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Disparities in Trend of Renal Cell Carcinoma Mortality in the United States

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Abstract. *Background/Aim: Renal cell carcinoma (RCC) accounts for 90% of malignant neoplasms of the kidney. Patients and Methods: In this report, the CDC WONDER database was accessed to retrieve age-adjusted mortality data from 1999 to 2020 due to RCC, defined as ICD-10 Code: C64 Malignant neoplasm of kidney except renal pelvis, for various demographics to investigate trends and potential disparities. Results: In 2020, the overall age-adjusted mortality rate (AAMR) due to RCC in the USA was 42.4 per 1,000,000. The average annual percent change (AAPC) for the USA from 1999 to 2020 was –0.6%. Notably, in 2020, men had a higher AAMR than women, 63.9 compared to 25.7, and a significant difference in AAPC trend was identified between men (–0.5%) and women (–1.0%). When investigating trends according to race in 2020, the Asian population displayed the lowest AAMR at 18.9. When determining AAPC from 1999 to 2020 according to race group, the American Indian group demonstrated the greatest decline in AAPC at –1.3%, followed by the Black (–1.2%) and White populations (-0.5%). The Asian population did not exhibit a significant AAPC. Moreover, the rates between these three groups were statistically significantly different-indicating disparities in trend based on race. Conclusion: This investigation assesses the AAMR for different demographic groups of the USA population to identify disparities and guide resource allocation strategies.*

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Renal cell carcinoma (RCC) constitutes 90% of kidney cancers (1). This cancer originates from renal tubular cells and presents symptoms such as hematuria and flank pain. Risk factors for RCC include smoking, hypertension, obesity, chronic kidney disease (CKD), environmental risk factors, and male sex (2). Due to its often incidental discovery during imaging for unrelated issues, RCC is frequently diagnosed at advanced stages, confirmed through biopsy or nephrectomy (1). Treatment of RCC depends on tumor stage and grade. For a localized tumor, complete or partial nephrectomy is indicated. Treatment for metastatic or unresectable disease includes immunotherapy and targeted anti-tumor agents. Since 1999, the development of new therapies, improved imaging for diagnosis, and further scientific discoveries in systemic therapies improved our ability to treat this disease (3, 4). To assess the impact of new therapies, we investigated trends in mortality rates due to RCC between 1999 and 2020, with a focus on individual demographics to identify potential disparities.

While previous studies have investigated mortality trends in RCC on a broader scale, they often lacked consideration for specific demographic parameters, including sex and race (5, 6). To address this gap, we utilized the CDC's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database, encompassing all demographic information all national death certificates between 1999 and 2020. This is the first study assessing mortality trends using this comprehensive database (7).

Our study presents significant trends in RCC mortality rates among various demographics and identifies possible disparities in trend. Based on previous literature suggesting systemic racism, we hypothesized that minority populations may exhibit a different trend compared to the White population from 1999 to our study's endpoint in 2020.

Patients and Methods

CDC WONDER is a publicly accessible online database containing mortality information in the USA. This database uses information from all national death certificates to collect mortality and demographic information (7). On a death certificate, up to 20

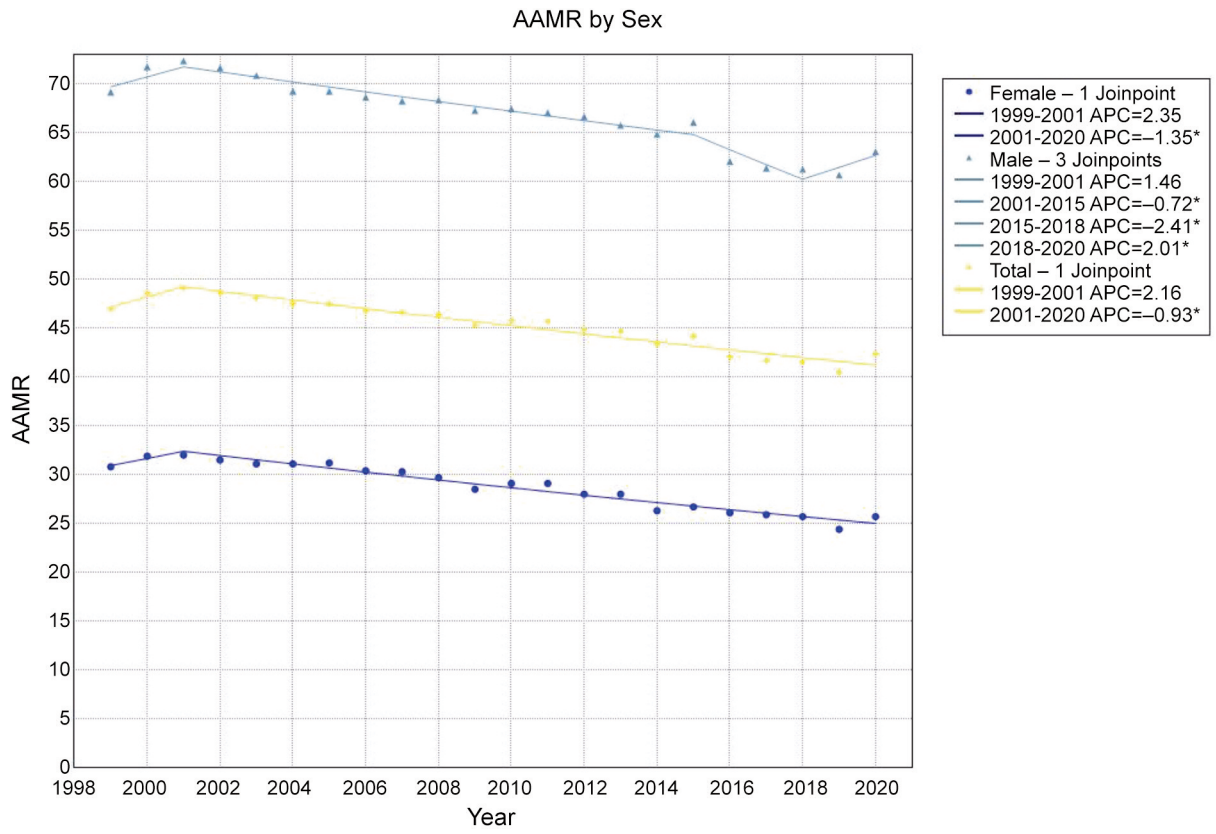

Figure 1. *Renal cell carcinoma (RCC) age-adjusted mortality rate (AAMR) from 1999 to 2020 according to sex. The graph depicts AAMR per 1,000,000 between 1999 and 2020, separated by sex, with "overall" signifying both males and females in the USA. The graph legend provides the Annual Percent Change (APC) if a significant trend is found in a group. *Significant APC.*

contributing causes of death are listed under multiple causes of death records. This record was probed to obtain mortality information due to RCC using ICD-10 Code: C64 (Malignant neoplasm of kidney except renal pelvis), from 1999 to 2020. While ICD-10 Code: C64 is not specific for RCC, RCC contributes up to 90% of malignant neoplasms of the kidney and is used to assess relevant trends in RCC. Throughout this analysis the, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed (8).

Mortality information and age-adjusted mortality rates (AAMR) for RCC as a contributing cause of death were collected for each demographic and separated according to sex, race, and age. In this study, male and female were the two categories of sex. Population race groups for this study included Native American or Alaskan Native (AI/AN), Asian or Pacific Islander (AAPI), Black or African American, and White. Since the CDC WONDER database uses public and deidentified information, local Institutional review board (IRB) approval was not pursued.

For each year from 1999 to 2020, the CDC's database provides the age-adjusted mortality rate per 1,000,000 due to RCC for each demographic group. The AAMR is calculated by dividing mortality number by total population), and then standardized to the 2000 U.S. Standard Population. Additionally, crude mortality rates were retrieved to investigate age-related data. The Joinpoint Regression Program (Joinpoint V 4.9.0.0, National Cancer Institute, Bethesda, MD, USA) was used to determine significant mortality rate trends. This was completed by calculating the annual percent change (APC) and average annual percent change (AAPC) of RCC for each group between 1999 and 2020 (9). Using log-linear regression models and the Grid Search Method (2,2,0), permutation, and parametric tests, the joinpoint program is able to determine significant trends of APC and corresponding 95% confidence intervals (CI) (10). In order to determine if there is a significant difference in trend from 1999 to 2020 between two groups by comparing regression models, a pairwise parallel comparison model was used (11). This program has been previously used to assess mortality trends for malignancies (12-14). For all tests in this study, significance is set at $p<0.05$.

Results

In the 22 years from 1999 to 2020 in the USA, there were a total of 335,045 events of mortality with RCC (ICD-10 Code: C64, Malignant neoplasm of kidney, except renal pelvis) as a contributing cause of death. In 1999, the AAMR due to RCC was 47.0 per 1,000,000 for the total USA population. This value decreased to 42.4 in 2020. In the total

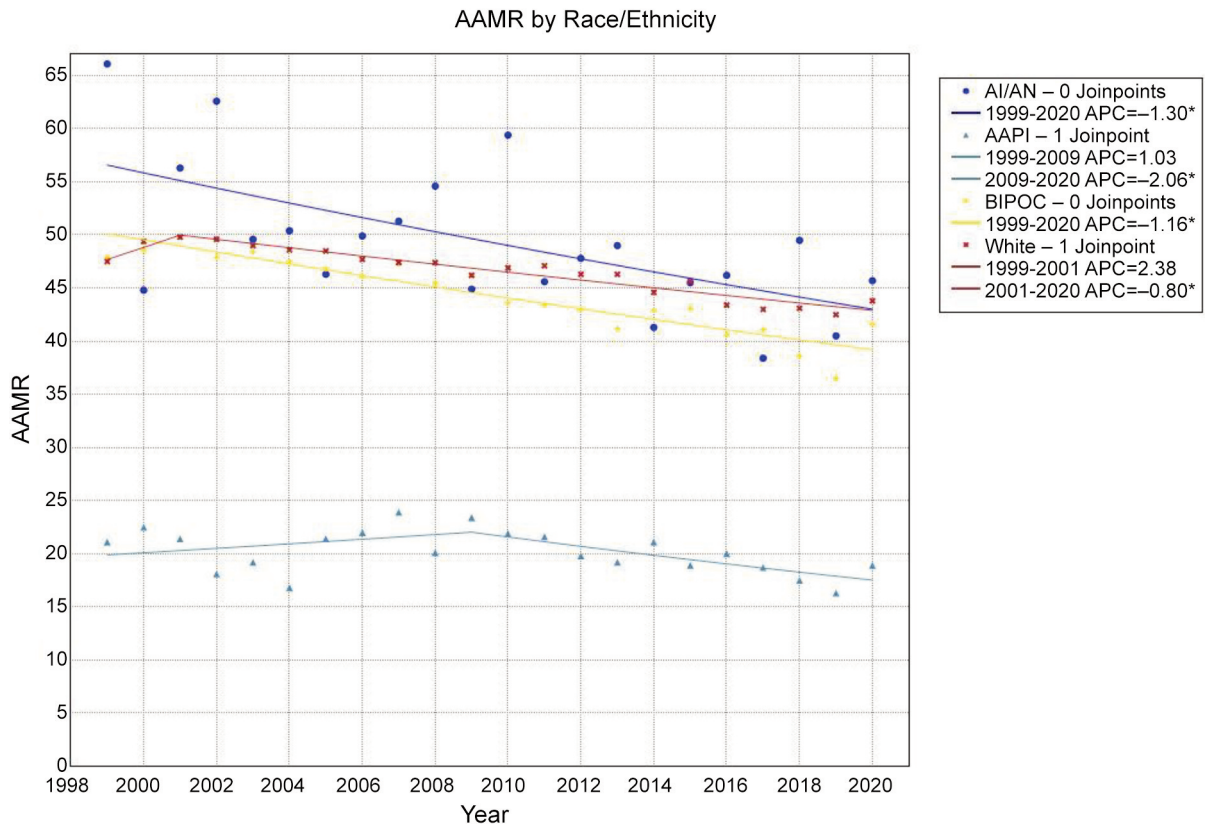

Figure 2. *Renal cell carcinoma age-adjusted mortality rate (AAMR) from 1999 to 2020 according to race. AAMR per 1,000,000 between 1999 and 2020 separated by race: American Indian or Alaskan Native (AI/AN), Asian or Pacific Islander (AAPI), Black or African American, and White. *Significant APC.*

USA population, a significant downtrend was observed from 2001 to 2020, with an annual percent change (APC) of –0.93% (95%CI=–1.1 to –0.8). The overall 1999 to 2020 AAPC for the total population was –0.6% (95%CI=–1.1 to –0.2) (Figure 1).

Sex. In 1999, the USA male population had an AAMR due to RCC of 69.2. In 2020, this number decreased to 63.9. The male population had three significant trends during this period, two downtrends and one uptrend. From 2001 to 2015, the AAMR decreased with an APC of –0.72% (95%CI=–0.8 to –0.6), and from 2015 to 2018, AAMR decreased with an APC of –2.41% (95%CI=–4.2 to –0.6). From 2018 to 2020, there was an uptrend with an APC of 2.01% (95%CI=0.1 to 3.9). The male population had an overall AAPC of –0.5% (95%CI=–0.8 to –0.2) (Figure 1).

For each year in this study, women had a lower RCC AAMR than men. In 1999, the AAMR for women was 30.8. In 2020, this value decreased to 25.7. Women had one significant trend from 2001 to 2020, there was a downtrend, APC –1.35% (95%CI=–1.5 to –1.2). Women had an overall AAPC of –1% (95%CI=–1.5 to –0.5). In addition, a parallel pairwise comparison test determined that the APC trend from 1999 to 2020 differed between men and women, wherein men had declined at a lower rate compared to women (p<0.01).

Racial group. In 1999, AAMR of RCC for the AI/AN population was the highest, at 66.1 per 1,000,00. This was followed by the Black or African American population (47.9), the White population (47.5), and then the AAPI population (21.1). In 2020, the AAMR improved across all populations. The AI/AN population had an AAMR of 45.7, White had 43.8, Black or African American had 41.6, and AAPI had 18.9. The AAPC from 1999 to 2020 improved in the AI/AN group: –1.3% (95%CI=–2.0 to –0.6), the Black or African American population: –1.2% (95%CI=–1.4 to –0.9), and the White population: –0.5% (95%CI=–0.9 to –0.1). The AAPI group did not have a statistically significant AAPC.

In the period of this study, the AI/AN population had a downtrend from 1999 to 2020, with an APC of –1.3% (95%CI=–2 to –0.6). The AAPI group had a significantly improved AAMR trend from 2009 to 2020 with an APC of –2.06 (95%CI=–3.4 to –0.7). The Black or African

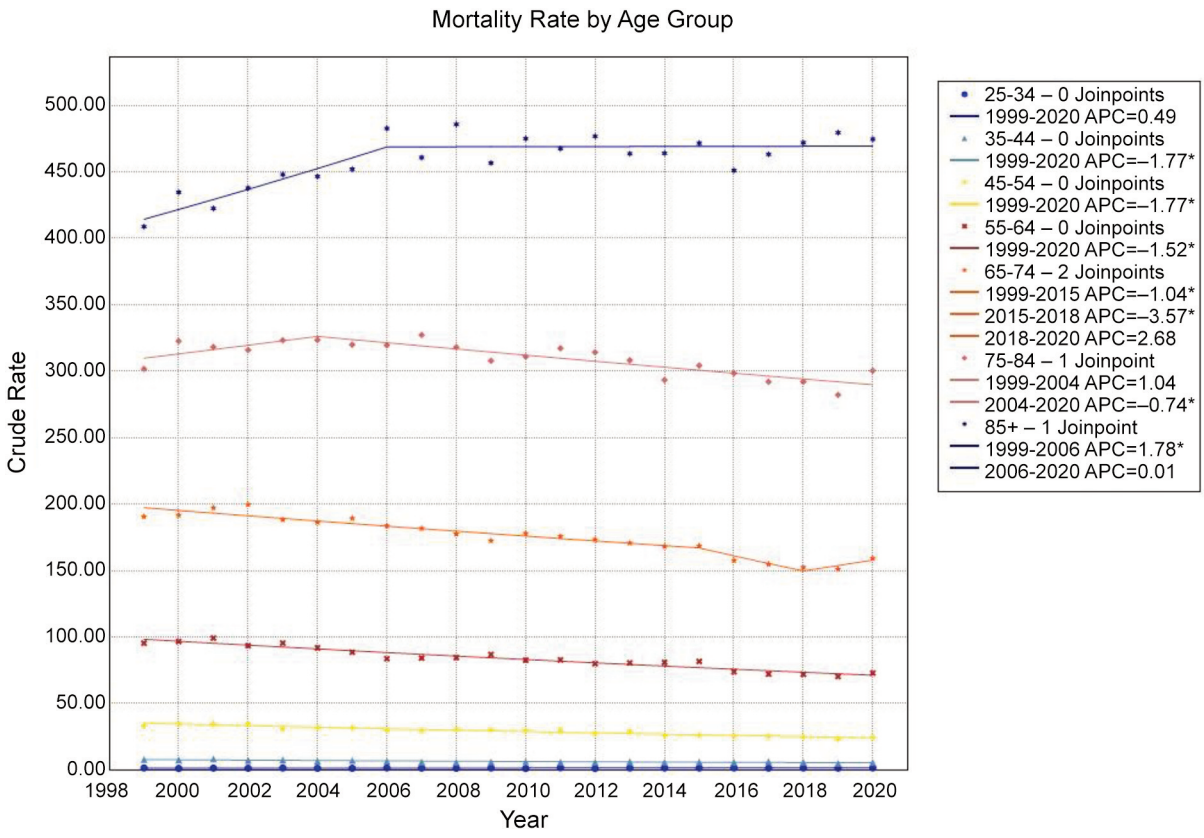

Figure 3. *Renal cell carcinoma (RCC) mortality rates from 1999 to 2020 according to age group. The graph depicts the mortality rate per 1,000,000 due to RCC for 10-year age groups. *Significant APC. A) Age-adjusted mortality rate (AAMR) due to Renal Cancer by State in 1999.B). AAMR due to Renal Cancer by State in 2020.*

American population had a significantly improved AAMR trend from 1999 to 2020 with APC of –1.16% (95%CI=–1.4 to –0.9). The White population had a trend from 2001 to 2020 with an APC of –0.80% (95%CI=–0.9 to –0.7). All groups had significant improvement in AAMR within the period of this study. Additionally, parallel pairwise comparison analysis determined that the rate of decline significantly differed between the AAPI and Black or African American populations, AAPI and White populations, and between the Black or African American and White populations (p<0.01 for all comparisons) (Figure 2).

Ten-year age groups. When investigating AAMR by 10-year age groups, we found AAMR increases with increased age group, with the 85+ population having the highest AAMR. When investigating temporal trends, the 85+ group had a significant trend from 1999 to 2006 with an APC of 1.78% (95%CI=0.8 to 2.7), 75 to 84 group had an APC of –0.74% (95%CI=–1.0 to –0.5) from 2004 to 2020, 65 to 74 had an APC of –1.04 (95%CI=–1.3 to –0.8) from 1999 to 2015, 55 to 64 had an APC of –1.52% (95%CI=–1.7 to –1.3) from 1999 to 2020, 45 to 54 group had an APC of –1.77% (95%CI=–2 to –1.5) from 1999 to 2020, and the 35 to 44 groups had an APC of –1.77% (95%CI=–2.2 to –1.3) from 1999 to 2020 (Figure 3).

State. In 1999, Utah had the lowest AAMR due to renal cancer with 2.8, followed by Hawaii with 3.2. In the same year, North Dakota had the highest rate with 7.3, followed by Alaska with 6.9. In 2020, Vermont had the lowest rate with 3.0, followed by Connecticut with 3.1. Oklahoma had the highest rate in 2020 with 6.6, followed by Arkansas with 5.5. When assessing the mortality rate by state from 1999 to 2020, no clear trend was found, with some states experiencing an increase in mortality while others decreased (Figure 4A and B).

Discussion

Here, we provide, to our knowledge, the first report on AAMRs and disparities for various demographics due to

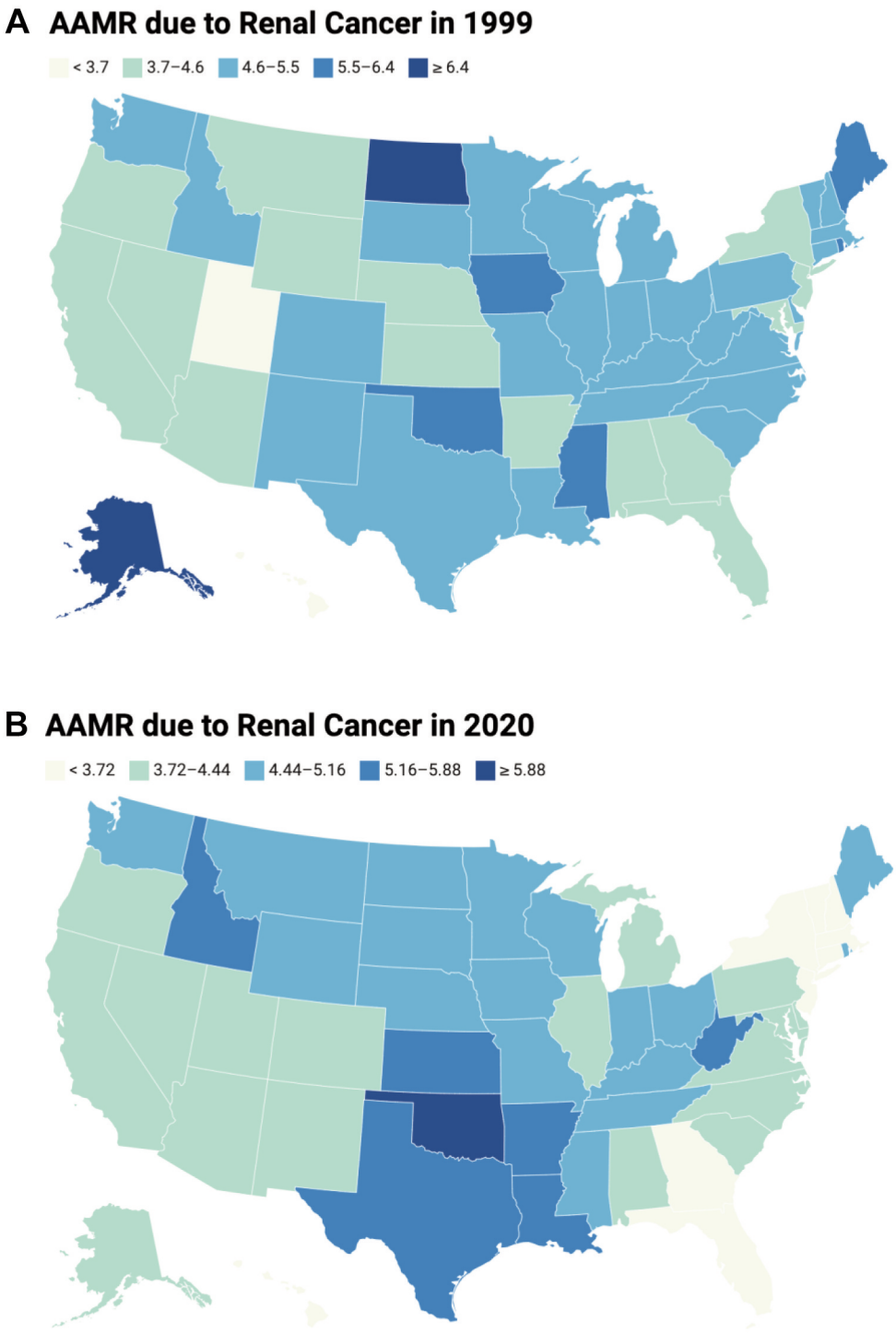

Figure 4. *Renal cell carcinoma age-adjusted mortality rate per state within the United States in A) 1999 and B) in 2020.*

RCC, specified as ICD-10 Code: C64 (Malignant neoplasm of kidney, except renal pelvis). This retrospective analysis reviewed all documented USA mortality events from 1999 to 2020 and selected deaths with RCC listed as a multiple cause of death on the death certificate. Information provided from the database allowed for AAMR trends to be determined per demographic group and for comparison of trends between groups for significant differences.

From 1999 to 2020, the AAMR due to RCC decreased for the overall USA population. Similar trends have been found in other USA population studies (5, 15). Concordant with current knowledge, we also found that as age increases, the mortality rate of RCC increases (16). A separate international study found that mortality rates have decreased and stabilized in developed countries, but not in developing countries (6). These findings suggest that the trend of declining and stabilizing RCC mortality rates may be due to the increased development of therapies in developed countries.

The mortality rates for men and women differed. In 2020, men had an AAMR due to RCC over twice that of women (Figure 1). Despite the difference in rates, both sexes had similar declining trends from 2001 onward. These results are concordant with previous literature that found decreasing mortality rates for both men and women from 2001 to 2015 in the USA (5). In addition, men having increased RCC mortality rates compared to women has been previously documented in Israel, but this study found no significant trend for either sex from 1980 to 2004 (17). While results are not definitive, recent findings suggest that molecular differences in RCC according to sex may impact pathogenesis (18). In addition, supportive data have found that women may have increased tumor-protective mechanisms, specifically increased expression of tumor suppressor genes (19). Furthermore, it has been suggested that women have a more active immune response, which may allow for this sex to mount a more robust response to biologics and cancer immunotherapies (20).

Differences in both average rates and trends were found when assessing mortality rates according to race group. The AAPI population had a much lower AAMR than other groups due to RCC. The AI/AN group had the highest AAMR followed by the White and Black or African American populations. All race groups observed an overall decreasing trend from 1999 to 2020; however, rates of change differed by group. Furthermore, a test for parallelism showed that the declining trend differed between the White population and the AAPI and Black or African American populations (data not shown). These results differ from those of other studies. In addition, a retrospective study found that Black or African American patients have lower survival and present with RCC at a younger age (21). When assessing the risk of RCC due to CKD according to race, disparities were found where CKD was associated with increased risk of RCC among Black or African American and AAPI groups, but not among the White population in the USA (22). Due to conflicting findings, additional research is required to understand race disparities in RCC outcomes.

Since 1999, several new therapies and treatment options have been introduced, contributing to the decreasing mortality rate of RCC. The diagnosis of RCC is often discovered through imaging performed for other reasons, mainly through computed tomography (CT), magnetic resonance imagining (MRI), and abdominal ultrasonography (USG). These modalities provide tumor information, including location, staging, tumor grade, and impact management. Developments in cross-sectional imaging have allowed for improvements in determining tumor staging and response to treatments (23, 24). Furthermore, in the near future, radiogenomics may allow for non-invasive investigation of both tumor microenvironment and histology (23). In addition to improved diagnostic and monitoring abilities, since 1999, the FDA has approved new immunotherapies for RCC. In 2009, the FDA approved pazopanib (a tyrosine kinase inhibitor) for metastatic RCC (25). Also, in 2009, the mTOR inhibitor everolimus was approved for mRCC (26). In 2016, the drug cabozantinib was approved for RCC (27). The first immunotherapy, PD-1 inhibitor nivolumab, was FDA approved in 2018 after a Phase III clinical trial determined this therapy had superior overall survival compared to everolimus in 2L advanced RCC (28). In 2019, another PD-1 inhibitor, pembrolizumab, was also approved for advanced RCC (29). From 1999 to 2020, the use of new immunotherapies and targeted systemic treatments along with improved imaging capabilities and identification of disease at earlier stage may have contributed to the declining RCC mortality rates in USA.

Study limitations. A limitation of this study includes possible underreporting in the CDC database, as the multiple causes of death record require a diagnosis to be included. This disproportionately impacts individuals, and underreports groups who are not able to access medical care for diagnosis. A second limitation is that the database was deficient in information regarding tumor status at time of mortality. Additionally, there may have been misclassifications of diseases when entering ICD-10 code information into the database or potential omission of this data on death certificates.

Conclusion

From 1999 to 2020, we found that the USA mortality rate due to RCC (assessed *via* ICD-10 Code: C64) decreased. It was determined that men had a higher AAMR than females, and that the AAPI population had a lower AAMR compared to other populations. Furthermore, when analyzing trends of changing AAMRs, disparities in rates of improvement were found both by sex and race group. This study also briefly reviews potential factors contributing to these disparities, findings in other regions, and developments in therapies for RCC since 1999. Overall, this study assessed the USA population for disparities in RCC and found significant differences in mortality rates by both sex and race group. These results show that therapies between 1999 and 2020

are impacting women and the Black or African American populations less effectively compared to male and White populations in the USA, and guide resource allocation strategies.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Sishir Doddi: Conceptualization, Methodology, Software, Data curation, Writing- Original draft preparation, Visualization, and Investigation. M. Hammad Rashid: Writing, Reviewing and Editing, Supervision.

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