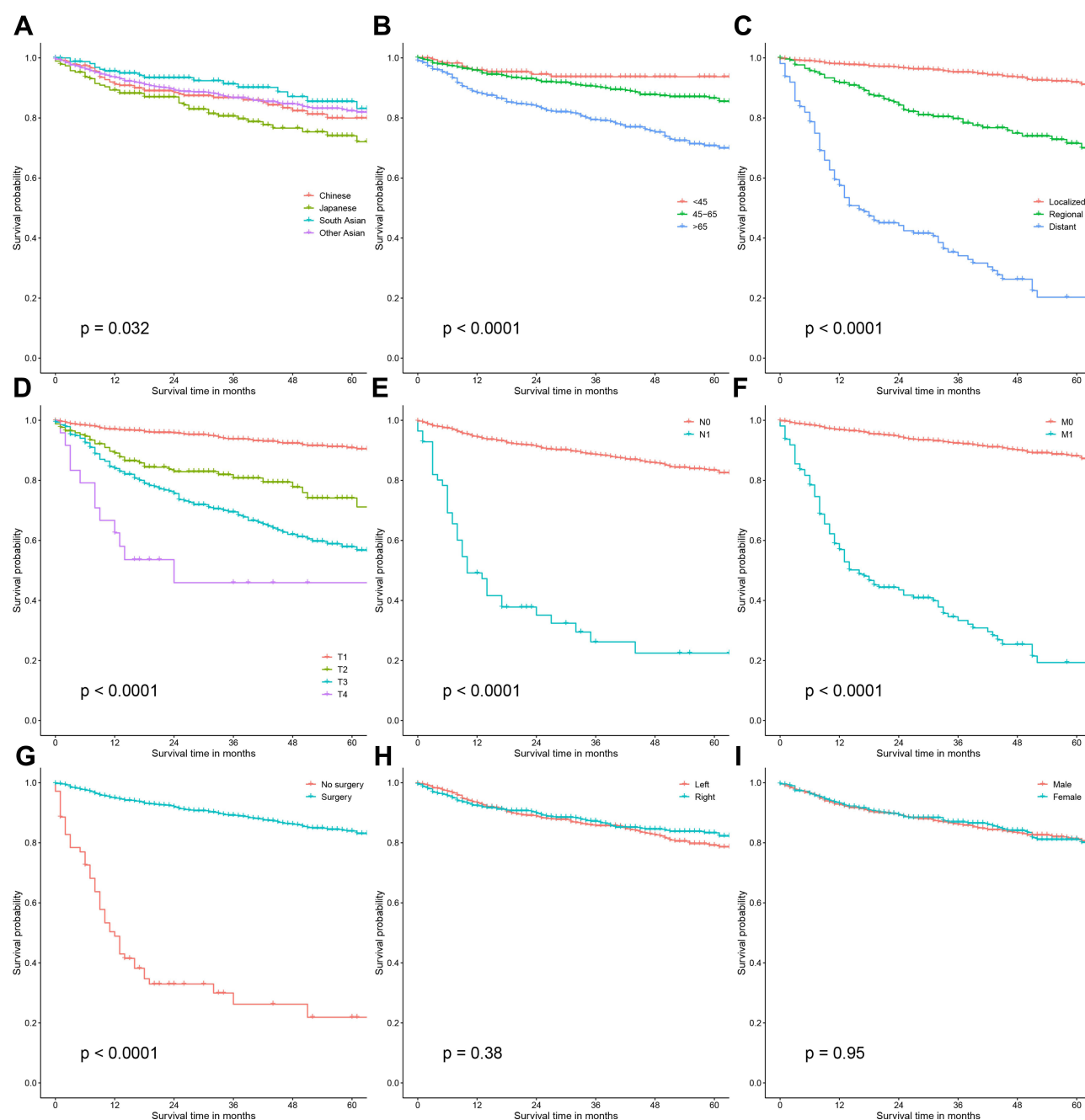


Figure 4 Kaplan–Meier curves of OS in Asian-patients with ccRCC, stratified by race/ethnicity (A), age at diagnosis (B), historic stage (C), T stage (D), N stage (E), M stage (F), the administration of surgery (G), tumor laterality (H) and sex (I). Younger age at diagnosis, earlier tumor stages (TNM, histological) and the administration of surgery were tightly associated with better OS in Asian-American patients.

Abbreviations: ccRCC, clear cell renal cell carcinoma; OS, overall survival.

when compared with White patients. Lastly, comparisons in survival outcomes between Asian and White patients were not statistically different.

Competing risk regression model revealed that younger age, earlier histological stage, earlier tumor grade, higher median household income and the administration of surgery were tightly associated with better CSS in ccRCC

patients. Previous studies have confirmed the potential prognostic value of these variables in RCC patients.^{23–25}

In our study, we performed a competing risk regression model to explore the potential prognostic factors rather than a Cox regression model, since the vast majority of patients included in the current work harbor organ-confined disease. Therefore, cancer-specific mortality is

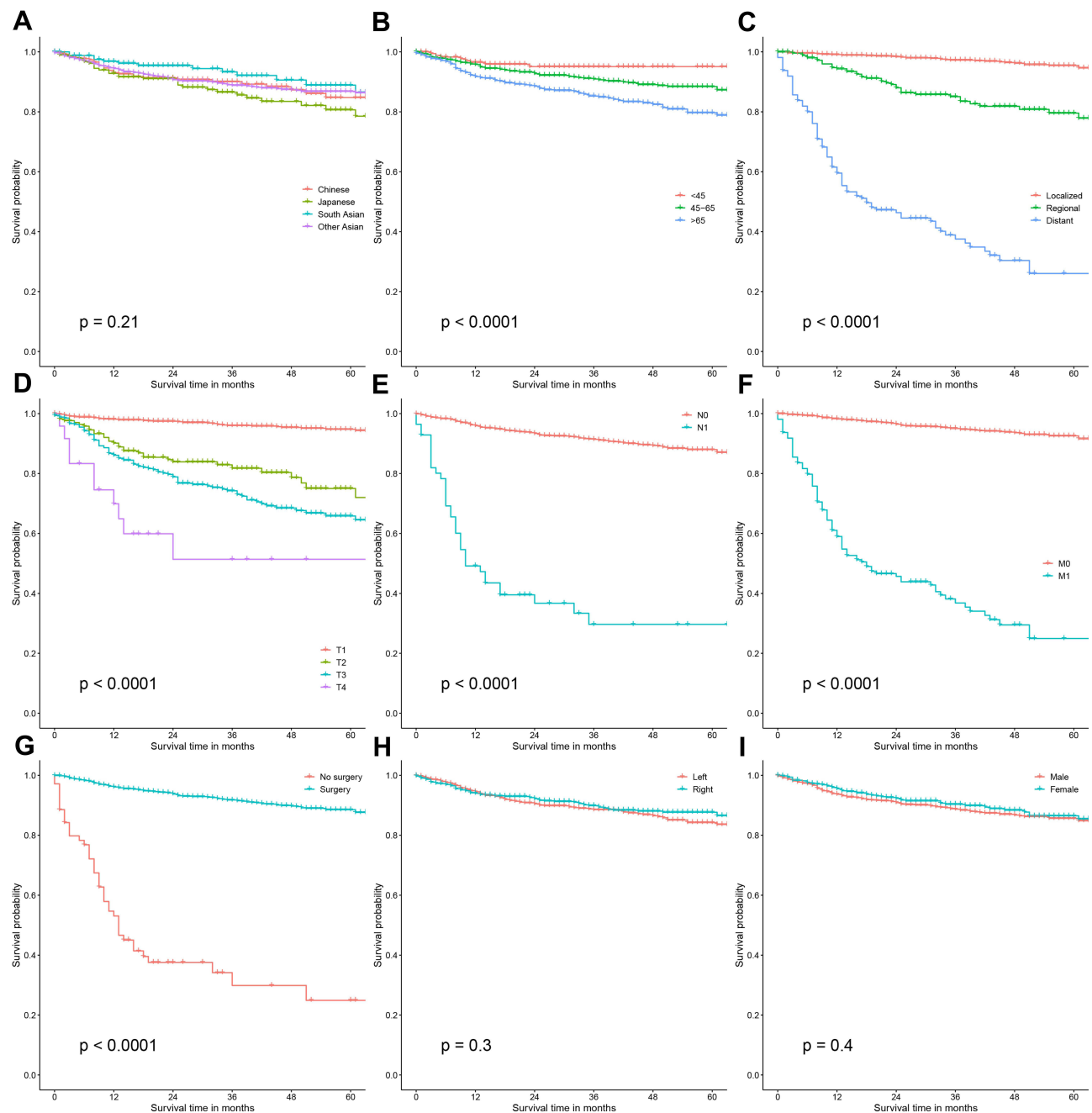


Figure 5 Kaplan-Meier curves of CSS in Asian-American patients with ccRCC, stratified by race/ethnicity (A), age at diagnosis (B), historic stage (C), T stage (D), N stage (E), M stage (F), the administration of surgery (G), tumor laterality (H) and sex (I). Younger age at diagnosis, earlier tumor stages (TNM, histological) and the administration of surgery were tightly associated with better CSS in Asian-American patients.

Abbreviations: ccRCC, clear cell renal cell carcinoma; CSS, cancer-specific survival.

similar, if not inferior, to other-cause mortality. We found that race/ethnicity was not a significant risk factor for survival outcomes after adjusting clinical variables. Similarly, Zhou et al constructed prognostic nomograms for CSS and OS in patients with kidney cancer on the basis of the SEER database, and they found that race was not a prognostic factor for OS and CSS. In Chinese

population, Zhu et al²⁶ found that age at diagnosis, Eastern Cooperative Oncology Group (ECOG) score, pre-operative platelet, neutrophil-to-lymphocyte ratio (NLR), tumor size, Fuhrman nuclear grade and T stage were independent risk factors for recurrence-free survival in ccRCC patients who underwent (partial) nephrectomy. However, some variables were missing in the SEER

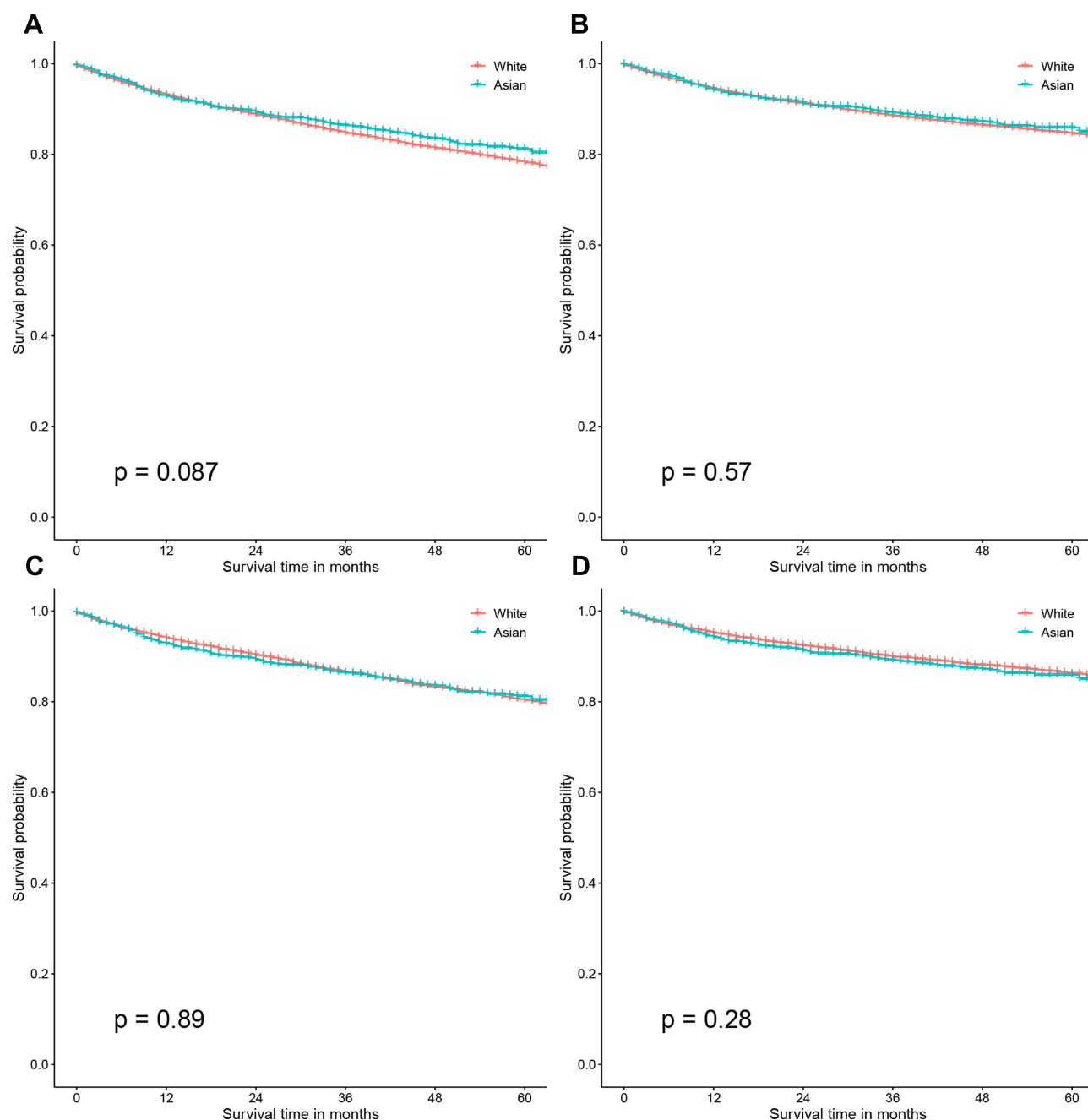


Figure 6 Kaplan-Meier curves of survival outcomes in Asian and White patients with ccRCC. OS before PSM (**A**), CSS before PSM (**B**), Asian American patients had comparable OS and CSS when compared with White patients before PSM. OS after PSM (**C**) and CSS after PSM (**D**), Asian American patients had comparable OS and CSS when compared with White patients after PSM.

Abbreviations: ccRCC, clear cell renal cell carcinoma; OS, overall survival; CSS, cancer-specific survival; PSM, propensity score matching.

database, such as ECOG score and gene expression, which made the prediction model a little insufficient.

Many studies have investigated the racial disparities in RCC patients in incidence rates basic characteristics and survival outcomes. Among American men in 2014, Black men were the most probably to suffer from renal and pelvic cancer (24.7/100,000), followed by White men

(22.0/100,000).²⁷ In addition, the distributions of histological subtypes in different races were also different. Previous studies have revealed that ccRCC was more common in Whites while Black patients were more likely to get pRCC.^{28,29} Chow et al¹⁰ found that White patients with RCC had better prognosis than Black patients, and similar survival trends were detected in subgroup analyses

Table 4 Competing Risk Regression Model for Predicting Cancer-Specific Survival in ccRCC Patients

Variable	HR	95% CI	P value
Race			
Asian	Reference		
White	0.961	0.802–1.150	0.662
Age	1.015	1.012–1.020	<0.001
Sex			
Male	Reference		
Female	1.008	0.922–1.101	0.866
Laterality			
Left	Reference		
Right	0.986	0.912–1.066	0.721
Grade			
Grade I–II	Reference		
Grade III–IV	2.569	2.317–2.849	<0.001
Unknown	1.674	1.464–1.914	<0.001
Histological stage			
Localized	Reference		
Regional	4.452	3.963–5.003	<0.001
Distant	21.156	18.882–23.704	<0.001
Marital status			
Never married	Reference		
Married	0.914	0.807–1.034	0.152
SDW	1.089	0.942–1.258	0.251
Median household income			
Low	Reference		
High	0.838	0.775–0.907	<0.001
Insurance status			
Any Medicaid	Reference		
Insured	0.899	0.790–1.022	0.104
Uninsured	1.117	0.882–1.416	0.359
Surgery			
No	Reference		
Yes	0.311	0.272–0.355	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; SDW, separated, divorced or widowed.

stratified by clinical variables. However, no studies that have comprehensively explored the clinical characteristics and prognosis of ccRCC in Asian populations. In our study, Asian patients had a higher proportion of male and higher household income when compared with White patients. However, no significant differences were found in survival outcomes between Asian and White patients before and after PSM. Jivanji et al³⁰ demonstrated that

Black patients had the best 5-year OS than other races, while those from American Indian/AK Native suffered the worst prognosis. However, they did not make further survival analyses between Asian and White patients. Moreover, in the adjusted COX regression model, they concluded that race was not a significant risk factor for 5-year CSS in ccRCC patients (Asian/Pacific Islander to White: Hazard Ratio=0.99, 95% CI=0.82–1.20).

Nowadays, cancer and CVD have been the two leading CODs worldwide. There are many similar risk factors between CVD and cancer occurrence (including obesity, smoking, diabetes, etc.), and there may be shared biological mechanisms between the two.³¹ In recent years, advances in medical treatment have also improved the prognosis of cancer patients, which has also increased the risk of CVD in cancer survivors. Additionally, some treatment methods and drugs for cancer patients are closely related to the risk of CVD.³² Some CVD-related factors, including smoking, hypertension and obesity, have already been recognized as risk factors for RCC.^{33,34} In PMR analyses, 12.28% of Asian patients and 13.33% of White patients were died of CVD. We found that older age and earlier stage and surgery were closely related to a higher risk of dying of CVD. Clearly, age is one of the most important risk factors leading to CVD. North et al³⁵ investigated the role of lifespan-related gene in regulating cardiovascular health. Moreover, earlier stage of diseases and the administration of surgery may represent better survival outcomes in RCC patients. Lastly, the proportion of different CODs was not different between White and Asian patients.

To our knowledge, previous studies on racial disparities in RCC patients mostly focused on Whites and Blacks. Our study comprehensively explored the basic characteristics, PMR, and survival outcomes of ccRCC in Asian patients through a population-based, large sample sized database for the first time, and made comparisons with White patients. However, there were some limitations that could not be ignored in our research. First, we cannot completely separate the incidence rate of Asian from Pacific Islander due to the design of SEER database itself. Therefore, comparisons between Whites and Asians in incidence rate could not be performed accurately. Secondly, some important data were missing in the SEER database, such as lifestyle (smoking, drinking, body mass index, ECOG score), genomics data, and other therapies (immunotherapy, targeted therapy, etc.), which made it difficult to build an accurate prediction model.

Finally, it is a retrospective, database-based study with unavoidable selection bias. In the future, well-designed and prospective studies are essential to verify our results.

Conclusion

Our study comprehensively analyzed the basic characteristics, PMR and survival outcomes of Asian Americans with ccRCC. Asian patients had comparable tumor characteristics and survival outcomes when compared with White patients. In Asian patients, those from South Asian had the youngest age at diagnosis and the earliest stage of diseases. Age, grade, histological stage, household income and surgery were considered to be prognostic factors for CSS. In the future, prospective and well-designed studies are needed to verify our findings. Our study may provide important value for the diagnosis and treatment of ccRCC patients while further studies are needed to verify our findings.

Data Sharing Statement

All data included in this study are available on reasonable request from the corresponding author.

Ethics Approval and Consent Participate

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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All information from the SEER program is available and free for public and approval was obtained from the Ethics Committee of Jiangsu Cancer Hospital. We used the SEER database with the username of 10977-Nov2019.

Funding

The Research Project of Jiangsu Cancer Hospital (ZM202015).

Disclosure

All authors declare that they have no conflicts of interest for this work.

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