Higher Mortality Following SARS-CoV-2 Infection in Rural Versus Urban Dwellers Persists for 2 Years Post-Infection

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A. Jerrod Anzalone,[1] Michael T. Vest,[2] Makayla E. Schissel,[1] Bradley Price,[3] William B. Hillegass,[4] Ronald Horswell,[5] San Chu,[5] Clifford J. Rosen,[6,7] Lucio Miele,[8] Susan L. Santangelo,[6,7] Sally L. Hodder,[3] on behalf of the National COVID Cohort Collaborative (N3C) Consortium

1. University of Nebraska Medical Center, Omaha, Nebraska, USA; 2. Christiana Care Health System, Newark, Delaware, USA; 3. West Virginia University, Morgantown, West Virginia, USA; 4. University of Mississippi Medical Center, Jackson, Mississippi, USA; 5. Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA; 6. MaineHealth Institute for Research, Scarborough, Maine, USA; 7. Tufts University School of Medicine, Boston, MA, USA; 8. Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA

BACKGROUND

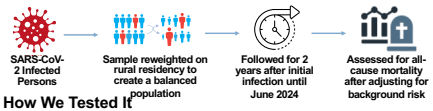
Rural populations in the United States face **longstanding health disparities**, including **higher rates of chronic disease, socioeconomic barriers,** and **limited healthcare access.** The **rural mortality penalty**,[1] defined as higher mortality rates in rural areas compared to urban areas, has been widening since the 1980s.

The COVID-19 pandemic **exacerbated these disparities**, with prior research showing **higher short-term mortality among rural dwellers after acute infection.**[2] However, the long-term persistence of this rural-urban mortality gap remains unclear.

This study investigates **long-term (two-year) mortality outcomes following SARS-CoV-2 infection in rural versus urban dwellers**. We hypothesized that **rural residents would experience higher mortality compared to urban dwellers** even after adjusting for **demographics, comorbidities, vaccination status,** and **social vulnerability**.

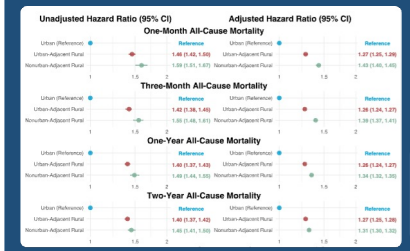
METHODS

- **Population**: SARS-CoV-2-infected patients between April 1, 2020 – June 30, 2022, with follow-up through June 30, 2024, using the National COVID Cohort Collaborative (N3C) Enclave.
- **Key Variables:**
  - **Rurality**: Urban, Urban-Adjacent Rural (UAR), and Nonurban-Adjacent Rural (NAR) based on Rural-Urban Commuting Area (RUCA) Codes at the residential ZIP Code level.
  - **Demographics**: Age, sex, race and ethnicity.
  - **Comorbidities**: Hypertension, diabetes, obesity, substance use, Charlson Comorbidity Index diseases.
  - **COVID-19 factors**: SARS-CoV-2 variant-dominant period, vaccination status at infection.
  - **Community Risk**: Social Vulnerability Index (SVI) at the county level.
- **Outcome**: All-cause mortality at 1-month, 3-months, 1-year, and 2-years post-infection.



- **How We Tested It**
  - **Mortality rates** were calculated at 1-month, 3-months, 1-year, and 2-years post-infection using event rates per 100,000 persons with 95% confidence intervals.
  - **Excess mortality** (per 100,000 persons) for UAR and NAR compared to urban dwellers was calculated at each time point to quantify absolute risk differences.
  - **Cox proportional hazards models** estimated adjusted hazard ratios (aHRs) for 2-year mortality, accounting for demographics, comorbidities, COVID-19 vaccination status, SARS-CoV-2 variant period, and SVI.
  - **Inverse probability weighting (IPW)** was used to reduce confounding and ensure balance across rural-urban strata.

Rural residents had a 27-31% higher adjusted risk of 2-year all-cause mortality post-SARS-CoV-2 infection compared to urban residents, highlighting significant geographic disparities in health outcomes.





Higher 2-Year Mortality

- Rural Residency
- Male Sex
- Older Age
- Black/African American Race
- Higher SVI
- Hypertension, diabetes, cardiovascular disease, chronic kidney disease
- Infection during Delta variant period



Lower 2-Year Mortality

- Urban Residency
- Female Sex
- Younger Age
- Lower SVI
- Lower Comorbid Burden/Multimorbidity
- COVID-19 vaccination(s) before infection
- Infection during Omicron variant period

RESULTS

Cohort Characteristics

- **Total patients (N = 2,658,202)**
  - **Urban:** 2,113,564 (80%)
  - **UAR:** 442,509 (16.6%)
  - **NAR:** 102,129 (3.8%)

Statistical Analyses

- **Adjusted hazard ratios** (Cox models):
  - **UAR:** aHR 1.27 (95% CI 1.25–1.28)
  - **NAR:** aHR 1.31 (95% CI 1.30–1.32)
- **Mortality rates and excess risk:**
  - At **2 years post-infection**, mortality rates were **2,689 per 100,000 (urban), 3,751 per 100,000 (UAR), and 3,887 per 100,000 (NAR)**.
  - **Excess mortality compared to urban dwellers:** +838 per 100,000 (UAR) and +975 per 100,000 (NAR).
- Rural decedents had **higher SARS-CoV-2 reinfection rates** but **lower documented post-COVID diagnoses,** suggesting possible underdiagnosis and reduced healthcare access.

The rural mortality penalty persisted beyond the acute phase of infection, with a **27–31% higher adjusted risk of death for rural dwellers compared to urban residents**.



CONCLUSIONS

This study demonstrates that rural populations face a persistent mortality penalty following SARS-CoV-2 infection, **with a 27–31% higher adjusted risk of two-year all-cause mortality compared to urban dwellers**. The highest excess mortality was observed in nonurban-adjacent rural (NAR) communities.

Why Are These Findings Important?

- **Public Health Implications**: The sustained rural mortality gap reflects **longstanding healthcare disparities**, including limited healthcare access, lower vaccination rates, and higher comorbid burden.
- **Healthcare System Considerations**: Rural decedents had **higher reinfection rates** but **lower post-COVID diagnoses**, suggesting underdiagnosis and reduced healthcare engagement.
- **Targeted Interventions Needed**: Findings highlight the need for rural-focused public health strategies, including improved post-COVID care, and stronger rural health infrastructure.

The long-term impact of COVID-19 on rural residents persisted for two years after infection. These findings reinforce the urgency of addressing rural health disparities and ensuring equitable healthcare access beyond the COVID-19 pandemic.

ADDITIONAL KEY INFORMATION

References

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Author Contact Information

Jerrod Anzalone, PhD
University of Nebraska Medical Center, Omaha, Nebraska, USA
alfred.anzalone@unmc.edu

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Data Availability

The N3C Enclave is available for public research use. More than 4,000 researchers have access to data in N3C, representing more than 300 US research institutions. Institutions must have a signed Data Use Agreement executed with the U.S. National Center for Advancing Translational Sciences (NCATS) to access data. Investigators must complete mandatory training and submit a Data Use Request (DUR) to N3C. To request N3C data access, follow the instructions at https://covid.cd2h.org/onboarding. This project utilized data from N3C release 178, which can be replicated within the Enclave by qualified N3C users.