



## Trends in Acute Kidney Injury Related Deaths in the US from 1999 to 2020

## Abstract

**Background:** Acute kidney injury requiring dialysis is linked to long-term care demands, higher hospital mortality, and increased healthcare expenses. We aim to assess nationwide trends and regional variations in acute kidney injury-related mortality in the US. **Materials and Methods:** We used death certificates from the CDC WONDER database (1999-2020) to calculate age-adjusted mortality rates (AAMRs) and annual percent change (APC). The data were stratified by year, gender, race/ethnicity, and geographic region. **Results:** From 1999 to 2020, there were a total of 4,599,652 deaths attributed to acute kidney injury. The AAMR for acute kidney injury-related deaths surged from 11.4 in 1999 to 20.1 in 2020. Men consistently exhibited higher AAMRs than women throughout the study period (overall AAMR in men: 20.1; women: 13.2). When examining average AAMRs by race/ethnicity, Black/African Americans recorded the highest rates at 21.9, followed by American Indian or Alaskan Native (16.4), Whites (15.6), Hispanics (14.5), and Asian/Pacific Islander (10.7). Significant regional disparities were observed, with the southern region reporting the highest AAMR (17.2) and non-metropolitan areas having higher AAMRs than metropolitan areas (18.3 vs. 15.6). States in the top 90<sup>th</sup> percentile for acute kidney injury deaths included Indiana, Kentucky and South Carolina, which had nearly double the AAMR compared to states like New York, Utah, and Vermont. **Conclusion:** In the last two decades, the United States has experienced a troubling increase in acute kidney injury-related deaths, emphasizing the urgent need for targeted and equitable healthcare interventions to address persistent disparities in gender, race, geography, and urbanization.

**Keywords:** CDC WONDER, AKI, Mortality, Renal failure

## Introduction

Acute kidney injury (AKI), a complication frequently observed in hospitalized individuals, is characterized by abrupt deterioration in renal function. This condition is notably associated with an elevated risk of mortality.<sup>1</sup> Studies shows that 25-30% of patients in the ICU develop AKI, which is associated with higher mortality, longer hospital stays, and substantial health resource utilization.<sup>2</sup>

In the United States, the incidence of AKI has been increasing, with an annual rise of 14% since 2001. Approximately 5-20% of all hospitalized patients are diagnosed with AKI.<sup>3</sup> The hospitalization costs associated with AKI range from \$5.4 - \$24 billion, though the costs are estimated to be much higher, highlighting the substantial economic impact of this health condition. A study in 2022 revealed that one in four patients diagnosed with AKI died within

1 year of hospitalization.<sup>4</sup> The incidence is expected to continue rising with the aging population, increasing comorbidities, and the expansion of intensive care unit capabilities.<sup>5</sup> Studies have shown a correlation between AKI mortality and certain factors, such as diabetes, admission to the intensive care unit (ICU), and treatment with renal replacement therapy (RRT).<sup>6,7</sup> There have been limited studies focusing on the occurrence of this disease across different demographics, encompassing various races and genders, throughout United States.

This study focuses on investigating the national pattern of mortality linked with AKI, with targeted emphasis on variables such as race, gender, and regional distribution. The objective is to provide a comprehensive understanding of how AKI-related deaths vary across different demographics and geographic areas within the nation. The

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goal is to enable timely intervention and reduce AKI-related mortality by targeting and addressing specific risk factors present within a group. In this way, health equity can be obtained by understanding demographic disparities and tailoring different policies accordingly to address populations who are at a higher risk for the disease. We sought to evaluate mortality trends associated with AKI from 1999-2019.

## Materials and Methods

For this descriptive study, we collected mortality data from death certificates using the Centres for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. The data were analyzed for AKI-related mortality spanning from 1999 to 2019. We utilized codes from the International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) specifically: N17.0, N17.1, N17.2, N17.8, and N17.9. Identical ICD codes have been previously used in administrative databases to identify cases of AKI.<sup>8</sup> The dataset comprises cause-of-death information sourced from death certificates across the 50 states and the District of Columbia. To conclude trends in the mortality of AKI, this database has widely been in use. For the analysis, the Multiple Cause-of-Death Public Use record death certificates were used to select AKI-related deaths, which were classified as those where AKI was reported anywhere on the death certification either as a contributing or underlying cause of death. As the study uses deidentified government-issued public dataset and adheres to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, institutional review board approval was not required.

### Data extraction

Various aspects of data were collected, including population size, year, location of death, demographics, urban-rural classification, states, and regions. The demographics studied encompassed sex, race, and urbanization to region. For race/ethnicity, categories included non-Hispanic (NH) white, NH black or African American, Hispanic or Latino, NH American Indian or Alaskan Native, and NH Asian or Pacific Islander. The National Centre for Health Statistics Urban-Rural Classification Scheme was utilized to aid in the population evaluation. It categorized areas as follows: urban (large metropolitan area [population  $\geq$  1 million], medium/small metropolitan area [population 50,000-999,999]), and rural (population  $<$  50,000) according to the 2013 U.S. census classification.<sup>9</sup> Regions were divided into Northeast, Midwest, South, and West based on US Census Bureau definitions.<sup>10</sup>

### Statistical analysis

For trend analysis, we calculated both crude and age-adjusted mortality rates (AAMR) per 100,000 population from 1999 to 2020, focusing on year, sex, race/ethnicity,

state, and urban-rural status with 95% CIs. The crude mortality rate was calculated by dividing the number of AKI-related deaths by the designated U.S. population of that year. The AAMR was standardized using the U.S population from the year 2000.<sup>10</sup> To analyze annual trends in AKI on a national scale, we utilized the Join Point Regression Program (Joinpoint V 4.9.0.0, National Cancer Institute). With the help of this tool, Annual Percent Change (APC) with 95 % CI in AAMR was calculated.<sup>11</sup> Significant changes in APC were identified using log-linear regression models to detect temporal variations. APC values were assessed as either increasing or decreasing based on whether or not the change was significantly different from zero, as determined by the 2-tailed t-test. A statistically significant value was taken as  $P < 0.05$ .

## Results

A total of 4,599,652 deaths occurred in individuals of all ages due to AKI from 1999 to 2020. Of these deaths, 1,180,886 were due to AKI with an AAMR of 16.1 (95% CI: 16.0-16.1). Information on the location of death was known for 1,177,785 cases. Of these, 77.9% occurred in medical facilities, 5.9% at home, and 11.3% in nursing homes [Table 1].

**Table 1: Location of death of patients due to acute kidney injury between the years of 1999-2020**

Place of death	Deaths	% of total deaths
Medical facility - inpatient	894766	75.80%
Medical facility - outpatient or ER	22785	1.90%
Medical facility - dead on arrival	803	0.10%
Medical facility - status unknown	888	0.10%
Decedent's home	69142	5.90%
Hospice facility	37246	3.20%
Nursing home/long-term care	133687	11.30%
Other	18468	1.60%
Place of death unknown	3101	0.30%

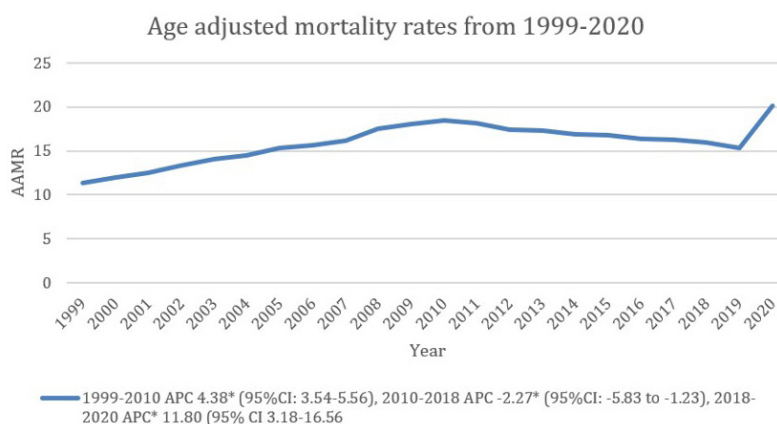
ER: Emergency room

### AKI related AAMR

The AAMR for AKI-associated deaths was 11.4 in 1999 and 20.1 in 2020 [Figure 1]. The overall AAMR increased from 1999 to 2010, with an APC of 4.38 (95%CI: 3.54-5.56). There was a decline in AAMR from 2010 to 2018 (APC -2.27; 95%CI: -5.83 to -1.23) followed by an increase in AAMR from 2018 to 2020 (APC 11.80; 95% CI 3.18-16.56) [Supplementary Table 1, Figure 1].

### AKI-related AAMR stratified by sex

Men had consistently higher AAMR than women throughout the study period (overall AAMR in men: 20.1; women: 13.2). The AAMR for men in 1999 was 15.3 (95% CI: 15.1-15.5) which increased to 22.9 (95% CI: 22.6-23.2) in 2010, with an APC of 3.69. This was followed by a decline to 19.7 (95% 19.4-19.9) in 2018, with an APC of -



**Figure 1:** Age-adjusted mortality rates due to acute kidney injury in between 1999-2020. \*Indicates that the annual percentage change (APC) is significantly different from zero at the alpha=0.05 level. CI: Confidence interval, AAMR: Age-adjusted mortality rates.

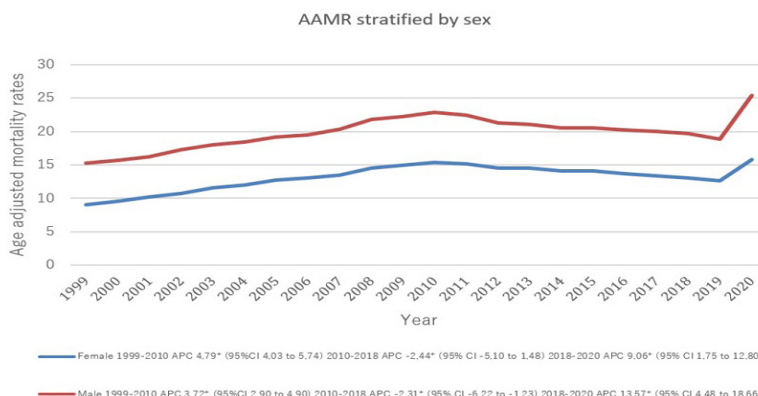
2.30. In 2020, AAMR increased to 25.4 (95% CI: 25.1-25.6), with an APC of 13.40 [Figure 2].

Similar trends of increasing AAMR were noticed in females, with rates rising from 9.0 (95% CI:8.9-9.2) in 1999 to 15.4 (95% CI: 15.2-15.6) in 2010, with an APC of 4.79. This was followed by a decline to 13.1 (95% CI:12.9=13.3) in 2018, with an APC of -2.40 and then an increase in AAMR to

15.8 (95% CI: 15.7-16.0), with an APC of 8.99 [Figure 2] [Supplementary Table 2, Figure 2].

**AKI-related AAMR stratified by race/ethnicity**

When data collected from 1999 to 2020 were stratified based on race, a significant difference was noticed in the mortality rates among different ethnicities [Figure 3]. The highest mortality rates were noticed in Black/African



**Figure 2:** Age-adjusted mortality rates in males and females due to acute kidney injury in between 1999-2020. \*Indicates that the annual percentage change (APC) is significantly different from zero at the alpha=0.05 level. CI: Confidence interval, AAMR: Age-adjusted mortality rates.

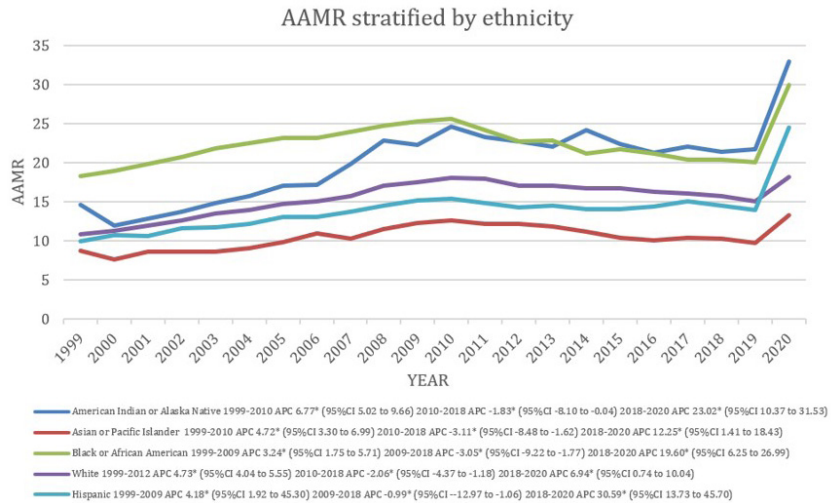
Americans and American Indian/Alaska Natives, with average age-adjusted mortality rates of 21.9 (95% CI: 21.8-22.1) and 16.4 (95% CI: 16.1-16.8), respectively. The average AAMR for Whites was 15.6 (95% CI: 15.6-15.6) and for Hispanics, it was 14.5 (95% CI: 14.4-14.6). Asian/Pacific Islanders had the lowest average age-adjusted rates, at 10.7 (95% CI: 10.5-10.8).

Changes in mortality rates were not consistent. Among American Indians, Whites, and Asians, an increase in mortality was observed from 1999 to 2010, with average percentage changes of 6.7, 4.73, and 4.72, respectively.

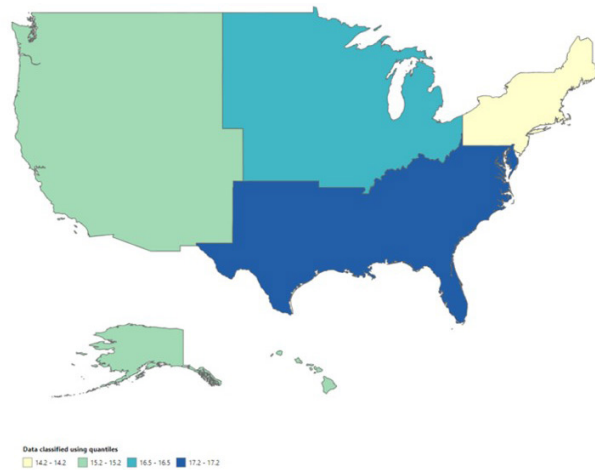
In Blacks and Hispanics, an increasing trend in AAMR was observed until 2009, with APC of 3.24 and 4.18, respectively. After 2009 and 2010, a drop in mortality rates was noticed in all the races until 2018, followed by an abrupt rise in 2019 and 2020.

**AKI-related AAMR stratified by geographic regions**

A significant difference in AAMR was observed among different states, with AAMR ranging from 10.6 (95% CI: 10.5-10.6) in Florida to 21.8 (95% CI: 21.7-21.9) in Texas. States in the top 90th percentile, such as Indiana, Kentucky, and South Carolina, had nearly double the AAMR compared



**Figure 3:** AAMR due to acute kidney injury among American Indian or Alaska Native, Asian or Pacific Islanders, Black or African American, White and Hispanics in years 1999-2020. \*Indicates that the annual percentage change (APC) is significantly different from zero at the alpha=0.05 level. CI: Confidence interval, AAMR: Age adjusted mortality rates.



**Figure 4:** Demographic distribution of age adjusted mortality rates due to acute kidney injury in United States of America.

to states like New York, Utah, and Vermont. On average, the highest mortality rates over the course of the study were observed in Southern states, with an AAMR of 17.2 (95% CI 17.1-17.2), followed by Midwestern States (AAMR 16.5; 95% CI 16.5-16.6), Western States (AAMR 15.2; 95% CI 15.2-15.3), and Northeastern States (AAMR 14.2; 95% CI 14.2-14.3) [Figure 4] [Supplementary Figure 3].

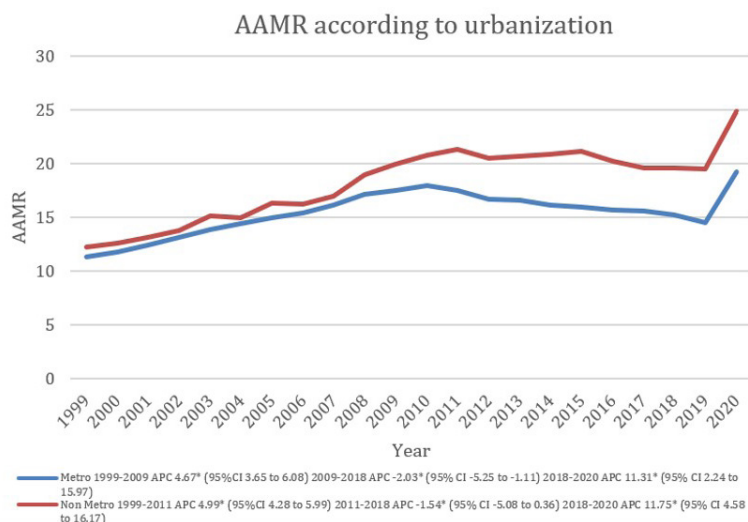
Metropolitan areas had an average mortality rate of 15.6 (95% CI: 15.5-15.6), which was lower compared to non-metropolitan areas (AAMR of 18.3; 95% CI:18.3-18.4). In Metropolitan areas, mortality rates increased between 1999 and 2009, with an APC of 4.67 (95%CI: 3.65-6.08), followed by a decline between 2009 and 2018 (APC: -2.03; 95% CI: -5.25 to -1.11) and increase between 2018 and 2020 (APC: 11.31; 95% CI: 2.24 to 15.97). In non-metropolitan areas, similar trends were observed, i.e., an

increase in mortality rates between 1999 and 2011 (APC: 4.99; 95%CI: 4.28 to 5.99), a decrease between 2011 and 2018 (APC: -1.54; 95% CI: -5.08 to 0.36), and another increase between 2018 and 2020 (APC: 11.75; 95% CI: 4.58 to 16.17) [Figure 5] [Supplementary Figure 4].

**AKI-related to age**

Upon analysis, a significant increase in incidence was observed in the age group of 85+ years compared to the rest, with a peak incidence in 2010 followed by a drop in 2018. The APC for this age group was 5.16 (95% CI: 6.26-4.15) from 1999 to 2010, -4.30 (95% CI: 4.95- -7.10) from 2010 to 2018, and 3.27 (95% CI: 6.77- -3.48) from 2018 to 2020.

The age group of 75-84 had a moderate incidence in comparison. The APC for this age group was 4.10 (95% CI:



**Figure 5:** AAMR due to acute kidney injury in metropolitan and non-metropolitan areas in USA in between 1999-2020. \*Indicates that the annual percentage change (APC) is significantly different from zero at the  $\alpha=0.05$  level. CI: Confidence interval, AAMR: Age adjusted mortality rates.

5.13-3.28) from 1999 to 2010, -3.14 (95% CI: 2.09- -6.45) from 2010 to 2018, and 9.54 (95% CI:-1.40-13.69) from 2018 to 2020. Peak incidence occurred in 2010, followed by a drop in 2018.

The rest of the age groups had a relatively low incidence.

For the age group 65-74 years, the APC was 3.36 (95% CI:5.72-2.25) from 1999 to 2010, -0.88 (95% CI: 0.49- -7.68) from 2010 to 2018, and 16.39 (95% CI:-23.17- 6.41) from 2018 to 2020. For the age group 55-64 years, the APC was 4.95 (95% CI:8.62-3.72) from 1999 to 2010, 1.07 (95% CI:2.74- -5.14) from 2010 to 2018, 15.30 (95% CI:22.41-3.93) from 2018 to 2020. For the age group 45-54 years, the APC was 5.72 (95% CI:8.52-4.28) from 1999 to 2009, 1.22 (95% CI: 2.35- -3.97) from 2009 to 2018, and 16.11(95% CI: 22.75-4.11) from 2018 to 2020. For the age group 35-44 years, the APC was 3.02 (95% CI:3.71- 2.26) from 1999 to 2018, 23.07 (95% CI:28.72-13.50) from 2018 to 2020. Finally, for the age group under 1 year, the APC from 1999 to 2020 was -1.52 (95% CI: -0.60- -2.55) [Supplementary Figure 5].

## Discussion

AKI is a prominent cause of death in the United States. In our research, we adopted a comprehensive approach by considering multiple causes of death. This decision was made because relying solely on a single cause could overlook important factors contributing to mortality. While the CDC database we used focuses on primary causes, the literature suggests that AKI is often associated with multiple comorbidities, such as congestive heart failure and other conditions.<sup>12,13</sup>

In a comprehensive two-decade analysis spanning from 1999 to 2020, examining mortality data collected by the

CDC, we report several significant findings. Firstly, there was an initial period of rising age-adjusted mortality rates associated with AKI from 1999 to 2010, followed by a gradual decline until 2018, and then a rapid increase from 2018 to 2020. This pattern was consistent among both genders. The Affordable Care Act (ACA), enacted in 2010, expanded health insurance coverage for many Americans. This led to better financial protection for hospital bills and likely improved early detection and prevention of AKI, contributing to a decline in AKI deaths.<sup>14</sup> However, the trend began to reverse in 2019, possibly due to a rise in hospital admissions and complications caused by COVID-19. The pandemic also resulted in job losses and a decrease in employer-sponsored health insurance, which may have further impacted the management of kidney disease.<sup>15</sup>

Secondly, African Americans exhibited the highest AAMR compared to other racial groups until 2009. Afterward, there was a gradual decrease in their mortality rates from 2013 to 2020.

Thirdly, there were significant regional variations, with Southern states having nearly 50% higher AAMR compared to states in the Northeast. Nonmetropolitan areas consistently showed higher mortality rates than metropolitan areas. These findings carry significant implications for the development of public health policies.

The overall increase in mortality trends could be attributed to multiple factors. Firstly, the increase in hospitalizations for diseases associated with lower eGFR has made patients more vulnerable to AKI.<sup>16</sup> For example, a study found that nearly two-thirds (64%) of patients admitted with acute decompensated heart failure (ADHF) in the US had an eGFR <60 ml/min per 1.73 m<sup>2</sup> at the time of hospitalization, and

one-third of these patients experienced worsening renal function during their stay.<sup>17</sup> This issue is compounded by increased hospitalizations for ADHF over the past few decades.<sup>18</sup> Additionally, diabetic patients with proteinuria and obese patients with high oxidative stress, as indicated by the NIS data, have also contributed to the rise in AKI cases.<sup>16,19</sup> Secondly, the older age group is experiencing AKI at a rapid rate. This group is experiencing critical illness in its most severe form. It is predicted that their population will double by 2030, increasing from 35 million to 71 million. Additionally, age-related structural changes lead to a loss of kidney function, which adds up to an increase in the overall numbers for AKI.<sup>20,11</sup>

Our data analysis indicated that males exhibited a higher mortality rate compared to females in cases of AKI. This gender-based difference in kidney injury may be attributed to the protective effects of sex hormones in females, including estrogen and silent information regulatory 2 homolog 1 (SIRT1). Estrogen plays an important role in maintaining mitochondrial hemostasis, modulating endothelin-1, and allowing kidney repair and regeneration. Furthermore, SIRT1, a histone deacetylase, is involved in inhibiting inflammation, fibrosis, and apoptosis of renal cells, and it upregulates the expression of ER $\alpha$ . In contrast, studies have shown that testosterone enhances kidney susceptibility to IRI-induced AKI, further proves that males are more vulnerable to AKI.<sup>21</sup> Blacks or African Americans initially had the highest mortality rates, potentially due to disparities in hospital care compared to whites.<sup>22</sup> In 2010, the trend shifted, with mortality among American Indians surpassing that of Blacks, likely due to a high prevalence of risk factors such as socioeconomic deprivation and exposure to pollutants. This population also became endemic to conditions such as obesity, type 2 diabetes mellitus, and hypertension, which are risk factors for AKI. Furthermore, differences in access to healthcare between poorer and richer neighborhoods contributed to these changing trends. From 1999 to 2018, whites exhibited an increasing death rate compared to Hispanics, Asians, or Pacific Islanders, but in 2018, the death rate among Hispanics increased and exceeded that of Whites. Notably, the mortality trend remained lowest among Asians compared to other racial groups. In 2011, there was a higher incidence of ESRD in Alaskan natives and American Indians, but their mortality rates were lower compared to other races.<sup>23</sup> However, our study noted a higher incidence of mortality associated with AKI. One possible reason for the higher mortality in AI/AN, as discussed in a CDC study, is the presence of health disparities, including, but not limited to, lower education and income levels and higher unemployment compared to other racial groups. These factors contribute to poor access to healthcare for American Indian/Alaska natives, leading to high prevalence of chronic conditions and poor outcomes.<sup>24</sup> Our study and data highlights a high incidence of mortality in this

population, which needs to be addressed to provide a better quality of life and outcomes for patients with AKI, especially in AI/AN.

Variations in mortality trends were also observed across regions. From 1999 to 2010, the mortality rate was similar in the South and Midwest and was the highest among all regions. From 2010 to 2021, the mortality rate in the South increased compared to the Midwest. After the Midwest and South, mortality rates were higher in the Northeast compared to the West from 1999 to 2010. Yet, from 2010 to 2021, mortality rates in the West increased and surpassed those in the Northeast. This shift might be attributed to factors such as urbanization in the West, improved access to healthcare facilities, and early diagnosis. In rural areas, where there are limited health facilities, infrastructure problems, and a shortage of nephrologists for early diagnosis, there is a possibility of under-reporting mortality rates.<sup>25</sup> This could explain the higher mortality rates observed in non-metropolitan areas compared to metropolitan areas.

Several limitations need to be mentioned. First, dependence on ICD codes and death certificates introduces a risk of misrepresentation or omission of AKI as a cause of death.<sup>25</sup> Second, the database lacks detailed information on clinical and diagnostic variables that could better describe the severity of AKI, such as vital signs, laboratory findings including, but not limited to, renal function tests, serum electrolytes, data regarding radiological studies, and genetic analysis.<sup>26</sup> Third, data on medical therapy and the management of renal failure are not available. Fourth, data regarding socioeconomic determinants of health are missing, which may affect access to care. Fifth, the detailed history and etiology of any pathology or underlying factors contributing to AKI are not known.<sup>1</sup> Finally, it must be acknowledged that the death certificates obtained from the CDC Wonder Database may not always be accurate, in the absence of a post-mortem examination these differences are submitted based on the best of the doctor's clinical judgment and knowledge.<sup>1</sup>

## Conclusion

From 1999 to 2009, there was a gradual rise in AAMR of AKI-related mortality. A declining trend was noticed from 2009 to 2018. A sudden increase in AAMR occurred between 2019 and 2020. The highest AAMR was noted among males, in rural areas, in the southern region of Black or African American origin. However, there was a demographic shift in AAMR towards the American Indian and Alaska Native population from 2012 to 2020. Since AKI is usually a result of reversible causes, preventive measures, and improved healthcare facilities could significantly reduce mortality associated with AKI.

## Conflicts of interest

There are no conflicts of interest.

## References

- Barretti P, Soares VA. Acute renal failure: Clinical outcome and causes of death. *Ren Fail* 1997;19:253–7. <https://pubmed.ncbi.nlm.nih.gov/9101600/>
- Saxena A, Meshram S. Predictors of mortality in acute kidney injury patients admitted to medicine intensive care unit in a Rural Tertiary Care Hospital. *Indian J Crit Care Med* 2018;22:231–7. [http://dx.doi.org/10.4103/ijccm.ijccm\\_462\\_17](http://dx.doi.org/10.4103/ijccm.ijccm_462_17)
- Brown JR, Rezaee ME, Marshall EJ, Matheny ME. Hospital mortality in the United States following acute kidney injury. *Biomed Res Int* 2016;2016:1–6. <https://pubmed.ncbi.nlm.nih.gov/27376083/>
- Sohaney R, Yin H, Shahinian V, Saran R, Burrows NR, Pavkov ME, et al. In-hospital and 1-year mortality trends in a national cohort of US veterans with acute kidney injury. *Clin J Am Soc Nephrol* 2022;17:184–93. <http://dx.doi.org/10.2215/cjn.01730221>
- Goldberg R, Dennen P. Long-term outcomes of acute kidney injury. *Adv Chronic Kidney Dis* 2008;15:297–307. <https://pubmed.ncbi.nlm.nih.gov/18565480/>
- Pavkov ME, Harding JL, Burrows NR. Trends in hospitalizations for acute kidney injury — United States, 2000–2014. *MMWR Morb Mortal Wkly Rep* 2018;67:289–93. <http://dx.doi.org/10.15585/mmwr.mm6710a2>
- Kellum JA, Hoste EAJ. Acute kidney injury: Epidemiology and assessment. *Scand J Clin Lab Invest* 2008;68:6–11. <https://pubmed.ncbi.nlm.nih.gov/18569958/>
- Savino M, Plumb L, Casula A, Evans K, Wong E, Kolhe N, et al. Acute kidney injury identification for pharmacoepidemiologic studies: Use of laboratory electronic acute kidney injury alerts versus electronic health records in hospital episode statistics. *Pharmacoepidemiol Drug Saf* 2021;30:1687–95.
- Aggarwal R, Chiu N, Locco EC, Kazi DS, Yeh RW, Wadhwa RK. Rural-urban disparities: diabetes, hypertension, heart disease, and stroke mortality among Black and White adults, 1999–2018. *J Am Coll Cardiol* 1999;77:1480–1.
- Ingram DD, Franco SJ. 2013 NCHS urban-rural classification scheme for counties. *Vital Health Stat* 2014;1-73. <https://pubmed.ncbi.nlm.nih.gov/24776070/>
- Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. *Natl Vital Stat Rep* 1998;47:1-16, 20. <https://pubmed.ncbi.nlm.nih.gov/9796247/>
- Wu Y, Hao W, Chen Y, Chen S, Liu W, Yu F, Hu W, Liang X. Clinical features, risk factors, and clinical burden of acute kidney injury in older adults. *Ren Fail*. 2020 Nov;42(1):1127–1134. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7671701/#:~:text=Age%2C%20dementia%2C%20moderate%2Fsevere,risk%20factors%20for%20HA%2DAKI>.
- Holgado JL, Lopez C, Fernandez A, Sauri I, Uso R, Trillo JL, Vela S, Nuñez J, Redon J, Ruiz A. Acute kidney injury in heart failure: a population study. *ESC Heart Fail*. 2020 Apr;7(2):415–422. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7160477/>
- Trivedi AN, Sommers BD. The affordable care act, medicaid expansion, and disparities in kidney disease. *Clin J Am Soc Nephrol*. 2018 Mar 7;13(3):480–482. doi: 10.2215/CJN.10520917. Epub 2017 Dec 14. PMID: 29242369; PMCID: PMC5967679.
- Neiman PU, Tsai TC, Bergmark RW, Ibrahim A, Nathan H, Scott JW. The affordable care act at 10 years: Evaluating the evidence and navigating an uncertain future. *J Surg Res*. 2021 Jul;263:102–109.
- Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol*. 2010;21:1757–64.
- Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J; ADHERE scientific advisory committee and investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail*. 2007;13:422–30. <https://pubmed.ncbi.nlm.nih.gov/17675055/>
- Executive Summary: Heart disease and stroke statistics-2010 update: A report from the american heart association (vol 121, pg 948, 2010). American Heart Association 2010;121.
- Billings FT, Pretorius M, Schildcrout JS, Mercaldo ND, Byrne JG, Ikizler TA, et al. Obesity and oxidative stress predict AKI after cardiac surgery. *J Am Soc Nephrol* 2012;23:1221–8.
- Nagamine M, Jiang HJ, Merrill CT. Trends in elderly hospitalizations, 1997–2004. 2006 Oct. In: Healthcare cost and utilization project (HCUP) statistical briefs. Rockville (MD): Agency for healthcare research and quality (US); 2006 feb. Statistical Brief #14. <https://www.ncbi.nlm.nih.gov/books/NBK63499/>
- Mahani D, Khaksari F, Raji-Amirhasani M. Renoprotective effects of estrogen on acute kidney injury: the role of SIRT1. *Int Urol Nephrol* 2021;53:2299–2310. <https://pubmed.ncbi.nlm.nih.gov/33458788/>
- Darvishzadeh Mahani F, Khaksari M, Raji-amirhasani A. Renoprotective effects of estrogen on acute kidney injury: the role of SIRT1. *Int Urol Nephrol* 2021;53:2299–310.
- Hall YN, Jolly SE, Xu P, Abrass CK, Buchwald D, Himmelfarb J. Regional differences in dialysis care and mortality among american indians and alaska natives. *Journal of the American Society of Nephrology* 22(12):p 2287–2295, December 2011.
- Adakai M, Sandoval-Rosario M, Xu F, et al. Health disparities among american indians/alaska natives — Arizona, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67:1314–1318.
- Grams ME, Matsushita K, Sang Y, Estrella MM, Foster MC, Tin A, et al. Explaining the racial difference in AKI incidence. *J Am Soc Nephrol* 2014;25:1834–41.
- Macedo E, Mehta RL. Regional differences in Acute Kidney Injury incidence and mortality in developing countries: recent trends. *J Bras Nefrol* 2020;42:268–70.

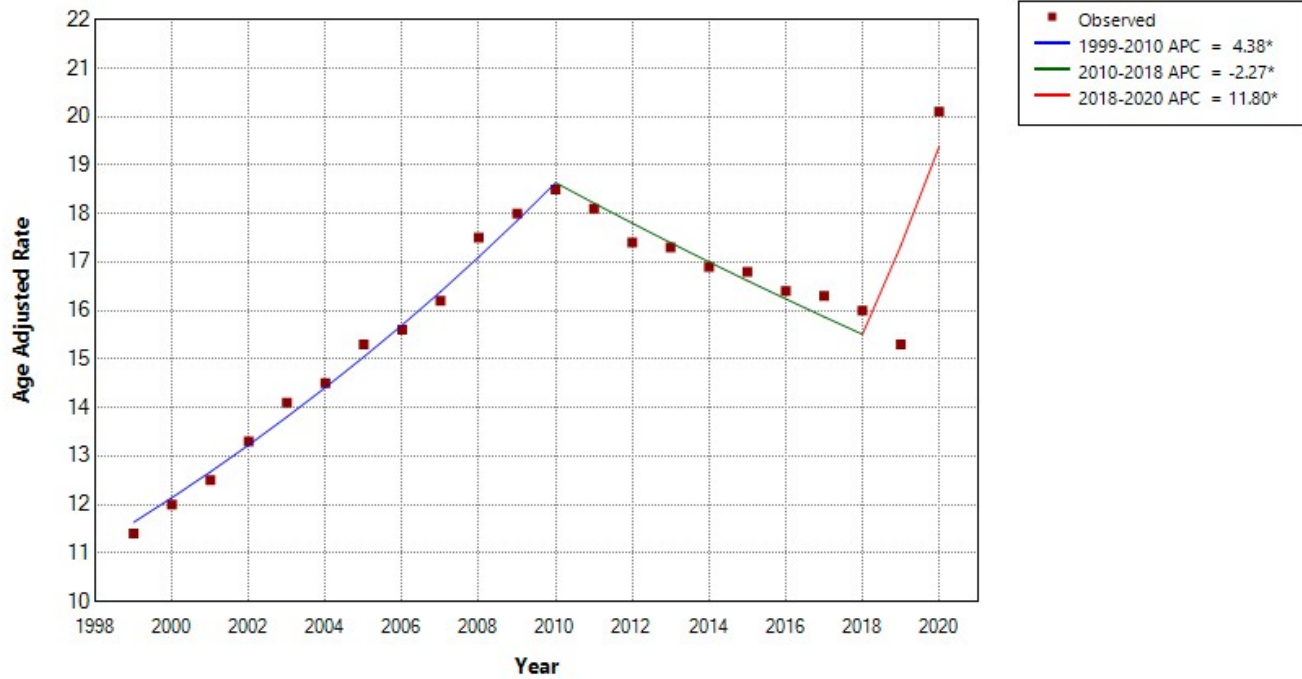
## Supplementary Files

**Supplementary Table 1 General trends of acute kidney injury-related mortality rates in the years 1999-2020**

Disease	Year	Age Adjusted Rate	Age Adjusted Rate Lower 95% Confidence Interval	Age Adjusted Rate Upper 95% Confidence Interval
AKI	1999	11.4	11.3	11.6
AKI	2000	12	11.8	12.1
AKI	2001	12.5	12.4	12.6
AKI	2002	13.3	13.1	13.4
AKI	2003	14.1	14	14.2
AKI	2004	14.5	14.4	14.6
AKI	2005	15.3	15.1	15.4
AKI	2006	15.6	15.4	15.7
AKI	2007	16.2	16.1	16.4
AKI	2008	17.5	17.3	17.6
AKI	2009	18	17.8	18.1
AKI	2010	18.5	18.3	18.6
AKI	2011	18.1	18	18.3
AKI	2012	17.4	17.2	17.5
AKI	2013	17.3	17.1	17.4
AKI	2014	16.9	16.7	17
AKI	2015	16.8	16.7	17
AKI	2016	16.4	16.3	16.6
AKI	2017	16.3	16.1	16.4
AKI	2018	16	15.8	16.1
AKI	2019	15.3	15.2	15.5
AKI	2020	20.1	19.9	20.2



AKI: 2 Joinpoints



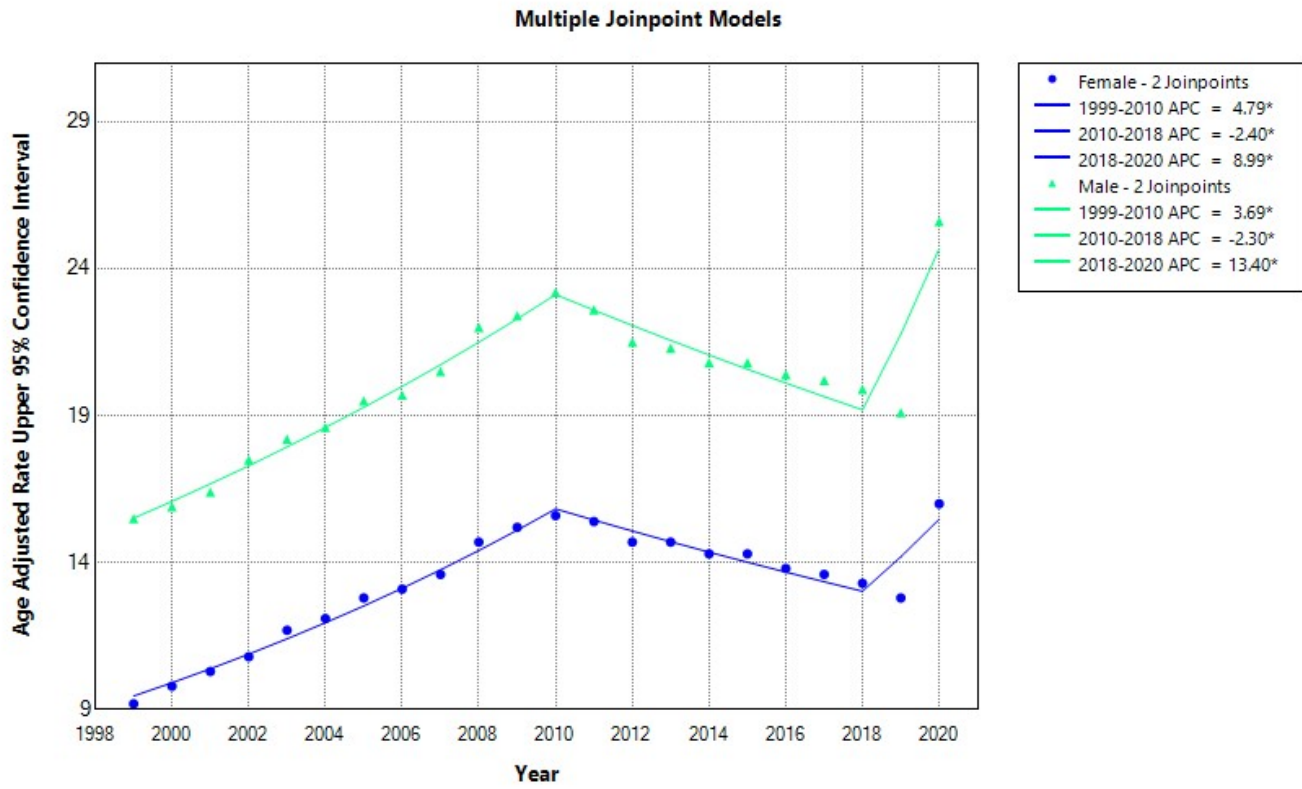
\* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.  
 -- Test Statistic and P-Value not available for the Empirical Quantile method.  
 Final Selected Model: 2 Joinpoints.

Supplementary Figure 1 General trends of acute kidney injury-related mortality rates in the years 1999-2020

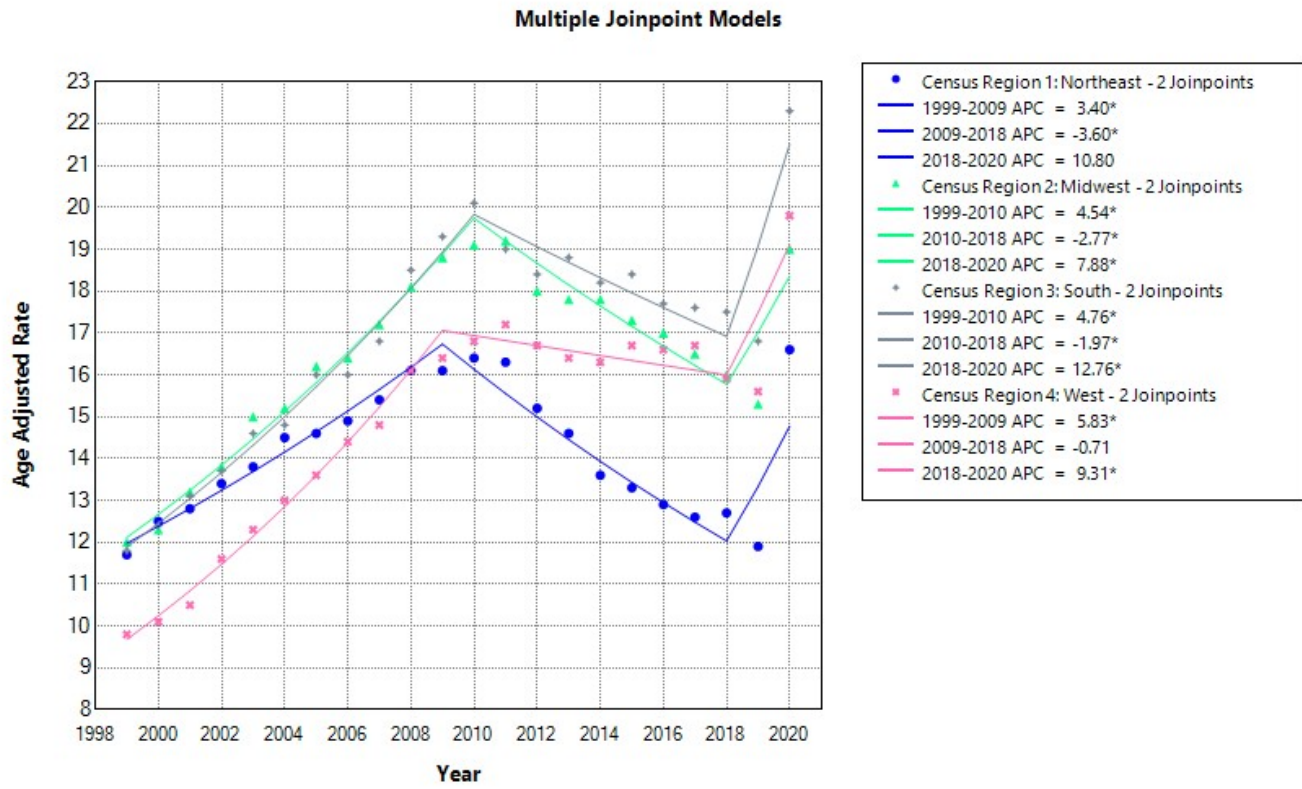
Supplementary Table 2 Gender-based trends of acute kidney injury-related mortality rates in the years 1999-2020

Gender	Year	Age Adjusted Rate	Age Adjusted Rate Lower 95% Confidence Interval	Age Adjusted Rate Upper 95% Confidence Interval
Female	1999	9	8.9	9.2
Female	2000	9.6	9.5	9.8
Female	2001	10.2	10	10.3
Female	2002	10.7	10.5	10.8
Female	2003	11.6	11.4	11.7
Female	2004	12	11.8	12.1
Female	2005	12.7	12.5	12.8
Female	2006	13	12.8	13.1
Female	2007	13.5	13.3	13.6
Female	2008	14.5	14.4	14.7
Female	2009	15	14.9	15.2
Female	2010	15.4	15.2	15.6
Female	2011	15.2	15	15.4

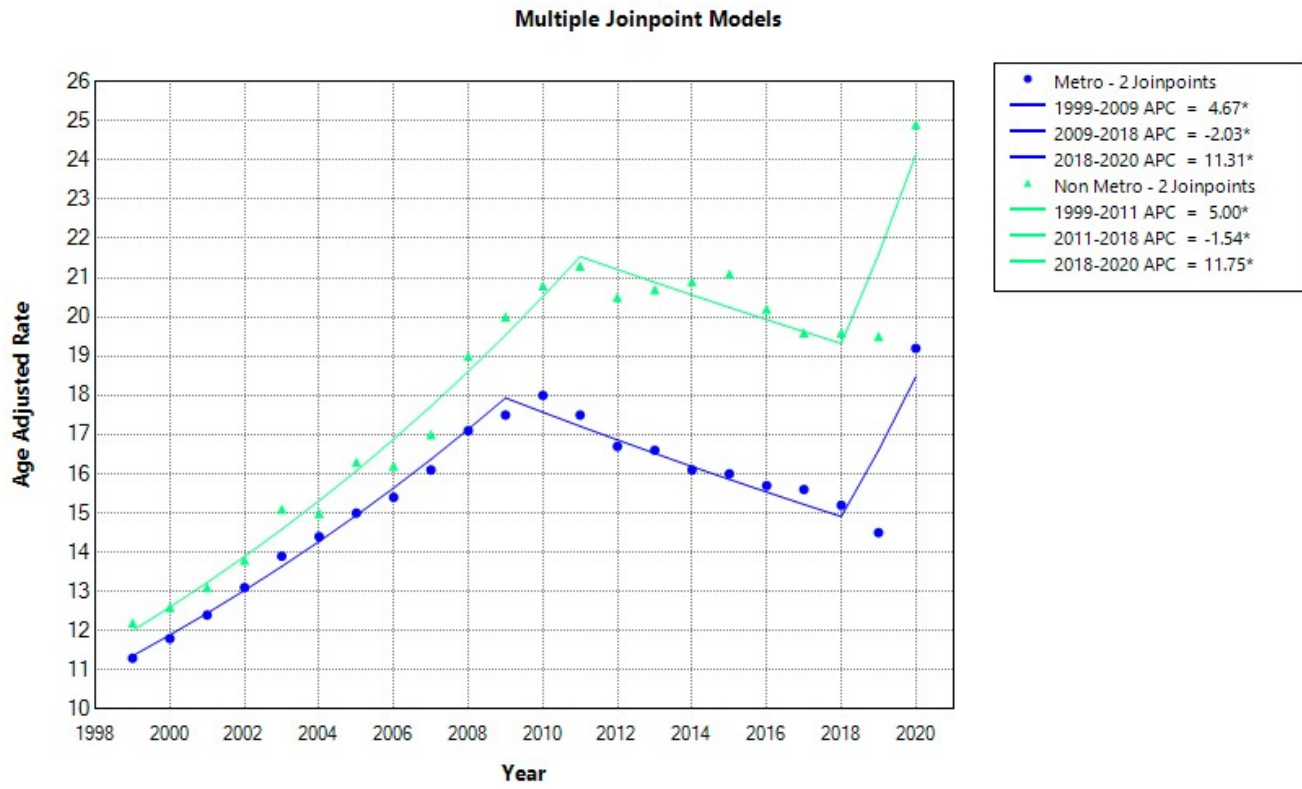
Female	2012	14.5	14.4	14.7
Female	2013	14.5	14.3	14.7
Female	2014	14.1	14	14.3
Female	2015	14.1	13.9	14.3
Female	2016	13.7	13.5	13.8
Female	2017	13.4	13.3	13.6
Female	2018	13.1	12.9	13.3
Female	2019	12.6	12.5	12.8
Female	2020	15.8	15.7	16
Male	1999	15.3	15.1	15.5
Male	2000	15.7	15.4	15.9
Male	2001	16.2	15.9	16.4
Male	2002	17.3	17	17.5
Male	2003	18	17.7	18.2
Male	2004	18.4	18.1	18.6
Male	2005	19.2	19	19.5
Male	2006	19.5	19.2	19.7
Male	2007	20.3	20	20.5
Male	2008	21.8	21.5	22
Male	2009	22.2	21.9	22.4
Male	2010	22.9	22.6	23.2
Male	2011	22.4	22.1	22.6
Male	2012	21.3	21.1	21.5
Male	2013	21.1	20.8	21.3
Male	2014	20.6	20.3	20.8
Male	2015	20.5	20.3	20.8
Male	2016	20.2	19.9	20.4
Male	2017	20	19.8	20.2
Male	2018	19.7	19.4	19.9
Male	2019	18.9	18.7	19.1
Male	2020	25.4	25.1	25.6



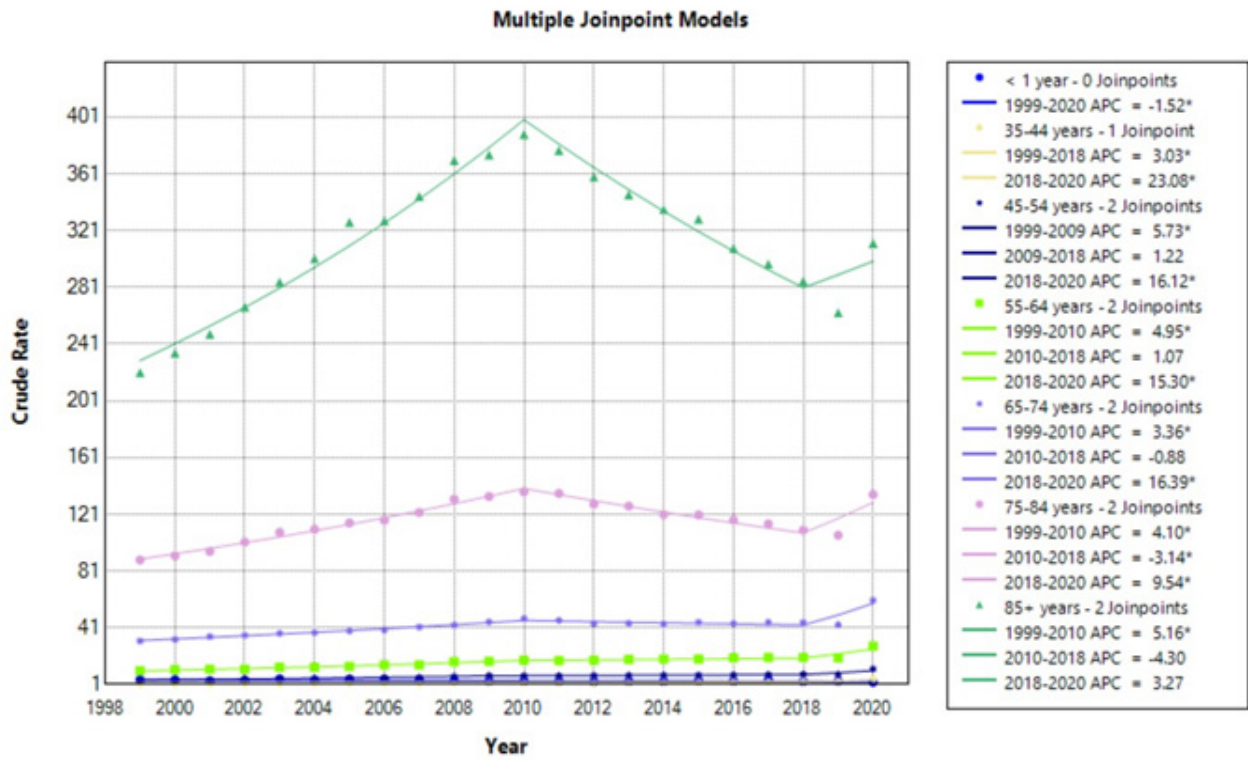
Supplementary Figure 2 Gender-based trends of acute kidney injury-related mortality rates in the years 1999-2020



Supplementary Figure 3 Acute kidney injury-related mortality rates based on census region in the years 1999-2020



Supplementary Figure 4 Acute kidney injury-related mortality rates based on urbanization in the years 1999-2020



Supplementary Figure 5 Acute kidney injury-related mortality rates based on age in the years 1999-2020