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Frequency, incidence and survival outcomes of clear cell renal cell carcinoma in the United States from 1973 to 2014

A SEER-based analysis

Xiao Feng, PhD[a], Lina Zhang, MS[b], Wenzhi Tu, PhD[c,*], Shundong Cang, MD[a,*]

Abstract

The epidemiological and prognostic data focusing on clear cell renal cell carcinoma (ccRCC) are rarely presented. This study was aimed to define the frequency, incidence, and survival outcomes of ccRCC in the United States.

The Surveillance, Epidemiology, and End Results (SEER) database was searched for patients with ccRCC from 1973 to 2014. Two patient cohorts were utilized: patient cohorts of SEER 18 registries and 9 registries. Overall survival was determined with Kaplan–Meier method and compared across groups with log-rank test.

The incidence rate of ccRCC increased with advancing age, peaked in individuals aged 60 to 79 years, and declined in individuals aged ≥80 years. The incidence rate of ccRCC was significantly higher in males than females (1.94: 1, $P < .0001$), in Whites than Blacks or others (1:0.79:0.91, $P < .0001$). The incidence rate of ccRCC with right side as primary origin was slightly but significantly higher than that with left side as primary origin (1:0.96, $P = .0006$). The incidence rate of ccRCC in Grade II was higher than other grades. Generally, the incidence rates of ccRCC in most circumstances started to surge in the middle 1990s. Survival outcomes of ccRCC worsened with advancing age at diagnosis, tumor grade, and stage. A better prognosis was observed in females than males, in Whites than Blacks, and in individuals diagnosed in 2006 to 2014 than 1973 to 2005.

To the best of our knowledge, the present study firstly presented long-term and updated epidemiological and prognostic data concerning ccRCC in the United States. Significant differences in incidence rates and survival outcomes stratified by different variables were identified.

Abbreviations: APC = annual percent change, ccRCC = clear cell renal cell carcinoma, OS = overall survival, RCC = renal cell carcinoma, SEER = Surveillance, Epidemiology, and End Results.

Keywords: SEER, clear cell renal cell carcinoma, survival

1. Introduction

Among all cancer types, the number of estimated new cases with kidney and renal pelvis cancer in the United States in 2018 ranks sixth in men and tenth in women,[1] which forebodes that a noticeable number of people would be afflicted by these malignancies. Renal cell carcinoma (RCC), also called renal adenocarcinoma, constitutes approximately 90% of all kidney malignancies,[2] and comprises a heterogeneous set of histological subtypes with diverse molecular and genetic characteristics.[3] The most common subtype of RCC is clear cell RCC (ccRCC), accounting for about 75% of all RCC cases, whereas other relatively less common subtypes of RCC contain papillary (type 1 and 2), chromophobe, collecting duct, medullary RCC, and so forth.[3,4]

To date, the long-term and updated epidemiological patterns of ccRCC are scarcely depicted. A recent study exhibited trends in incidence rates of RCC in the United States from 1992 to 2015.[5] Although ccRCC accounts for the majority of all RCC, the epidemiological features of RCC do not necessarily coincide with that of ccRCC owing to heterogeneity among RCC subtypes. In this study, to provide a long-term viewpoint on ccRCC epidemiology, we analyzed the trend in incidence rates of ccRCC patients in the United States from 1973 to 2014, spanning a period of >4 decades.

Previous studies have reported the prognostic role of demographic and tumor factors in RCC patients, including

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[a] Department of Oncology, [b] Henan Provincial Key Laboratory of Kidney Disease and Immunology, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, School of Clinical Medicine, Henan University, Zhengzhou, Henan, [c] The Comprehensive Cancer Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

[*] Correspondence: Shundong Cang, Department of Oncology, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, School of Clinical Medicine, Henan University, Zhengzhou, Henan 450003, China (e-mail: cangshundong@163.com); Wenzhi Tu, The Comprehensive Cancer Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 201620, China (e-mail: wenzhitu@126.com).

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age,[6,7] sex,[8–10] race,[11,12] tumor grade,[13] and stage.[14] However, the conclusions these studies have drawn are inevitably restricted by population size, region, period, and other confounding factors. More importantly, studies concerning the prognotic role of demographic and tumor factors in ccRCC rather than RCC are rarely presented. Therefore, in this study, we comprehensively analyzed the prognostic role of basic demographic and tumor factors in ccRCC patients in the United States by utilizing SEER database.

In this study, we hope to convey a panoramic and updated viewpoint on ccRCC epidemiology and prognosis. The trend in incidence rates of ccRCC uncovered in this study may be helpful in disease prevention, screening, and exploring potential risking factors. In clinical scenarios, it might be instructive to estimate prognosis of ccRCC patients in light of the demographic and tumor factors presented in this study.

2. Materials and methods

2.1. Database and patient cohorts

The Surveillance, Epidemiology, and End Results (SEER) Program provides massive epidemiologic and prognostic information on cancer in the United States. In this study, we performed a retrospective study on the frequency, incidence, and survival outcomes of ccRCC in the United States by extracting data from SEER database. To select the data of patients with ccRCC from SEER database, we combined 2 *International Classification of Diseases* for *Oncology* (*ICD-O-3*) codes: C649 (kidney) and 8310/3 (clear cell adenocarcinoma). Two cohorts of patients with ccRCC in SEER database were utilized. On one hand, to count the patients with ccRCC and estimate their survival outcomes, we used the patient cohort of SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, November 2016 Sub (1973–2014 varying)[15]; on the other hand, to evaluate the incidence rate of ccRCC and annual percent change (APC) in incidence rate, we adopted another patient cohort of SEER 9 Regs Research Data, November 2016 Sub (1973–2014).[16] This study utilized existing deidentified data in SEER database. Therefore, it was exempt from institutional review board approval and informed consent of patients.

2.2. Variables

Patient demographic and tumor variables we examined from SEER database included: age at diagnosis, sex, race, year of diagnosis, laterality, grade, survival months, vital status. Age at diagnosis was stratified into 5 groups: <20, 20 to 39, 40 to 59, 60 to 79, and ≥80 years. Race was classified as white, black and other (American-Indian/AK Native, Asian/Pacific Islander and unknown). Laterality contained 5 conditions: right-origin of primary, left-origin of primary, unilateral-side unspecified, bilateral-single primary, and no information about laterality. Grade included Grade I (well differentiated), Grade II (moderately differentiated), Grade III (poorly differentiated), Grade IV (undifferentiated or anaplastic), and Grade unknown. Information concerning survival months and vital status of patients with ccRCC was extracted when conducting survival anaylsis. The Food and Drug Administration in the United States approved sorafenib On December 20, 2005 and sunitinib malate on January 26, 2006 for treating advanced RCC. Herein we artificially deemed the year 2006 as a cutoff point and then evaluated the difference in survival outcomes between ccRCC patients diagnosed in 1973 to 2005 and 2006 to 2014.

2.3. Statistical analyses

The patients with ccRCC in SEER 18 registries were counted according to baseline demographic variables with SEER*Stat software of the version 8.3.4.[17] With the database of SEER 18 registries, overall survival (OS) of patients was assessed with Kaplan–Meier method and compared across groups with log-rank test in IBM SPSS Statistics 20. Survival analyses were performed after excluding patients with survival time of 0 month. However, incidence rate, incidence rate ratio (IRR), and APC in incidence rate were calculated based on SEER 9 registries with SEER*Stat software and Joinpoint Regression Program 4.7.0.0. Incidence rate per 100,000 population was age-adjusted to the 2000 US standard population (19 age groups, Census P25–1130). We assessed significance at the alpha = 0.05 level.

3. Results

3.1. Frequency of ccRCC in SEER 18 registries, 1973 to 2014

Overall, a total number of 87,325 ccRCC patients were identified in the database of SEER 18 registries from 1973 to 2014 with a median age at diagnosis of 62 years.[15] Supplementary Figure 1, http://links.lww.com/MD/D149 presented the number of patients with ccRCC in terms of various patient demographic and tumor variables, including age at diagnosis, sex, race, year of diagnosis, laterality, and grade. To display long-term trends in number of ccRCC patients from 1973 to 2014, we drew curve plots using the number of ccRCC patients in every single year (Supplementary Figure 2, http://links.lww.com/MD/D149).

3.2. Incidence rate of ccRCC and APC in incidence rate estimated with SEER 9 registries, 1973 to 2014

The overall incidence rate of ccRCC was estimated to be 3.59 cases per 100,000 population with the database of SEER 9 registries from 1973 to 2014.[16]Table 1 demonstrated the incidence rates of ccRCC by different patient demographic and tumor variables. The incidence rate of ccRCC increased with advancing age and peaked in individuals aged 60 to 79 years (13.61 cases per 100,000 population), whereas the incidence rate in individuals aged not less than 80 years declined compared with that in individuals aged 60 to 79 years (Table 1). Compared with females, a significantly higher incidence rate was observed in males (IRR: 1.94, $P < .001$, Table 1). The disease incidence rate was significantly lower in blacks (IRR: 0.79, $P < .001$, Table 1) or others (IRR: 0.91, $P < .001$, Table 1) than whites. The incidence rate of ccRCC with left side as primary origin was slightly lower than that with right side as primary origin (IRR: 0.96, $P = .0006$, Table 1). The incidence rate of ccRCC in Grade II ranked highest: 1.35 cases per 100,000 population (Table 1). In addition, to better visualize long-term trends in incidence rate from 1973 to 2014, we drew curve charts using incidence rate in every single year (Fig. 1). We observed that the incidence rates of ccRCC in most circumstances began to surge in the middle 1990s (Fig. 1). To calculate the APC in incidence rate of ccRCC, Joinpoint Regression Program was employed and the results of APC stratified by variables were shown in Figures 2–4. The intuitional observation stemming from Figure 1 that the incidence rates of ccRCC generally started to notably rise since the middle 1990s was statistically confirmed in Figures 2–4. For example, the APC in incidence rate in individuals aged 20 to 39 years from

Table 1

The incidence rates of ccRCC by different variables in the database of SEER 9 registries from 1973 to 2014.

	Incidence rate per 100,000 population (95% CI)	IRR (95% CI)	P*
Age, y			
<20	0.01 (0.01–0.01)	Reference	
20–39	0.51 (0.49–0.54)	65.17 (43.62–102.04)	.001
40–59	5.12 (5.03–5.21)	651.38 (437.48–1017.06)	.001
60–79	13.61 (13.41–13.81)	1731.76 (1163.23–2703.71)	.001
≥80	8.87 (8.54–9.21)	1128.66 (756.72–1764.81)	.001
Sex			
Female	2.52 (2.48–2.57)	Reference	
Male	4.88 (4.82–4.95)	1.94 (1.89–1.98)	.001
Race			
White	3.69 (3.65–3.73)	Reference	
Black	2.93 (2.81–3.05)	0.79 (0.76–0.83)	.001
Other†	3.37 (3.25–3.50)	0.91 (0.88–0.95)	.001
Laterality			
Right-origin of primary	1.81 (1.78–1.84)	Reference	
Left-origin of primary	1.75 (1.72–1.77)	0.96 (0.94–0.98)	.0006
Unilateral-side unspecified	0.01 (0.00–0.01)	0.003 (0.002–0.004)	.001
Bilateral, single primary	0.01 (0.00–0.01)	0.003 (0.002–0.004)	.001
No information about laterality	0.03 (0.02–0.03)	0.01 (0.01–0.02)	.001
Grade			
Grade I; well differentiated	0.41 (0.39–0.42)	Reference	
Grade II; moderately differentiated	1.35 (1.33–1.38)	3.32 (3.21–3.44)	.001
Grade III; poorly differentiated	0.67 (0.65–0.68)	1.64 (1.58–1.71)	.001
Grade IV; undifferentiated	0.15 (0.14–0.16)	0.37 (0.35–0.39)	.001
Unknown	1.02 (1.00–1.04)	2.50 (2.41–2.59)	.001

CI = confidence interval, IRR = incidence rate ratio.

* *P* value for IRR compared with reference.

† Other includes American Indian/AK Native, Asian/Pacific Island,er and unknown.

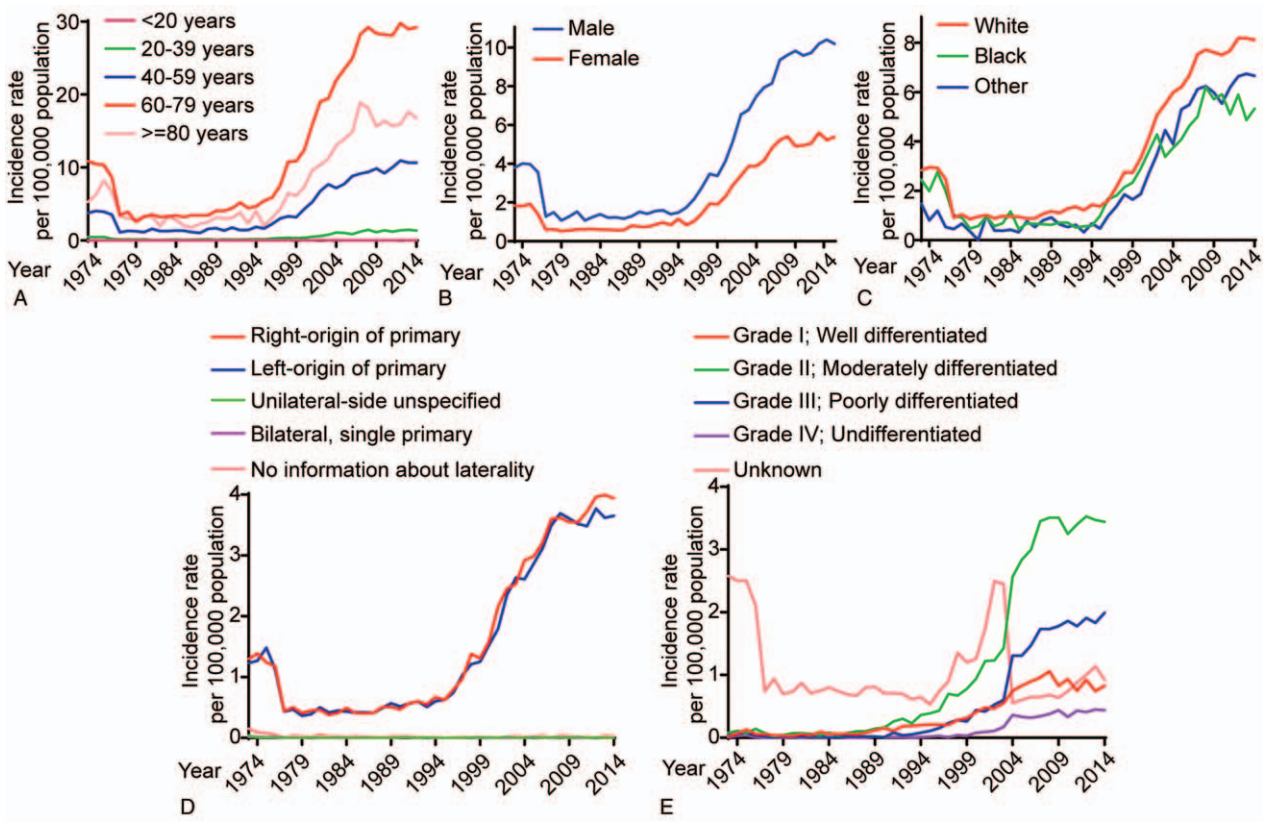

Figure 1. Curve plots showed the long-term trends in incidence rate of patients with clear cell renal cell carcinoma in the database of Surveillance, Epidemiology, and End Results 9 registries from 1973 to 2014 by different variables.

1994 to 2004 is statistically significant (APC = 20.72, $P < .05$); the APC in incidence rate in individuals aged 40 to 59 years from 1994 to 2003 is statistically significant (APC = 19.03, $P < .05$); the APC in incidence rate in individuals aged 60 to 79 years from 1994 to 2002 is statistically significant (APC = 18.54, $P < .05$); the APC in incidence rate in individuals aged not less than 80 years from 1995 to 2001 is statistically significant (APC = 20.66, $P < .05$) (Fig. 2A).

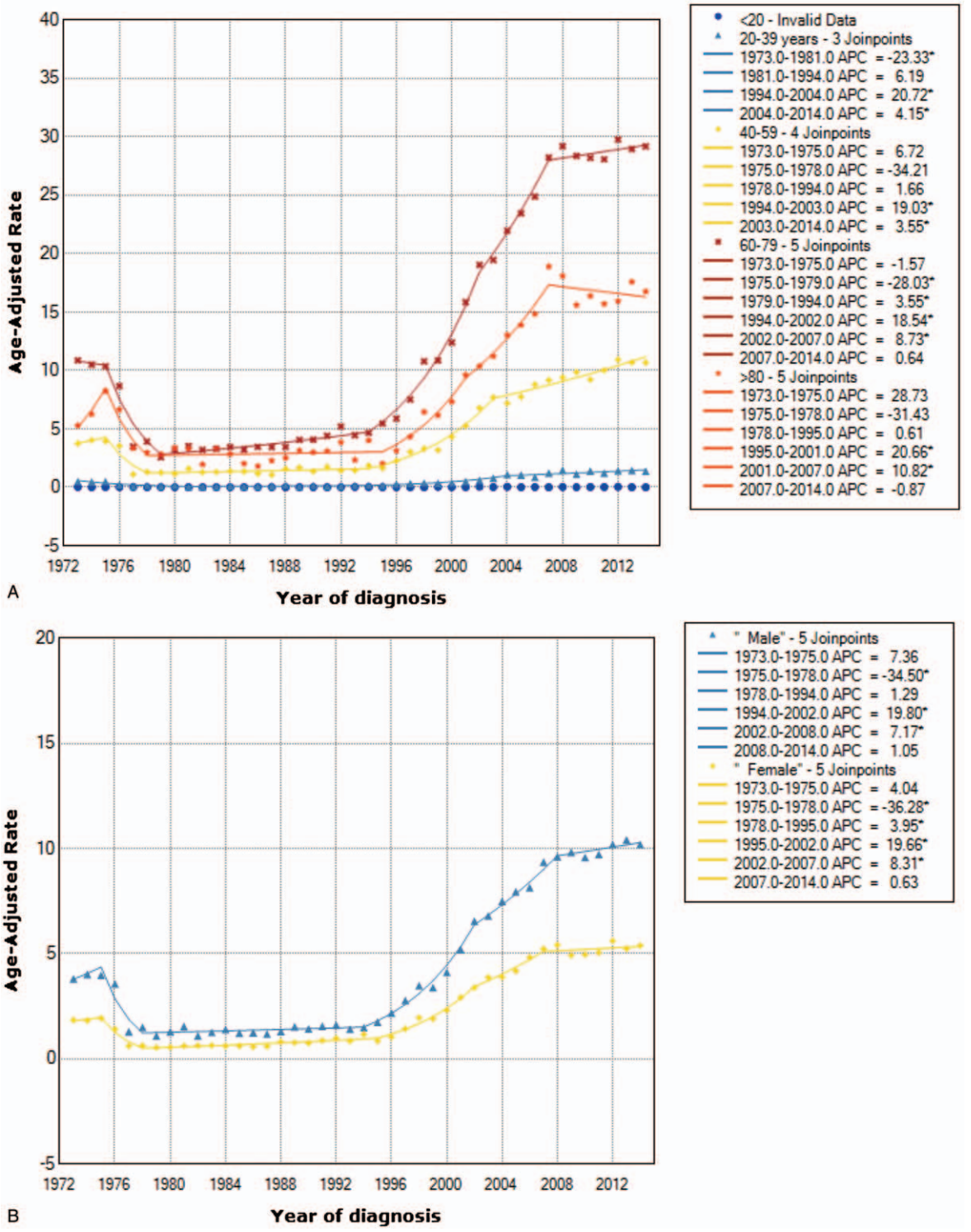

Figure 2. With Joinpoint Regression Program, the APC in incidence rates of clear cell renal cell carcinoma stratified by age (A) and sex (B) was analyzed in the database of Surveillance, Epidemiology, and End Results 9 registries from 1973 to 2014. *Indicates that the APC is significantly different from zero at the alpha = 0.05 level. APC = annual percent change.

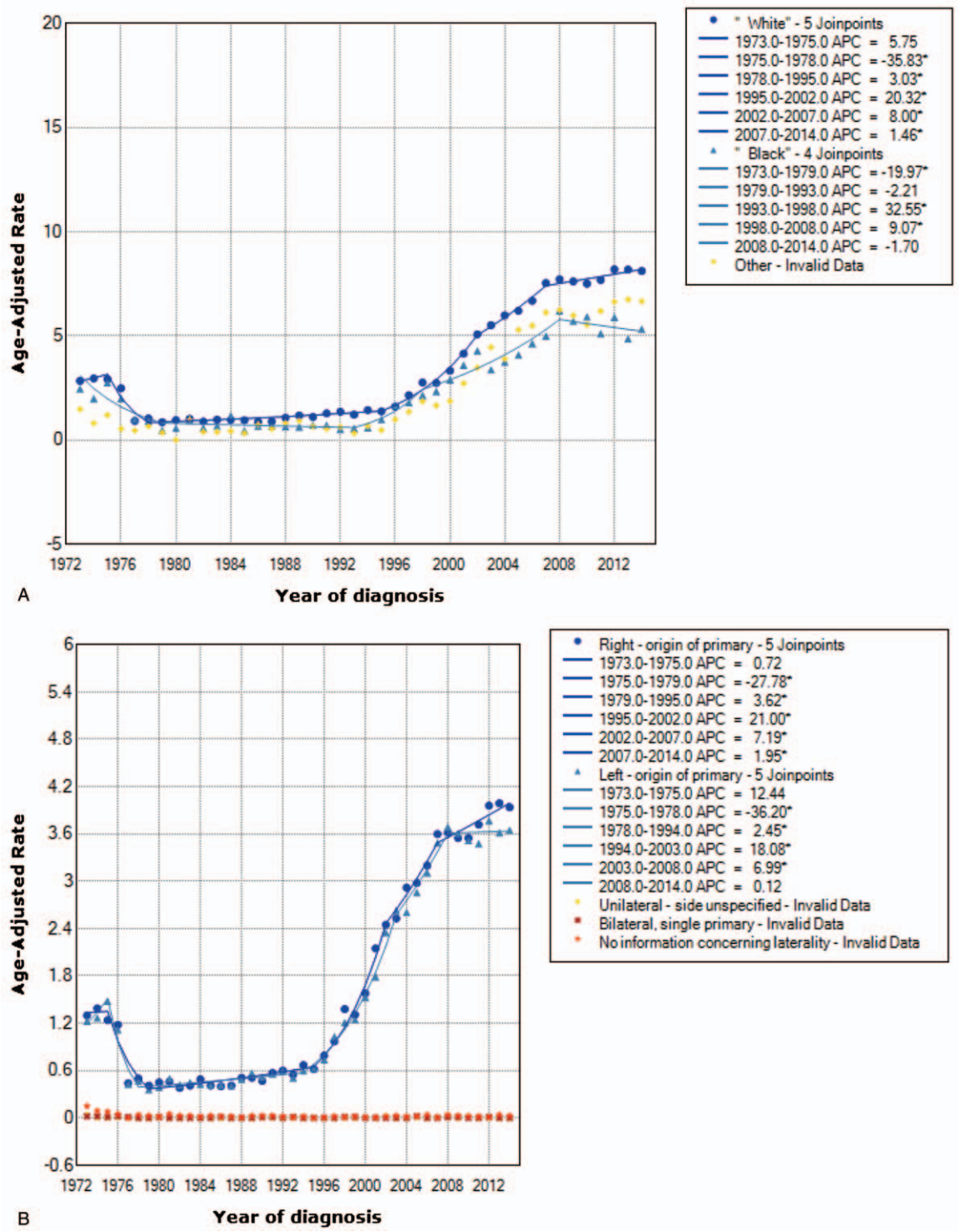

Figure 3. With Joinpoint Regression Program, the APC in incidence rates of clear cell renal cell carcinoma stratified by race (A) and laterality (B) was analyzed in the database of Surveillance, Epidemiology, and End Results 9 registries from 1973 to 2014. * Indicates that the APC is significantly different from zero at the alpha = 0.05 level. APC = annual percent change.

Additionally, we also analyzed trend in incidence rates of primary ccRCC as the only cancer with Joinpoint Regression Program. Consistently, these results also indicated that incidence rates of primary ccRCC as the only cancer generally start to surge in the middle 1990s (Supplementary Fig. 3–5, http://links.lww.com/MD/D149).

3.3. Survival outcomes of ccRCC in SEER 18 registries, 1973 to 2014

Survival outcomes of ccRCC patients by different variables were estimated with the database of SEER 18 registries from 1973 to 2014.[15] Generally, the median OS of the ccRCC population was

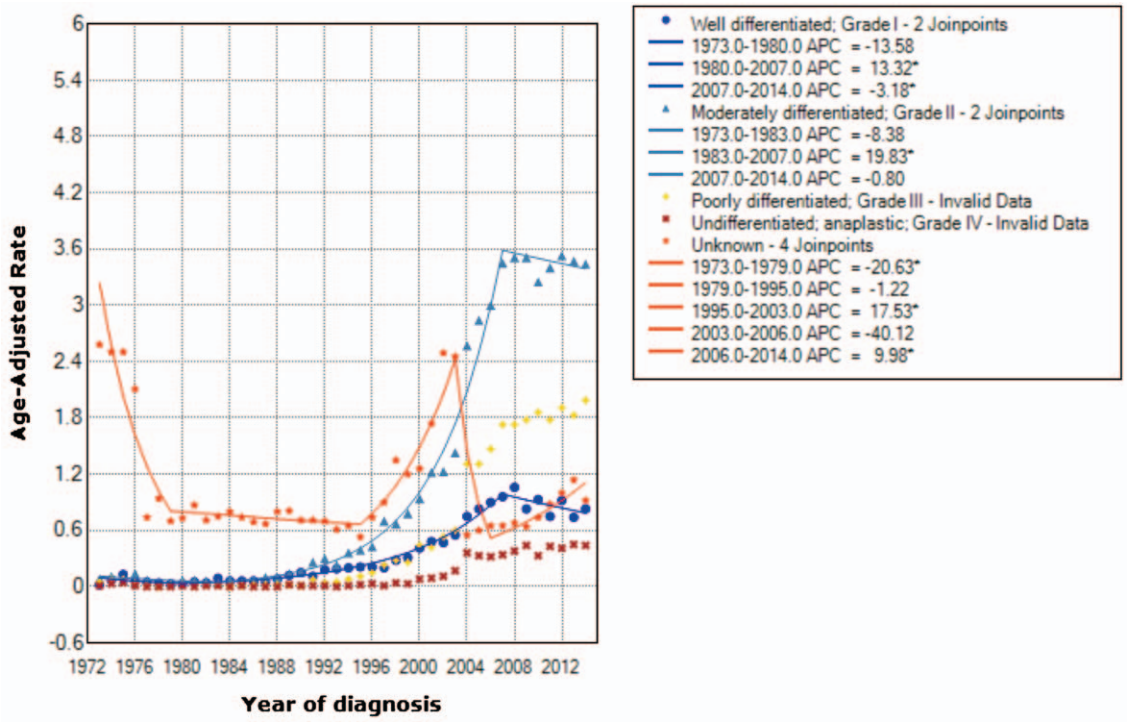

Figure 4. With Joinpoint Regression Program, the APC in incidence rates of clear cell renal cell carcinoma stratified by grade was analyzed in the database of Surveillance, Epidemiology, and End Results 9 registries from 1973 to 2014. *Indicates that the APC is significantly different from zero at the alpha = 0.05 level. APC = annual percent change.

141 months (range: 0–503 months). Regarding the influence of age at diagnosis on prognosis, we observed that OS decreased significantly with advancing age at diagnosis (median OS for age 20–39: 421 months, median OS for age 40–59: 220 months, median OS for age 60–79: 112 months, median OS for age ≥80: 58 months, $P < .001$, Fig. 5A). The survival in females was significantly superior to that in males (median OS for females: 156 months, median OS for males: 132 months, $P < .001$, Fig. 5B). The survival outcomes differed significantly by race (median OS for whites: 140 months, median OS for blacks: 134 months, median OS for others: 176 months, $P < .001$, Fig. 5C).

The survival of ccRCC patients with right side as primary origin was slightly but significantly better than that with left side as primary origin (median OS of right side: 146 months, median OS of left side: 140 months, $P < .001$, Fig. 5D). Concerning the role of tumor grade in survival outcomes, we found that OS declined significantly with increasing grade (median OS for Grade I: 189 months, median OS for Grade II: 171 months, median OS for Grade III: 118 months, median OS for Grade IV: 41 months, median OS for Grade unknown: 94 months, $P < .001$, Fig. 5E). Similarly, we found that OS decreased significantly with advancing AJCC stage by Derived AJCC Stage Group, 6th ed (2004+): 5-year survival for stage I: 86%, 5-year survival for stage II: 79%, 5-year survival for stage III: 68%, 5-year survival for stage IV: 18%, $P < .001$, Figure 5F. The survival of ccRCC patients diagnosed in 2006 to 2014 was significantly superior to that in 1973 to 2005 (5-year survival of patients diagnosed in 2006 to 2014: 75%, 5-year survival of patients diagnosed in 1973 to 2005: 68%, $P < .001$, Fig. 5G).

4. Discussion

Nowadays, a fund of knowledge in tumor genesis, diagnosis, therapeutics of ccRCC has been acquired, whereas the epidemiological and prognostic data focusing on ccRCC are insufficiently exploited and rarely provided. A recent study showed trends in incidence rates of RCC based on SEER 13 registries from 1992 to 2015.[5] However, in this study, we presented the frequency, incidence rate, and survival outcomes of ccRCC in the United States from 1973 to 2014 by utilizing SEER database and hoped to provide a panoramic and updated view on ccRCC epidemiology in the United States in a period of >4 decades.

Using the database of SEER 18 registries from 1973 to 2014, we found that the number of ccRCC with the age at diagnosis of ≥40 years accounted for 95.57% of all cases (Supplementary Fig. 1A, http://links.lww.com/MD/D149). The incidence rate of ccRCC in individuals aged ≥40 years was estimated to be 8.01 cases per 100,000 population, whereas that in individuals aged <40 years was 0.26 cases per 100,000 population (data not shown). These results collectively reflected that ccRCC mainly afflicted people aged ≥40 years. Table 1 showed that the IRR of male ccRCC to female in the database of SEER 9 registries from 1973 to 2014 was 1.94, indicating that men are more susceptible to ccRCC than women. Table 1 and Figure 1C together displayed that the incidence rate of ccRCC in whites was higher than in blacks and others, suggesting that white people are more prone to ccRCC than other races. Although Table 1 showed that the incidence rate of ccRCC with right side as primary origin was significantly higher than that with left side as primary origin, the

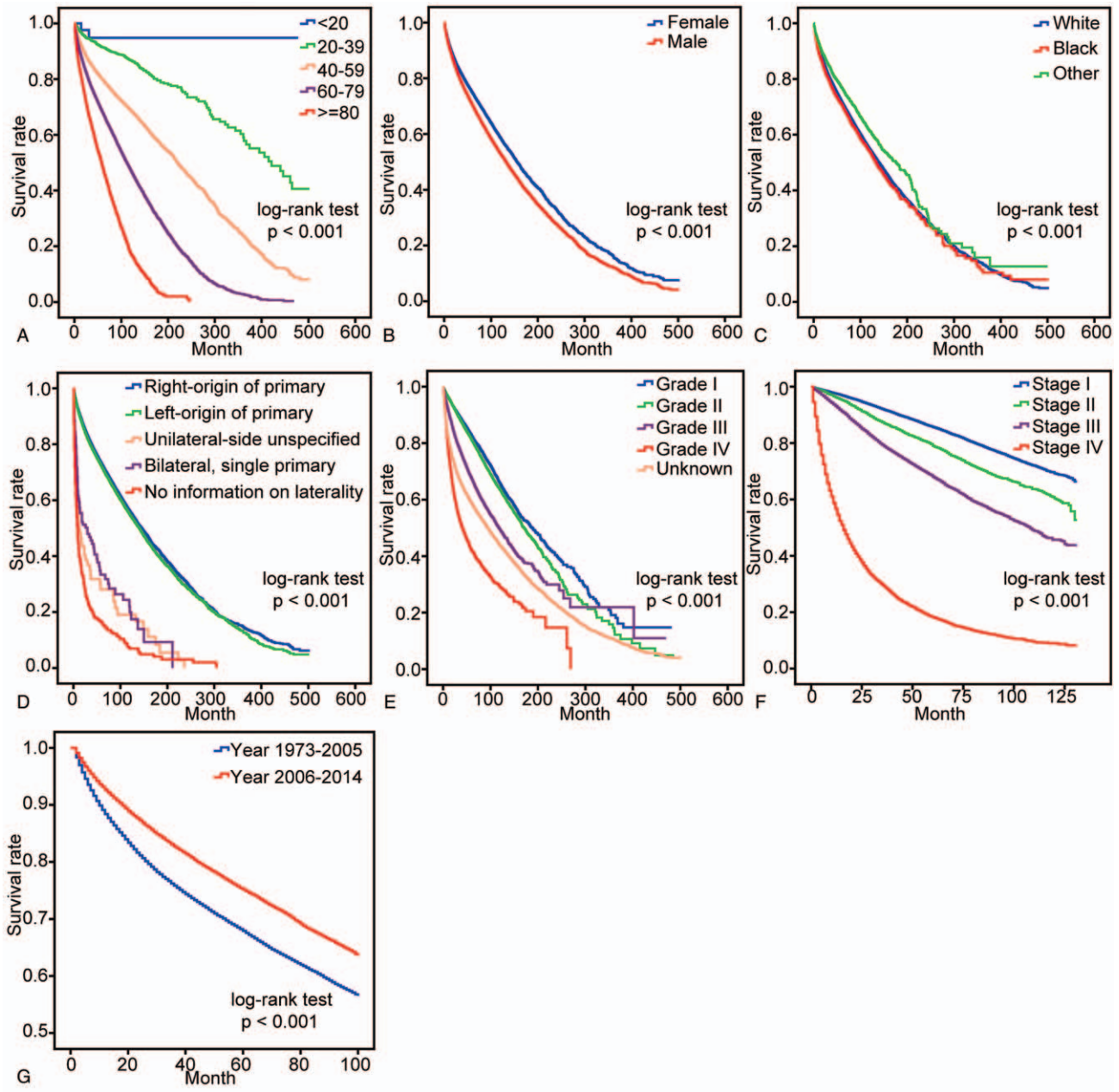

Figure 5. Kaplan–Meier survival curves showed the survival outcomes of patients with clear cell renal cell carcinoma (ccRCC) stratified by different variables. (A) Overall survival (OS) decreased significantly with advancing age at diagnosis (log-rank test, $P < .001$). (B) The survival in females was significantly superior to that in males (log-rank test, $P < .001$). (C) The survival outcomes differed significantly by race (log-rank test, $P < .001$). (D) The survival of ccRCC patients with right side as primary origin was slightly but significantly better than that with left side as primary origin (log-rank test, $P < .001$). (E) OS declined significantly with increasing grade (log rank test, $P < .001$). (F) OS declined significantly with increasing stage (log rank test, $P < .001$). (G) The survival of ccRCC patients diagnosed in 2006 to 2014 was significantly superior to that in 1973 to 2005 (log-rank test, $P < .001$).

IRR of left side to right side was approximately towards 1, which suggested that the incidence rate of ccRCC with right or left side as primary origin did not differ much in spite of statistical significance. Additionally, Figure 1D illustrated that the disparity in incidence rate of ccRCC between right and left side was slight. The incidence rate of ccRCC in Grade II was the highest (Fig. 1E), implying that people appear more predisposed to ccRCC in Grade II than other Grades.

Figures 1–4 collectively indicated that the incidence rates of ccRCC generally began to markedly rise since the middle 1990s. The variation of incidence rates of ccRCC may be influenced by numerous factors as discussed below. First, the rise in incidence rates of ccRCC since the middle 1990s may be partly attributable to increasingly widespread use of imaging methods such as ultrasonography and computed tomography.[18–25] In addition, the established risk factors for RCC incorporate cigarette smoking, obesity, acquired cystic kidney disease, and inherited susceptibility, whereas other potential risk factors for RCC requiring further study include dietary factors, hypertension, analgesics, reproductive factors and hormones, occupational

exposures, and so forth.[26,27] It may be arbitrary to attribute the variation of ccRCC incidence rates to one solitary factor because these established and potential risk factors collectively affect the changing pattern in incidence rates of ccRCC.

Although some previous studies have implicated the relationships between basic epidemiological factors and survival outcomes of RCC patients, the conclusions they have arrived at still need more validations due partly to limited sample size, regions, or periods. More importantly, we would like to emphasize that the conclusions derived from RCC populations are not necessarily applicable to ccRCC patients, although ccRCC accounts for almost 75% of all RCC cases[3] because survival characteristics among different histological subtypes of RCC vary widely.[28–33] This study aimed at illustrating survival outcomes of ccRCC patients rather than all RCC cases by utilizing data of ccRCC in SEER database.

Figure 5A showed that OS of ccRCC worsened with advancing age at diagnosis. However, one previous observation from Thompson et al[7] did not find significant differences in RCC-specific survival by age. On one hand, we used OS as endpoint event, whereas the study from Thompson et al adopted RCC-specific survival; on the other hand, the research population in Thompson et al's study were RCC patients comprising different histological subtypes. As for the prognostic role of sex in ccRCC, a more favorable prognosis was observed in women than men (Fig. 5B). Consistent with this result, a previous study based on a Japanese cohort found significantly better prognosis in female ccRCC patients than male ccRCC cases; however, no significant difference in prognosis was found between female RCC patients and male RCC cases.[8] In addition, an early SEER study using the data of RCC patients diagnosed from 1988 to 2004 found significantly better OS in women.[9] The relevant studies about sex as prognostic factor in RCC have been reviewed.[10] Regarding racial disparity in survival outcome of ccRCC patients, we found a superior prognosis in whites compared with blacks. Likewise, the median survival of white RCC patients was significantly longer than that of Black RCC patients among all groups stratified by stage and age.[11] Evidence has already revealed that tumor grade and stage are highly important prognostic determinants of RCC;[13,14] similarly, our study found that OS of ccRCC patients significantly decreased with advancing tumor grade or stage (Fig. 5E, F), indicating the prognostic role of tumor grade and stage in ccRCC.

This study bears certain limitations. Although this study analyzed the survival outcomes of ccRCC stratified by several patient demographic and tumor variables (eg, age at diagnosis, sex, race, tumor laterality, grade, and stage), all survival analyses were based on one single variable. It would provide more survival information if survival analyses were stratified by both patient demographic and tumor variables (eg, sex and tumor grade, race and tumor stage). In addition, we did not analyze the mortality rates of ccRCC in this study, whereas a previous study suggested that examining trends in mortality rates of RCC with SEER data should take into account the missing data and incidence rates.[34]

5. Conclusion

In summary, this study presents the frequency, incidence rate, and survival outcomes of ccRCC patients in the United States in a period of >4 decades, providing a long-term and updated understanding of ccRCC epidemiology in the United States.

- Incidence rates of ccRCC start to surge in the middle 1990s.
- Survival outcomes of ccRCC worsen with advancing age at diagnosis, tumor grade and stage.
- A better prognosis is shown in females than males, in whites than blacks, and in individuals diagnosed in 2006 to 2014 than 1973 to 2005.

Author contributions

Conceptualization: Xiao Feng, Wenzhi Tu, Shundong Cang.
Data curation: Xiao Feng.
Formal analysis: Xiao Feng, Wenzhi Tu, Shundong Cang.
Funding acquisition: Xiao Feng, Wenzhi Tu, Shundong Cang.
Investigation: Xiao Feng.
Methodology: Xiao Feng, Lina Zhang.
Project administration: Xiao Feng, Wenzhi Tu, Shundong Cang.
Software: Xiao Feng, Lina Zhang.
Supervision: Xiao Feng.
Validation: Xiao Feng, Lina Zhang.
Visualization: Xiao Feng.
Writing – original draft: Xiao Feng.
Writing – review & editing: Wenzhi Tu, Shundong Cang.

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