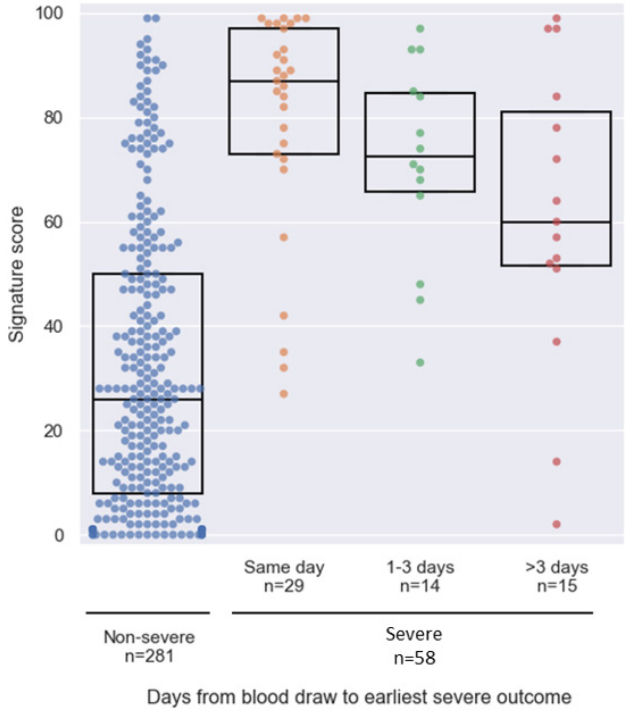
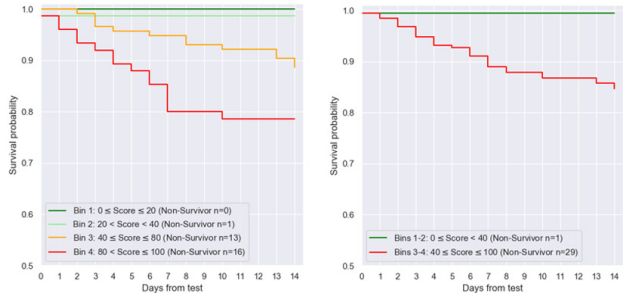
Dots represent patients and boxes denote median and interquartile range (IQR)

The signature score of patients meeting a severe outcome on or after the day of blood draw is significantly ($p < 0.001$) higher than the signature score of non-severe patients.




Dots represents patients and boxes denote median and IQR

Kaplan-Meier survival estimates for signature score bins




***Conclusion.*** The derived signature combined with a rapid measurement platform has potential to serve as an accurate predictive tool for early detection of COVID-19 patients at risk for severe outcome, facilitating timely care escalation and de-escalation and appropriate resource allocation.

***Disclosures.*** **Alon Angel, n/a, MeMed** (Employee, Shareholder) **Niv Samuel Mastboim, BSc, MeMed** (Employee, Shareholder) **Oded Shaham, PhD, MeMed** (Employee, Shareholder) **Tahel Ilan Ber, MD, MeMed** (Employee, Shareholder) **Roy Navon, MSc, MeMed** (Employee, Shareholder) **Einav Simon, PhD, MeMed** (Employee, Shareholder) **Michal Rosenberg, PhD, MeMed** (Employee) **Yael Israeli, PhD, MeMed** (Employee) **Mary Hainrichson, PhD, MeMed** (Employee, Shareholder) **Noa Avni, PhD, MeMed** (Employee) **Eran Reiner, MD, MeMed** (Employee) **Kfir Oved, MD, PhD, MeMed** (Board Member, Employee, Shareholder) **Ilya Kagan, MD, MeMed** (Scientific Research Study Investigator) **Shaul Lev, M.D, MeMed** (Scientific Research Study Investigator) **Dror Diker, MD, MeMed** (Scientific Research Study Investigator) **Amir Jarjou'i, MD, MeMed** (Scientific Research Study Investigator) **Ramzi Kurd, MD, MeMed** (Scientific Research Study Investigator) **Guy Danziger, MD, MeMed** (Scientific Research Study Investigator) **Cihan Papan, MD, MeMed** (Scientific Research Study Investigator) **Sergey Motov, MD, MeMed** (Scientific Research Study Investigator) **Maanit Shapira, Ph.D, MeMed** (Scientific Research Study Investigator) **Tanya Gottlieb, PhD, MeMed** (Employee, Shareholder) **Eran Eden, PhD, MeMed** (Board Member, Employee, Shareholder)

## 33. Evaluation of Rural-Urban Differences in Hospitalization and Mortality Rates for US COVID-19 Patients in the United States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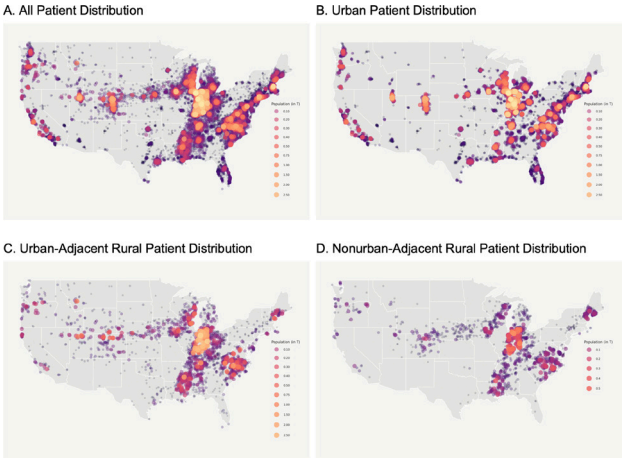
**Session:** O-07. COVID-19 Complications, Co-infections and Clinical Outcomes 2

***Background.*** Rural communities are among the most vulnerable and resource-scarce populations in the United States. Rural data is rarely centralized, precluding comparability across regions, and no significant studies have studied this population at scale. The purpose of this study is to present findings from the National COVID Cohort Collaborative (N3C) to provide insight into future research and highlight the urgent need to address health disparities in rural populations.

N3C Patient Distribution

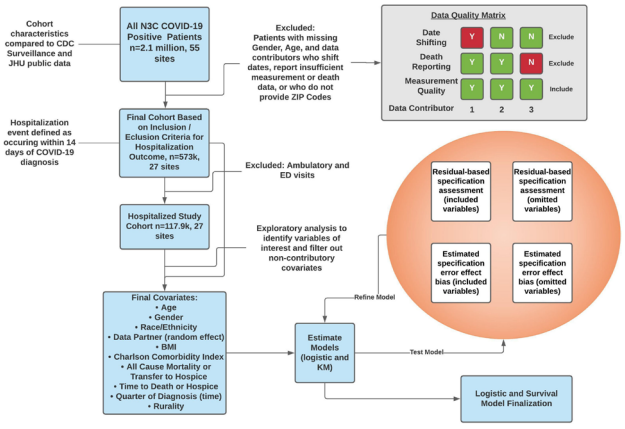



This figure shows the geospatial distribution of the N3C COVID-19 positive population. N3C contains data from 55 data contributors from across the United States, 40 of whom include sufficient location information to map by ZIP Code centroid spatially. Of those sites, we selected 27 whose data met our minimum robustness qualifications for inclusion in our study. This bubble map is to scale with larger bubbles representing more patients. A. shows all N3C patients. B. shows only urban N3C distribution. C. shows the urban-adjacent rural patient distribution. D. shows the nonurban-adjacent rural patient distribution, representing the most isolated patients in N3C.

***Methods.*** This retrospective cohort of 573,018 patients from 27 hospital systems presenting with COVID-19 between January 2020 and March 2021, of whom 117,897 were admitted (see Data Analysis Plan diagram for inclusion/exclusion criteria), analyzes outcomes and 30-day survival for the hospitalized population by the degree of rurality.

Multivariate Cox regression analysis and mixed-effects models were used to estimate the association between rurality, hospitalization, and all-cause mortality, controlling for major risk factors associated with rural-urban health discrepancies and differences in health system outcomes. The difference in distribution by rurality is described as well as supplemented by population-level statistics to confirm representativeness.

Data Analysis Plan




This data analysis plan includes an overview of study inclusion and exclusion criteria, the matrix for data robustness to determine potential sites to include, and our covariate selection, model building, and residual testing strategy.

***Results.*** This study demonstrates a significant difference between hospital admissions and outcomes in urban versus urban-adjacent rural (UAR) and

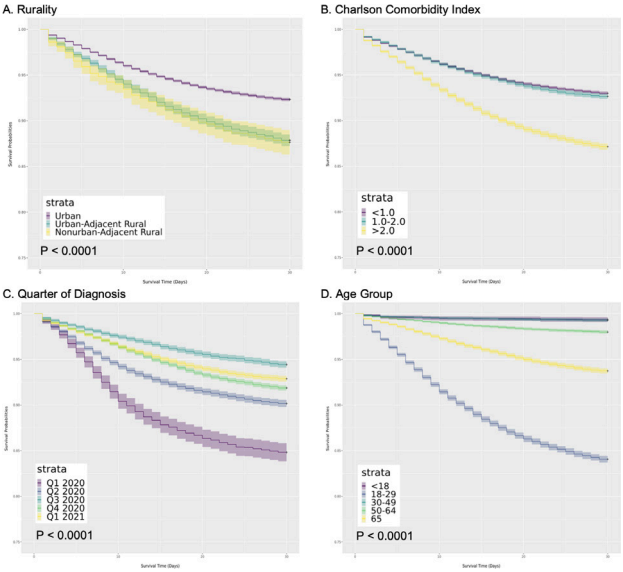
nonurban-adjacent rural (NAR) lines. Hospital admissions for UAR (OR 1.41, p< 0.001, 95% CI: 1.37 – 1.45) and NAR (OR 1.42, p< 0.001, 95% CI: 1.35 – 1.50) were significantly higher than their urban counterparts. Similar distributions were present for all-cause mortality for UAR (OR 1.39, p< 0.001, 95% CI: 1.30 – 1.49) and NAR (OR 1.38, p< 0.001, 95% CI: 1.22 – 1.55) compared to urban populations. These associations persisted despite adjustments for significant differences in BMI, Charlson Comorbidity index Score, gender, age, and the quarter of diagnosis for COVID-19.

Baseline Characteristics Hospitalized COVID-19 Positive Population by Rurality Category, January 2020 – March 2021

| Characteristic | Urban, N = 104,051[1] | Urban-Adjacent Rural, N = 11,121[1] | Nonurban-Adjacent Rural, N = 2,725[1] | *P* value[2] |
|---|---|---|---|---|
| **Gender** | | | | <0.001 |
| Female | 53,905 (52%) | 5,597 (50%) | 1,310 (48%) | |
| Male | 50,146 (48%) | 5,524 (50%) | 1,415 (52%) | |
| **Age Group** | | | | <0.001 |
| <18 | 4,261 (4.1%) | 540 (4.9%) | 91 (3.3%) | |
| 18-29 | 10,199 (9.8%) | 948 (8.5%) | 194 (7.1%) | |
| 30-49 | 24,602 (24%) | 2,117 (19%) | 400 (15%) | |
| 50-64 | 26,583 (26%) | 2,978 (27%) | 770 (28%) | |
| >=65 | 38,406 (37%) | 4,538 (41%) | 1,270 (47%) | |
| **Race** | | | | <0.001 |
| White | 48,067 (46%) | 7,238 (65%) | 1,974 (72%) | |
| Black or AA | 25,858 (25%) | 2,171 (20%) | 473 (17%) | |
| Asian or NHPI | 4,252 (4.1%) | 69 (0.6%) | <20 | |
| Other | 772 (0.7%) | 154 (1.4%) | 47 (1.7%) | |
| Missing/Unknown | 25,102 (24%) | 1,489 (13%) | 224 (8.2%) | |
| **Ethnicity** | | | | <0.001 |
| Not Hispanic or Latino | 77,099 (74%) | 9,649 (87%) | 2,487 (91%) | |
| Hispanic or Latino | 20,611 (20%) | 1,166 (10%) | 172 (6.3%) | |
| Missing/Unknown | 6,341 (6.1%) | 306 (2.8%) | 66 (2.4%) | |
| **BMI Category** | | | | <0.001 |
| <18.5 | 3,856 (3.7%) | 340 (3.1%) | 71 (2.6%) | |
| 18.5-24.9 | 21,035 (20%) | 1,989 (18%) | 496 (18%) | |
| 25-29.9 | 26,721 (26%) | 2,727 (25%) | 669 (25%) | |
| >30 | 41,884 (40%) | 5,367 (48%) | 1,331 (49%) | |
| Unknown/Missing | 10,555 (10%) | 698 (6.3%) | 158 (5.8%) | |
| **Charlson Comorbidity Index Composite** | | | | <0.001 |
| <1.0 | 54,937 (53%) | 5,676 (51%) | 1,328 (49%) | |
| 1.0-2.0 | 23,002 (22%) | 2,283 (21%) | 558 (20%) | |
| >2.0 | 26,112 (25%) | 3,162 (28%) | 839 (31%) | |
| Composite Score (CI) | 0.00 (0.00, 3.00) | 0.00 (0.00, 3.00) | 1.00 (0.00, 3.00) | |
| **Comorbidity Incidence** | | | | |
| Hypertension | 38,141 (37%) | 4,357 (39%) | 1,115 (41%) | <0.001 |
| Diabetes Mellitus | 23,846 (23%) | 2,814 (25%) | 720 (26%) | <0.001 |
| Myocardial Infarction | 6,337 (6.1%) | 799 (7.2%) | 210 (7.7%) | <0.001 |
| Congestive Heart Failure | 11,969 (12%) | 1,501 (13%) | 388 (14%) | <0.001 |
| Peripheral Vascular Disease | 8,964 (8.6%) | 1,166 (10%) | 284 (10%) | <0.001 |
| Stroke | 9,614 (9.2%) | 1,087 (9.8%) | 276 (10%) | 0.061 |
| Dementia | 4,395 (4.2%) | 444 (4.0%) | 129 (4.7%) | 0.2 |
| Chronic Pulmonary Disease | 17,371 (17%) | 1,933 (17%) | 482 (18%) | 0.081 |
| Rheumatologic Disease | 4,088 (3.9%) | 460 (4.1%) | 114 (4.2%) | 0.5 |
| Mild or Severe Liver Disease | 7,426 (7.1%) | 807 (7.3%) | 220 (8.1%) | 0.2 |
| Hemiplegia or paraplegia | 1,835 (1.8%) | 261 (2.3%) | 48 (1.8%) | <0.001 |
| Renal Disease | 13,731 (13%) | 1,716 (15%) | 476 (17%) | <0.001 |
| Any malignancy (except skin) | 10,134 (9.7%) | 1,153 (10%) | 317 (12%) | <0.001 |
| Metastatic solid tumor | 2,426 (2.3%) | 276 (2.5%) | 73 (2.7%) | 0.3 |
| HIV/AIDS | 1,039 (1.0%) | 47 (0.4%) | <20 | <0.001 |
| Multiple Comorbidities | 54,110 (52%) | 5,940 (53%) | 1,509 (55%) | <0.001 |
| Current or former smoker | 38,099 (37%) | 2,384 (21%) | 714 (26%) | <0.001 |
| **Outcomes** | | | | |
| Any Oxygen Support | 13,388 (13%) | 2,079 (19%) | 588 (22%) | <0.001 |
| Any Mechanical Ventilation | 10,087 (9.7%) | 1,867 (17%) | 477 (18%) | <0.001 |
| Hospital Readmission | 3,306 (3.2%) | 188 (1.7%) | 32 (1.2%) | <0.001 |
| ECMO or MACE | 947 (0.9%) | 174 (1.6%) | 46 (1.7%) | <0.001 |
| All-Cause Mortality | 11,240 (11%) | 1,763 (16%) | 455 (17%) | <0.001 |
| Time to Death in Days (CI) | 13 (6, 28) | 14 (7, 27) | 14 (5, 27) | 0.6 |
| **Quarter of Diagnosis** | | | | <0.001 |
| Jan-Mar 2020 | 6,145 (5.9%) | 85 (0.8%) | 25 (0.9%) | |
| Apr-Jun 2020 | 24,478 (24%) | 1,507 (14%) | 438 (16%) | |
| Jul-Sep 2020 | 15,851 (15%) | 2,114 (19%) | 482 (18%) | |
| Oct-Dec 2020 | 32,856 (32%) | 4,337 (39%) | 995 (37%) | |
| Jan-Mar 2021 | 24,721 (24%) | 3,078 (28%) | 785 (29%) | |

[1] Statistics presented: n (%)
[2] Statistical tests performed: chi-square test of independence

Survival Curves in Hospitalized Patients Over 30 Days from Day of Admission




This figure shows a survival plot of COVID-19 positive hospitalized patients in N3C by rural category (A), Charlson Comorbidity Index (B), Quarter of Diagnosis (C), and Age Group (D) from hospital admission through day 30. Events were censored at day 30 based on the incidence of death or transfer to hospice care. These four factors had the highest predictive power of the covariates evaluated in this study.

Unadjusted and Adjusted Odds Ratios for Hospitalization and All-Cause Mortality by Rural Category, January 2020 – March 2021

| **A. Unadjusted Odds-Ratios for COVID-19 Hospitalization** | | | **B. Unadjusted Odds-Ratios for All-Cause Mortality** | |
|---|---|---|---|---|
| **Covariate** | Odds ratio (95% CI) | *P* Value | Odds ratio (95% CI) | *P* Value |
| Rurality | | | | |
| Urban | Reference | | Reference | |
| Urban-Adjacent Rural | 1.62 (1.58, 1.66) | <0.001 | 1.45 (1.37, 1.54) | <0.001 |
| Nonurban-Adjacent Rural | 1.61 (1.54, 1.69) | <0.001 | 1.56 (1.41, 1.74) | <0.001 |
| **C. Adjusted Odds-Ratios for COVID-19 Hospitalization** | | | **D. Adjusted Odds-Ratios for All-Cause Mortality** | |
| **Covariate** | Odds ratio (95% CI) | *P* Value | Odds ratio (95% CI) | *P* Value |
| Gender | | | | |
| Female | Reference | | Reference | |
| Male | 1.25 (1.23, 1.27) | <0.001 | 1.49 (1.43, 1.55) | <0.001 |
| Race | | | | |
| White | Reference | | Reference | |
| Black or AA | 1.65 (1.61, 1.68) | 0.3 | 1.00 (0.95, 1.06) | 0.9 |
| Asian or NHPI | 1.61 (1.55, 1.69) | 0.002 | 1.29 (1.15, 1.44) | <0.001 |
| Other | 1.68 (1.54, 1.84) | 0.002 | 1.77 (1.43, 2.18) | <0.001 |
| Missing or Unknown | 1.51 (1.47, 1.55) | 0.5 | 1.16 (1.08, 1.25) | 0.14 |
| Ethnicity | | | | |
| Not Hispanic/Latinx | Reference | | Reference | |
| Hispanic/Latinx | 1.44 (1.40, 1.48) | 0.7 | 1.06 (0.98, 1.15) | <0.001 |
| Missing or Unknown | 0.61 (0.59, 0.64) | 0.036 | 1.34 (1.20, 1.49) | <0.001 |
| BMI | 1.01 (1.01, 1.01) | <0.001 | 1.01 (1.00, 1.01) | <0.001 |
| Age | 1.03 (1.03, 1.03) | <0.001 | 1.06 (1.05, 1.06) | <0.001 |
| CCI Index | 1.17 (1.16, 1.17) | <0.001 | 1.09 (1.08, 1.09) | <0.001 |
| Quarter of Diagnosis | | | | |
| Jan-Mar 2020 | 3.14 (3.00, 3.29) | <0.001 | 2.83 (2.57, 3.12) | <0.001 |
| Apr-Jun 2020 | 1.38 (1.35, 1.42) | <0.001 | 1.92 (1.79, 2.06 | <0.001 |
| Jul-Sep 2020 | Reference | | Reference | |
| Oct-Dec 2020 | 0.90 (0.88, 0.92) | <0.001 | 1.11 (1.04, 1.19 | 0.002 |
| Jan-Mar 2021 | 1.00 (0.97, 1.02) | <0.001 | 0.88 (0.82, 0.95) | <0.001 |
| Rurality | | | | |
| Urban | Reference | | Reference | |
| Urban-Adjacent Rural | 1.41 (1.37, 1.45) | <0.001 | 1.39 (1.30, 1.49) | <0.001 |
| Nonurban-Adjacent Rural | 1.42 (1.35, 1.50) | <0.001 | 1.38 (1.22, 1.55) | <0.001 |

This figure shows the adjusted and unadjusted odds ratios for being hospitalized or dying after hospitalization for the COVID-19 positive population in N3C. Risk is similar between adjusted and unadjusted models, suggesting a real impact of rurality on all-cause mortality. A shows the unadjusted odds ratios for admission to the hospital after a positive COVID-19 diagnosis for all N3C patients. B shows the unadjusted odds ratios for all-cause mortality at any point after hospitalization for COVID-19 positive patients. C shows the adjusted odds ratios for being admitted to the hospital after a positive COVID-19 diagnosis for all N3C patients. D shows the adjusted odds ratios for all-cause mortality for all-cause mortality at any point after hospitalization for COVID-19 positive patients. Adjusted models include adjustments for gender, race, ethnicity, BMI, age, Charlson Comorbidity Index (CCI) composite score, rurality, and quarter of diagnosis. The data provider is included as a random effect in all models.

***Conclusion.*** In N3C, we found that hospitalizations and all-cause mortality were greater among rural populations when compared to urban populations after adjustment for several factors, including age and co-morbidities. This study also identified key demographic and clinical disparities among rural patients that require further investigation.

***Disclosures.*** **Sally L. Hodder, M.D., Gilead** (Advisor or Review Panel member)**Merck** (Grant/Research Support, Advisor or Review Panel member)**Viiv Healthcare** (Grant/Research Support, Advisor or Review Panel member)

**34. Long-term clinical outcomes following SARS-CoV-2 infection include persistent symptoms and cardiovascular disease beyond 3 months post-infection**

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