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Urban-Rural Differences in Acute Kidney Injury Mortality in the United States

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Abstract

Introduction: Acute kidney injury (AKI) is associated with increased mortality. AKI-related mortality trends by U.S. urban and rural counties were assessed.

Methods: In the cross-sectional study, based on the Centers for Disease Control and Prevention WONDER (Wide-ranging ONline Data for Epidemiologic Research) Multiple Cause of Death data, age-standardized mortality with AKI as the multiple cause was obtained among adults aged ≥25 years from 2001–2020, by age, sex, race and ethnicity, stratified by urban-rural counties. Joinpoint regressions were used to assess trends from 2001–2019 in AKI-related mortality rate. Pairwise comparison was used to compare mean differences in mortality between urban and rural counties from 2001–2019.

Results: From 2001–2020, age-standardized AKI-related mortality was consistently higher in rural than urban counties. AKI-related mortality (per 100,000 population) increased from 18.95 in 2001 to 29.46 in 2020 in urban counties and from 20.10 in 2001 to 38.24 in 2020 in rural counties. In urban counties, AKI-related mortality increased annually by 4.6% during 2001–2009 and decreased annually by 1.8% until 2019 (p<0.001). In rural counties, AKI-related mortality increased annually by 5.0% during 2001–2011 and decreased by 1.2% until 2019 (p<0.01). The

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overall urban-rural difference in AKI-related mortality was greater after 2009–2011. AKI-related mortality was significantly higher among older adults, men, and non-Hispanic Black adults than their counterparts in both urban and rural counties. Higher mortality was concentrated in rural counties in the Southern United States.

Conclusions: Multidisciplinary efforts are needed to increase AKI awareness and implement strategies to reduce AKI-related mortality in rural and high-risk populations.

INTRODUCTION

Acute kidney injury (AKI) is characterized by an abrupt reduction or loss of kidney function.[1] Causes of AKI are multifactorial including sepsis, certain medications, undergoing cardiac surgeries, hospital or intensive care unit stay, and older age.[2] AKI-associated hospitalizations significantly increase length of stay and costs compared with non-AKI associated hospitalizations.[3] Whether hospital- or community-acquired, AKI occurs more commonly among adults with comorbidities, mainly those with type 2 diabetes, cardiovascular diseases, or chronic kidney disease (CKD).[4] Additionally, AKI increases the risk of new or progressive CKD and major cardiovascular events, as well as short- and long-term mortality.[5] A study based on a national veteran cohort with AKI followed from 2008 to 2017 reported 6% in-hospital mortality, with 28% of patients dying within 1 year of hospitalization.[6] The substantial AKI-associated postdischarge mortality indicates that timely and effective follow-up care is paramount.

In the U.S., urban-rural disparities in health outcomes have been well documented.[7] Due to lower socioeconomic status and fewer resources than urban settings, rural residents are more likely to encounter barriers to healthcare access and affordability, transportation, preventive care, and disease diagnosis and treatment.[8] As a result, the prevalence of chronic conditions and deaths is higher in rural than urban counties.[9,10]

Kidney disease remains one of the leading causes of death in the U.S.[11] However, to the best of the authors' knowledge, urban-rural differences in AKI-related mortality have not been reported to date. These differences and their trends are important because they may reflect both environment- and health system-related barriers to prevention and treatment of diseases with high mortality risk. As AKI is a common complication of critical diseases and a potential risk for mortality, it is important to assess trends in urban-rural disparities in AKI-related mortality. The findings will help healthcare providers and policy makers address these disparities and guide public health actions and implement strategies to reduce AKI-related mortality in these geographic areas. Therefore, the hypothesis is that AKI-related mortality is higher in rural than urban counties. The objectives of the study are to (1) examine urban-rural differences in AKI-related mortality, (2) assess trends in AKI-related mortality by age, sex, and race and ethnicity in urban and rural counties, and (3) describe geographic differences in AKI-related mortality.

METHODS

Study Population

A cross-sectional study was designed using the aggregated Multiple Cause of Death Data from the National Vital Statistics System available from Centers for Disease Control and Prevention Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER).[12] Besides death, the publicly available system includes other data queries, such as AIDS, birth, cancer statistics, and population, for public health research. The mortality data are based on death certificates containing a single underlying cause of death, multiple causes of death, and demographics. The data provided through CDC WONDER have been used to study trends in chronic diseases.[13,14] CDC WONDER produces data, such as population counts for all U.S. counties, number of deaths, crude and age-adjusted death rates, urban-rural county status, place of death, age group, sex, race, Hispanic origin, year, and causes of death based on *International Classification of Disease 10th Revision* (ICD-10) codes.

AKI was identified as a multiple cause of death (ICD-10 code: N17), i.e., reported anywhere on the death certificate, among U.S. residents aged ≥25 years from 2001–2020, henceforth called AKI-related mortality. AKI as the underlying cause of death (the condition which initiated the train of morbid events leading directly to death) was not assessed because it substantially underestimates AKI-related mortality. Coexisting conditions (e.g., sepsis) usually lead to death with AKI as a strong impact on death.[15]

Measures

Based on the 2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties,[16] urban counties were defined as counties of large central metro (metropolitan statistical areas [MSA] of population ≥1 million), large fringe metro (MSA of population ≥1 million), medium metro (MSA of population greater than 250,000 but less than 1 million), and small metro (MSA of population less than 250,000). Rural counties were defined as micropolitan (counties in micropolitan statistical areas) and noncore counties (counties not in micropolitan statistical areas). Demographic variables include age (25–64, 65–74, and ≥75 years), sex, race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic others), and U.S. regions (Northeast, South, Midwest, and West). American Indian and Alaska Native and Asian or Pacific Islander were combined into “other” race category due to small population sizes.

Statistical Analysis

Annual AKI-related mortality was defined as the number of deaths per 100,000 adult population by urban and rural counties and demographic characteristics. The CDC WONDER Multiple Cause of Death data uses the 2000 U.S. Standard Population for age standardization. Age-standardized estimates were derived to eliminate the bias that resulted from the differences in age-composition of urban and rural counties and the changing age structure during the study period. Z tests of population proportions were used for group comparisons and presented age-standardized AKI-related mortality from combined 2001–2020 data categorized by tertiles on a map by urban and rural counties. A linear regression with an interaction between region and urban-rural counties was constructed for comparisons.

Temporal trends from 2001–2019 in AKI-related mortality overall and by age, sex, and race and ethnicity were assessed using the JoinPoint Trend Analysis Software (V5.0.2, National Cancer Institute).[17] Joinpoint regression models were constructed to estimate natural-logarithm transformed AKI-related mortality, weighted on inversed standard errors taking annual variations into account. The optimal number of joinpoints (0–3) was selected by best fit of regressions based on permutation tests. Annual percent change (APC) with 95% confidence interval (CI) weas reported for periods determined by Joinpoint regressions. Due to a rapid increase in AKI and its associated death due to the COVID-19 pandemic,[18] the 2020 data was not included in the trend analysis as it was an influential point. For comparison of the overall trend from 2001–2019 in AKI-related mortality by urban and rural counties, a joinpoint pairwise test was performed to test the null hypothesis of temporal parallelism of mean functions (mean difference in urban-rural counties by joinpoints during the study period). For differences in AKI-related mortality in the study periods, difference-in-differences analysis was performed based on the primary joinpoints for the overall trend from 2001–2019 by urban and rural counties. A linear regression separately for urban and rural counties was then constructed with an interaction between demographic groups and year. The analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and considered all comparisons significant below the level of 0.05.

The study was exempted for CDC's Institutional Review Board approval because CDC WONDER is a publicly accessible database.

RESULTS

During the study period, the total number of AKI-related deaths among U.S. adults aged ≥25 years was 887,819 for urban counties (ranging from 27,951 in 2001 to 65,719 in 2020) and 222,684 for rural counties (ranging from 6,864 in 2001 to 16,458 in 2020). Annual AKI-related mortality in rural counties was consistently and significantly higher than those in urban counties from 2001 to 2020 (Figure 1). The AKI-related mortality was significantly higher in 2020 compared with that in 2001 and was higher in rural than urban counties overall and by demographic characteristics in 2020 (Appendix Table 1). Age-standardized AKI-related mortality increased annually by 4.6% until 2009 and then decreased annually by 1.8% until 2019 in urban counties and increased annually by 5.0% until 2011 and decreased by 1.2% until 2019 in rural counties (Appendix Table 2).

The pairwise comparison based on permutation tests confirmed that the mean change in mortality rate differed significantly by urban and rural settings across the study period ($p<0.001$). Further, the difference-in-differences analysis showed on average a significantly higher mortality in rural than urban counties and a larger difference after 2009 than before 2009 (4.86 deaths per 100,000 population after 2009, $p=0.002$) or after 2011 than before 2011 (4.65 deaths per 100,000 population after 2011, $p=0.01$, Figure 1).

From 2001–2020, annual AKI-related mortality per 100,000 population in urban and rural counties was substantially higher in older adults (urban range: 131.10–177.91 [age ≥75 years], 34.57–57.65 [age 65–74 years], 3.84–10.78 [age 25–64 years]; rural range: 145.74–224.94 [age ≥75 years], 35.57–73.83 [age 65–74 years], 4.16–15.82 [age 25–64 years]), and higher among men than women (urban range: 24.66–37.62 [men], 15.34–23.00 [women]; rural range: 25.65–46.37 [men], 16.56–31.60 [women]) (Figure 2, Appendix Table 1). All group comparisons within urban or rural counties were statistically significant ($p<0.001$).

Each year from 2001–2020 in urban counties, non-Hispanic Black adults had a higher age-standardized AKI-related mortality per 100,000 population (range: 30.54–44.14) than non-Hispanic White adults (17.92–26.38), Hispanic adults (range: 16.23–36.62), or those with other races (range: 13.71–21.99). Similarly, in rural counties, age-standardized AKI-related mortality was higher in non-Hispanic Black adults (range: 28.74–63.93) than non-Hispanic White adults (range: 19.49–35.13), Hispanic adults (range: 16.34–53.09) or those with other races (range: 17.53–47.70) (Figure 2, Appendix Table 1).

Similar to the overall trend pattern in urban and rural counties, trends in each of the age, sex, and race and ethnicity groups generally increased from 2001 until 2009–2011 and then decreased until 2019 with a few exceptions (Appendix Table 2). Specifically, AKI-related mortality rate continued to increase after 2009–2011 at an attenuated rate among adults aged 25–64 years in both urban and rural counties and remained unchanged during 2010–2019 among rural adults aged 65–74 years. AKI-related mortality remained unchanged among rural Hispanic adults during 2009–2019 (Appendix Table 2).

The highest tertile of age-standardized AKI-related mortality rates were observed to be concentrated in rural counties in the Southern United States (Figure 3). Compared with the other U.S. regions, mean mortality rate was significantly higher in the Southern region for both urban and rural counties. Age-standardized AKI-related mortality rate was higher in rural than urban counties in the Southern and Midwestern regions but did not differ significantly by urban and rural counties in the North-eastern and Western regions (Table 1).

DISCUSSION

This study evaluated urban-rural differences in mortality when AKI was a multiple cause of death during the recent two decades and highlighted several important findings. First, AKI-related mortality was higher in rural than urban counties, especially in the southern counties. Second, substantial demographic differences in AKI-related mortality were observed in both urban and rural counties. AKI-related mortality was significantly higher among older adults, men, and non-Hispanic Black adults than their counterparts. Third, from 2001–2019, the overall trends in age-standardized mortality rates were increasing in the first 9–11 years followed by a decline. A similar pattern was observed among adults aged ≥75 years, men and women, and all racial and ethnical populations in both urban and rural counties except for the Hispanic population in rural counties.

The key finding of consistently higher AKI-related mortality in rural than urban counties during the past 2 decades is not unexpected. The prevalence of unhealthy lifestyles and chronic conditions is higher in rural than urban counties.[8,9] Specifically, rural residents are more likely to have excess death than their urban counterparts in 5 leading causes of death (i.e., heart disease, cancer, unintentional injury, chronic lower respiratory disease, and stroke).[10] Sepsis is the most common cause of AKI and its associated in-hospital mortality.[19] A previous study reported that sepsis-associated mortality remained higher in rural than urban counties from 2010 to 2019.[20] Timely nephrology consultation is associated with lower AKI mortality,[21] but ambulatory care utilization including office visit with a specialist (e.g., nephrologists) is unfortunately lower in rural than urban counties while acute care utilization is disproportionally higher.[22] Furthermore, in rural communities, primary care providers (PCPs) play a key role in detecting and preventing AKI or sepsis-related AKI.[23] A previous study showed that density of PCPs increased in both urban and rural counties, but more rapidly in urban counties indicating widening urban-rural disparities.[24] Optimal posthospitalization care including medication reconciliation and blood pressure management is crucial to prevent AKI complications and death, which requires effective coordination between nephrologists and PCPs. Expanding telemedicine in rural communities may address some of the health care access barriers, such as long-distance travel and costs.[25] The American Society of Nephrology has launched an initiative aimed at increasing awareness and promoting early detection and intervention of AKI with efforts from a multidisciplinary care team[26] which can be adopted in rural community settings. Besides the acute events (i.e., sepsis, surgery, and COVID-19), chronic conditions, such as diabetes and hypertension and their complications that are associated with AKI, also substantially affect the rural communities.[27,28] Screening, awareness, education, and effective self-management strategies targeting these chronic conditions are needed as well to reduce AKI-related mortality, especially in rural counties.

The demographic disparities in AKI-related mortality are pronounced in both urban and rural counties. The findings of higher AKI-related mortality rate among men than women correlate with higher AKI-associated hospitalization among men than women in a previous study[29] and men were found to be more likely to have AKI and AKI-related mortality than women.[30,31] Although the biological mechanism is not clear, evidence has shown that female sex hormones might have reno-protective effects, such as vasodilatory effects on the renal vasculature and decreased inflammation.[32] As would be expected, AKI-related mortality was significantly higher among adults aged ≥75 years than younger adults. Nonetheless, the declining trend in this age group after 2009–2011 (except for 2020) is encouraging. In contrast, AKI-related mortality rate for adults aged 25–64 years continued to increase after 2009, although at a slower rate. The exact reason for the different trend patterns in AKI-related mortality by age is unknown, but the findings suggest increased clinical awareness for AKI and its risk factors may be considered in patients younger than 65 years. The continued rapid increase in AKI-related mortality among adults aged 25–64 years in rural counties after 2009 may warrant future investigation. Noticeably, AKI-related mortality was significantly higher among non-Hispanic Blacks than other racial and ethnic populations across the 20-year observation period. AKI incidence has been reported to be higher in non-Hispanic Blacks than non-Hispanic Whites in a review study.[33] Lower socioeconomic status among non-Hispanic Black adults may explain these findings as they may be more likely to receive suboptimal care in prevention, diagnosis and management of

AKI and therefore poorer health outcomes and death.[33] The current study further showed that while AKI-related mortality was overall higher in rural than urban counties, it was substantially higher in southern rural counties. One possible explanation is that adults residing in the southern rural counties have higher poverty, health-risk behaviors, limited health care access, overall morbidities and mortality than their urban counterparts or those in rural counties in other regions.[34] Continued efforts are needed to expand Medicaid in these areas with limited resources to improve health care access.[35]

The current study showed an initial increasing trend in AKI-related mortality followed by a decline from 2009–2019. Despite unknown reasons, the findings are consistent with previous studies although direct comparison was not possible due to different study measures and settings.[4,6,36,37] For example, a study of veterans that measured both in-hospital and 1-year mortality in which most AKI mortality occurred after hospital discharge also showed a decline during 2009–2017.[6] The absolute number of AKI-related deaths in the current study increased during 2001–2009, which was consistent with other studies using the National Inpatient Sample data during the similar time period.[36,37] The decline in AKI-related mortality rates during the later period until 2020 shown in the study might be due to increased awareness of AKI management from dissemination of clinical practice guidelines published in 2012.[38] Notably, the more pronounced decline from 2009–2019 in urban than rural counties has widened urban-rural disparities which warrants further investigation. Although the declining trend was interrupted by COVID-19, future studies should continue to monitor the difference in AKI-related mortality and assess the impact of social determinants of health on these differences in urban and rural counties.

The findings have several health policy implications. Factors perpetuating disparities may be mitigated through tailored public health actions and strategies.[39] To prevent AKI and its mortality, it is important to expand healthcare resources to high-risk populations, especially in rural counties in the Southern United States. As such, local health policy makers could consider innovative strategies to improve rural access to nephrology visits. Meanwhile, in areas where nephrologists are limited, training of primary care providers to increase awareness to identify AKI risk factors and promote prevention has proven to be effective.[40] To reduce AKI-related mortality and improve AKI management, primary care providers' role in integrated care is particularly important in rural counties, such as enhancing patient communications and improving clinical decision-making by using electronic medical records and optimizing telehealth resources to monitor post-AKI CKD, increase specialist referrals, and consult on medications. Finally, prioritizing AKI research in rural counties could identify evidence-based strategies to achieve health equity.

LIMITATIONS

The study has at least four limitations. First, AKI may be underreported on death certificates as it is not always clear how or whether AKI caused or contributed to death, especially for decedents with multiple comorbidities.[15] As such, AKI-related mortality may be subject to underestimation. Second, CDC WONDER is aggregated data which limits the ability for analysis at individual level. Additionally, sociodemographic variables, such as income and healthcare insurance status, that may also affect AKI-related mortality risk,[41] were not included in the analysis as they are unavailable in the data. Third, the American Indian or Alaska Natives and Asian or Pacific Islanders were combined into a “non-Hispanic other” category which does not accurately reflect mortality risk for either group. Last, race and Hispanic origin may be misclassified in death certificate reporting, which may bias the findings in the Hispanic ethnicity to a certain degree.[42]

CONCLUSIONS

During 2001–2020, AKI-related mortality was consistently higher in rural than urban counties, especially in the Southern United States. The findings showed age, sex, and race and ethnicity disparities in AKI-related mortality in both urban and rural counties. Coordinated efforts from government agencies, payers, healthcare professionals, and policy makers to increase AKI awareness and implement strategies to decrease AKI-related mortality in rural and high-risk populations may help to close the widening gap in urban and rural counties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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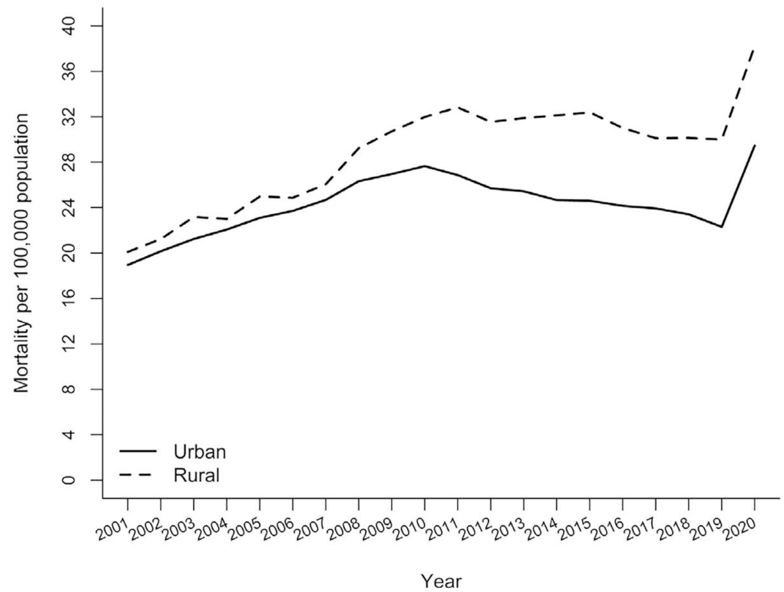

Figure 1.

Age-standardized acute kidney injury-related mortality by urban and rural counties, 2001–2020

Note: Urban counties were defined as counties of large central metro, large fringe metro, medium metro, and small metro. Rural counties were defined as counties of micropolitan and noncore counties. Mean difference in age-standardized mortality rate by rural and urban counties is 4.86 per 100,000 population (95% CI: 1.86–7.86, p=0.002) between 2009–2019 and 2001–2009, and 4.65 per 100,000 population (95% CI: 1.03–8.27, p=0.01) between 2011–2019 and 2001–2011. The null hypothesis of parallelism in the Joinpoint pairwise test was rejected (p<0.001).

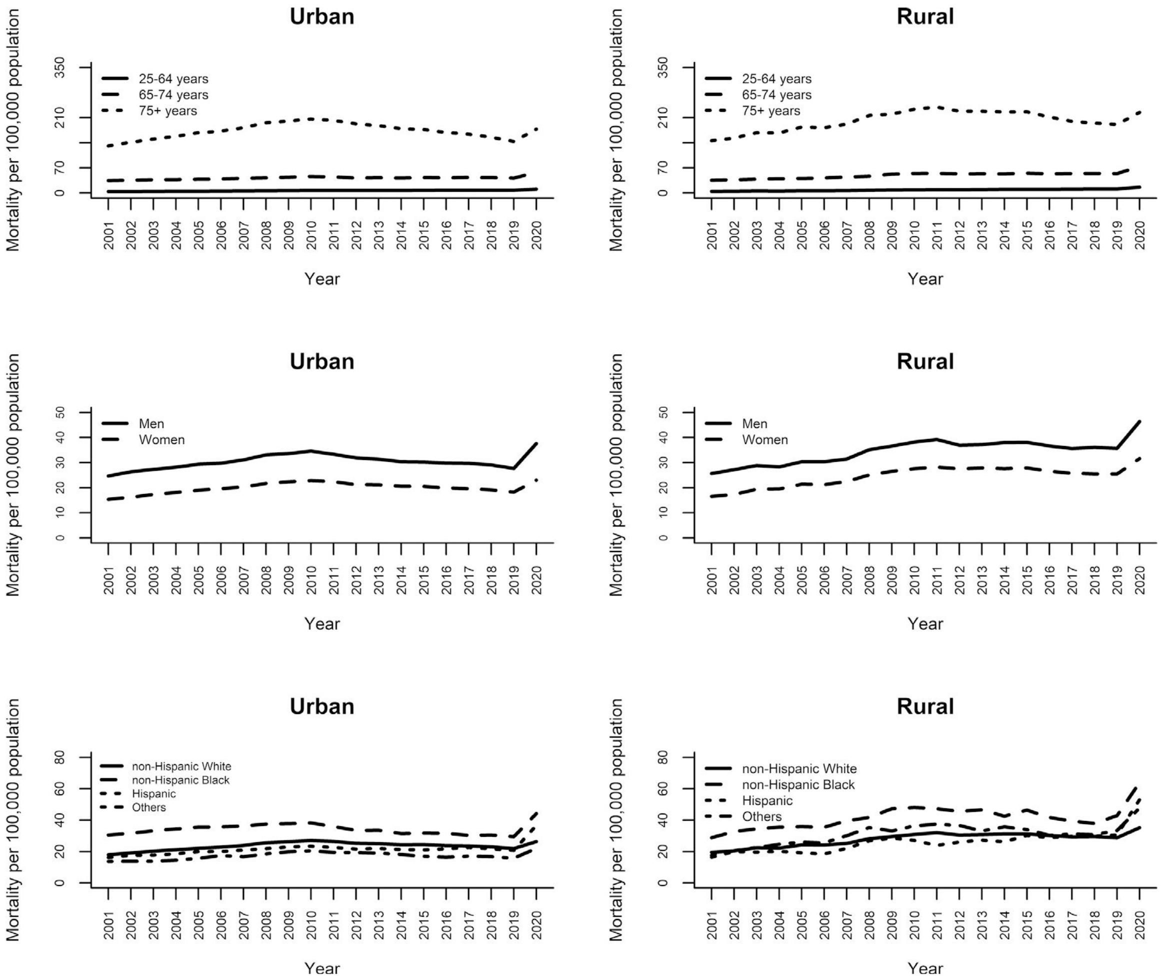

Figure 2.

Age-standardized[a] acute kidney injury-related mortality rate (per 100,000 population) by age, sex, and race and ethnicity, 2001–2020

[a]Except for age-specific estimates.

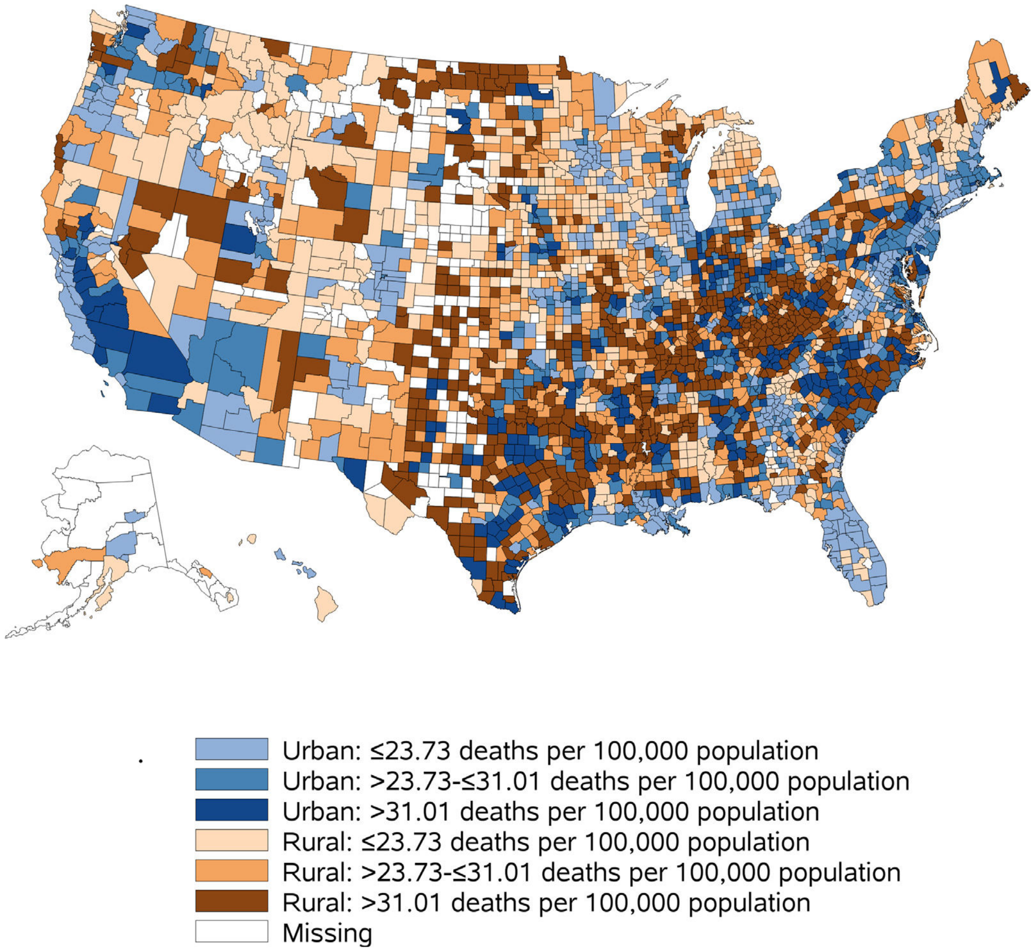

Figure 3.

Age-standardized acute kidney injury-related mortality per 100,000 population, by county, 2001–2020

Note: The missing category indicates number of deaths less than 20. Estimates were suppressed due to confidentiality or unreliability.

Table 1.

Mean of Acute Kidney Injury-Related Mortality Between Region, Urban and Rural Counties, 2001—2020

Region	Urban Mortality Per 100,000 (95% CI)	p Value (Comparison by Region)	Rural Mortality Per 100,000 (95% CI)	p Value (Comparison by Region)
South (ref)	28.7 (27.9–29.4)	-	33.1(32.5–33.8)***	-
Northeast	**24.1 (23.1–25.2)**	<0.001	**25.5 (24.2–26.9)**	<0.001
Midwest	**26.0 (25.1–26.9)**	<0.001	**28.6 (27.8–29.4)*** **	<0.001
West	**23.4 (22.2–24.6)**	<0.001	**24.2 (23.1–25.3)**	<0.001

Note: Boldface indicates statistical significance ($p<0.05$). Comparisons between urban and rural counties for each U.S. region is indicated by *p<0.05 **$p<0.01$ ***$p<0.001$.

CI, confidence interval; ref, referent group; –, not available.