

RESEARCH ARTICLE

Rural-urban outcome differences associated with COVID-19 hospitalizations in North Carolina

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Abstract

People living in rural regions in the United States face more health challenges than their non-rural counterparts which could put them at additional risks during the COVID-19 pandemic. Few studies have examined if rurality is associated with additional mortality risk among those hospitalized for COVID-19. We studied a retrospective cohort of 3,991 people hospitalized with SARS-CoV-2 infections discharged between March 1 and September 30, 2020 in one of 17 hospitals in North Carolina that collaborate as a clinical data research network. Patient demographics, comorbidities, symptoms and laboratory data were examined. Logistic regression was used to evaluate associations of rurality with a composite outcome of death/hospice discharge. Comorbidities were more common in the rural patient population as were the number of comorbidities per patient. Overall, 505 patients died prior to discharge and 63 patients were discharged to hospice. Among rural patients, 16.5% died or were discharged to hospice vs. 13.3% in the urban cohort resulting in greater odds of death/hospice discharge (OR 1.3, 95% CI 1.1, 1.6). This estimate decreased minimally when adjusted for age, sex, race/ethnicity, payer, disease comorbidities, presenting oxygen levels and cytokine levels (adjusted model OR 1.2, 95% CI 1.0, 1.5). This analysis demonstrated a higher COVID-19 mortality risk among rural residents of NC. Implementing policy changes may mitigate such disparities going forward.

Wake Forest University) to provide for use of these data. These DUAs prohibit us from sharing the data outside of UNC Chapel Hill. Additionally, the University of North Carolina at Chapel Hill also employs strict data security controls which require that the data be stored and analyzed on a UNC Chapel Hill provided secure research workspace. No investigators have the authority to remove these data from the secure workspace for sharing or any purpose. While we understand and appreciate the journal's data sharing policy, we are unable to provide these data to the journal due to these legal and security restrictions. A letter from Mr. Andy Johns has been uploaded along with this submission to detail our legal restriction to the public sharing of data. The University of North Carolina at Chapel Hill can be listed as the institutional body to which general data requests can be sent and emails communications can go to andy_johns@unc.edu.

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Introduction

Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a global pandemic. As of July 22, 2021, COVID-19 has resulted in 607,289 deaths in the US. Although numerous analyses have been devoted to understanding what patient comorbidities, demographics, behaviors, laboratory values and medical interventions received are associated with dying of COVID-19 [1–5], few studies have specifically tried to determine if “rurality” of a patient's residence increases mortality risk [6–9] and none to date have focused on residents of North Carolina (NC).

One in seven Americans reside in one of the 1,976 counties designated as rural by the 2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties in 2018 [10]. Rural populations in the US have shorter life expectancies [11], lower median incomes [11], greater prevalence of comorbid health conditions such as cancer, heart disease, diabetes, hypertension, and obesity [12, 13]. They are also older [14] with a population mean age of 51 in rural compared to 45 in urban regions [15]. As well, they have lower access to healthcare: only 1% of the nation's ICU beds are located in rural areas [16]. Over 4.7 million people live in 460 rural counties across the nation where there are no general medical or surgical hospital beds, and 16.4 million people live in rural areas with no medical/surgical intensive care unit (ICU) beds [17]. Health care facilities within rural communities are typically less resourced with reduced access to personal protective equipment, ICU beds, testing, and the necessary equipment to effectively treat people most severely affected by COVID-19 infection complications, which are commonly older adults [18]. As a result, many rural hospitals find themselves needing to transfer residents with more serious cases of COVID-19 to larger facilities in urban areas for treatment [19]. Hospital transfers require time, and that can affect disease outcomes in critical situations. Relocating patients to urban areas may present additional challenges if the receiving hospital is already overwhelmed [20].

With rural communities at a notable disadvantage in terms of COVID-19 health outcomes related to healthcare and population demographics, and with COVID-19 proving to be a more intense burden on older populations, we hypothesize that individuals in rural areas will face more risk of COVID-19-associated death compared to comparable individuals in urban areas [7, 21].

NC has 21.2% of its people living in rural areas [22]. Similar to national trends, NC rural areas are inhabited by people who are older, and more likely to be uninsured [23]. NC reported a significant increase in COVID-19 burden in rural areas in September 2020, with rural areas making up the majority of state cases and deaths [24]. NC has also endured 7 rural hospital closures since 2010 [25]. Thus, it is important to understand NC-level data specific to rurality.

The purpose of this study is to understand if rural patients with COVID-19 experienced a different risk of death compared to their urban counterparts. This study describes the demographics, baseline comorbidities, clinical test results, and deaths among hospitalized patients with COVID-19 in three academic health systems in NC.

Methods

Study setting and population

We identified hospital patients with infection and/or a COVID-19 diagnosis who received care in one of three large, NC-based academic health systems: University of North Carolina Chapel Hill (UNC Chapel Hill), Duke University and Wake Forest Baptist Health. These three health systems have 17 hospitals spanning 13 counties of NC (Fig 1) and are part of a distributed research network named PCORnet, the National Patient-Centered Clinical Research

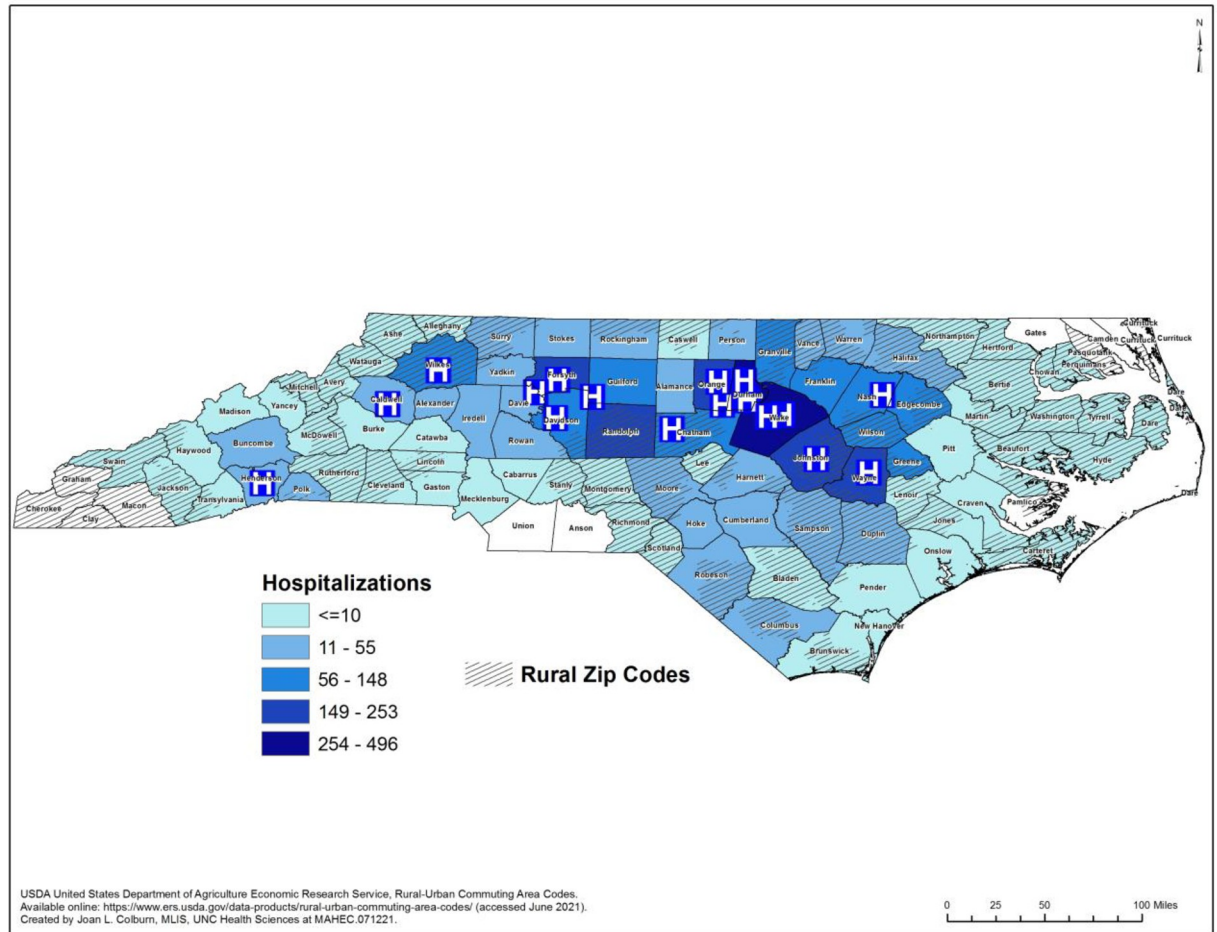


Fig 1. Map of hospitalizations by rural and urban zip codes. Map of rural and urban zip codes with the number of COVID-19 hospitalizations per county between March 1 and September 30, 2020. Locations of hospitals included in this study are shown with an “H”.

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Network® [26]. PCORnet is funded in part by the Patient Centered Outcomes Research Institute where institution-specific patient data such as vital signs, demographics, laboratory test results and care delivered are harmonized. In NC, many larger health systems have invested in methods to harmonize and aggregate hospital level data generated initially from electronic health record data in order to better understand the care processes and outcomes of patients. UNC Health, Duke and Wake Forest Baptist Health have worked for over 10 years to engage in such efforts to support multi-site research studies and during the COVID-19 pandemic, developed limited data sets, as defined by the Health Insurance Portability and Accountability Act (HIPAA), to better understand outcomes of patients cared for in consortium hospitals. As a result, those data have a common format to facilitate data aggregation, multi-site involvement and analyses. PCORnet uses a common data model to facilitate queries of standardized data [26] and during the COVID-19 pandemic, supported the creation of a COVID-19 specific common data model to allow for ready access to harmonized COVID-19 specific clinical data.

We collaborated with investigators at UNC-Chapel Hill to develop a COVID-19 case definition and query program, which was initially run at the UNC site and then at the Duke University and Wake Forest Baptist Health sites to identify inpatients (including emergency to inpatient stays) who had an identified SARS-CoV-2 infection and/or a COVID-19 diagnosis

and had a discharge date (which includes those that died) between March 1, 2020 and September 30, 2020. COVID-19 diagnosis was determined by the patient having a diagnosis code of B97.29, B97.21 (before April 1, 2020) or U07.1 [27]. SARS-CoV-2 identification was based on having a positive or detected status on a SARS-CoV-2 lab. For patients with multiple visits, the first inpatient encounter during the study time period with noted COVID-19 was included. People who were identified as prisoners were removed from the dataset. This study was deemed exempt from further review by the UNC-Chapel Hill, Duke University Health System, Wake Forest School of Medicine School of Medicine and UNC Asheville Institutional Review Boards. Since this study analyzed existing clinical data using a limited data set, the reviewing Institutional Review Boards deemed the data as secondary research for which consent is not required. Therefore, individual participant consent was waived for this study.

Data elements and analysis

We electronically collected information on patient demographics (age, sex, race/ethnicity, insurance status and zip code), hospital stay characteristics (dates of admission and discharge, intensive care unit stay, ventilator use, and discharge status), smoking status, vital measurements and specific laboratory values (as listed in the tables), and all encounter-related ICD-10-CM diagnosis codes (discharge and final). The main outcome of interest was a composite of in-hospital death or discharge to hospice.

Rural status was determined from patient zip code using Rural Urban Commuting Area Codes [28] with zip codes in metropolitan areas (codes 1–3) categorized as urban and the remaining zip codes (codes 4–10) as rural. Patient zip code was also used to assign a patient county of residence using a method developed by the United States Department of Housing and Urban Development [29]. Race and ethnicity were combined into a race/ethnicity variable following the approach adopted by the Agency for Healthcare Research and Quality [30, 31]. For insurance status, patients with unknown payor who were 65 years or older were considered to have Medicare.

The Comorbidity package in R [32] was used to identify the presence of relevant comorbidities from ICD-10 diagnosis codes (acute myocardial infarction, congestive heart failure, hypertension, chronic obstructive pulmonary disease (COPD), diabetes, renal disease, cancer, liver disease, coagulopathy, or obesity) and to calculate both the Charlson [33, 34] and Elixhauser comorbidity [35] scores. The coding algorithm used by the Comorbidity package can be found in Quan et al. 2005 [36].

We conducted descriptive analyses including: percentage of patient population with assessed characteristics that had the composite outcome of death/discharge to hospice, the percentage point difference in risk of outcome from a chosen reference stratum (subtraction of percentages) and the relative risk of outcome compared to a reference stratum (division of proportions). Additionally, we used logistic regression to evaluate rurality in association with the composite outcome of odds of death/hospice discharge. To explore how much of the increase in outcome of death/hospice discharge seen for rural-dwelling individuals could be explained by socio-demographic characteristics, comorbid conditions, and presenting health status, we used a multivariable model including rural zip code (yes/no); age (age, age², age³), sex (female/male), race/ethnicity (non-Hispanic Black; Hispanic; non-Hispanic White; Other, non-Hispanic; and Missing race, non-Hispanic), insurance status (Commercial, Medicaid, Medicare, Self-pay, and missing), smoking status (current, former, never and missing), comorbidities (Charlson comorbidity index: 0, 1–2, 3–4, > = 5, missing), first recorded oxygen saturation with hospital or emergency room visit (<93%, > = 93%, missing), indicators of an inflammatory response [yes: low lymphocyte (< = 0.8 10³/uL), or elevated levels of troponin (> = 0.1

ng/ml), procalcitonin (>0.5 ng/mL), or C-reactive protein (CRP) (> 15 mg/dL); no: having a normal result present for any of the above listed criteria; missing: missing all 4 values] and hospital system (Duke, UNC, Wake). Analyses were performed using R version 3.5.2 (R Project for Statistical Computing; R Foundation) and SAS version 9.4 (SAS Institute Inc., Cary, NC). The map was created using ArcGIS version 10.8.1 (ESRI, Redlands, CA).

Results

There were 3,991 inpatients with SARS-CoV-2 infection or COVID-19 diagnosis hospitalized in one of the 17 hospitals during the timeframe, with 1,977 seen at a UNC health system hospital, 1,220 at a Duke system hospital, and 735 at a Wake Forest system hospital. The majority of patients (3,856) lived in one of 89 NC counties (Fig 1). Sixty-seven patients lived out-of-state, and 68 patients were missing zip code information. Most of the included patients (76%) came from urban settings (See Table 1 for overall descriptive data including Urban vs. Rural comparisons). Hypertension was the most common comorbidity (72.2% of the study population) followed by diabetes (52.3%). The median age in the rural cohort was 63 (IQR 49–73) years and 62 (IQR 26–74) in the urban group. While Medicare was the most common insurance type overall (49% overall), Medicaid coverage was the second most common coverage for urban patients, with commercial coverage second for rural patients. Smoking status was similar across the urban and rural patient populations. All comorbidities were more common in the rural patient population as compared to the urban patient population, and the number of comorbidities per patient was also more common among the rural population which resulted in higher Charlson and Elixhauser comorbidity indices (Fig 2).

Table 2 shows the percentage of patients overall who died/were discharged to hospice within each stratum (row) by study characteristic. Overall, 505 patients (13%; rural, urban and missing zip code) died prior to discharge and 63 patients (2%) were discharged to hospice. Among patients living in rural areas, 16.5% died or were discharged to hospice vs. 13.3% in the urban cohort resulting in a 3.2 (CI 0.6–5.9) percentage point increase in death for the rural cohort. The percentage of patients who died/were discharged to hospice was higher among males and increased with age. While 3% of patients aged 35–45 died/were discharged to hospice, this was the outcome for 32% of those aged 75+. Patients with comorbidities had a higher percentage of death/hospice discharge as compared to patients without the comorbidity for all assessed conditions except for uncomplicated hypertension and obesity (Table 2). Patients

Table 1. Demographics, characteristics and comorbidities of patients hospitalized with a SARS-CoV-2 infection or COVID-19 diagnosis, total and stratified by rural/urban zip codes.

	Total n = 3991		Urban n = 2978		Rural n = 945	
	n	Column %	n	Column %	n	Column %
Age						
Median age (IQR)	62 (47–74)		62 (46–74)		63 (49–73)	
0 to 17	114	2.9	81	2.7	33	3.5
18 to 34	426	10.7	326	10.9	90	9.5
35 to 44	370	9.3	297	10.0	71	7.5
45 to 54	520	13.0	392	13.2	116	12.3
55 to 64	795	19.9	572	19.2	207	21.9
65 to 74	843	21.1	596	20.0	234	24.8
75+	922	23.1	713	23.9	194	20.5
Missing	1	0	1	0	0	0
Sex						

(Continued)

Table 1. (Continued)

	Total n = 3991		Urban n = 2978		Rural n = 945	
	n	Column %	n	Column %	n	Column %
Female	2037	51.0	1587	53.3	432	45.7
Male	1953	48.9	1390	46.7	513	54.3
Missing	1	0	1	0	0	0
Race/Ethnicity						
Black, NH	1365	34.2	1053	35.4	293	31.0
Hispanic	903	22.6	650	21.8	233	24.7
White, NH	1489	37.3	1095	36.8	371	39.3
Other, NH	166	4.2	138	4.6	28	3.0
Unknown, NH	68	1.7	42	1.4	20	2.1
Insurance Status						
Commercial	492	12.3	344	11.6	148	15.7
Medicaid	595	14.9	458	15.4	131	13.9
Medicare	1962	49.2	1457	48.9	479	50.7
Self-pay	192	4.8	157	5.3	32	3.4
Missing	750	18.8	562	18.9	155	16.4
Smoking						
Current Smoker	231	5.8	170	5.7	58	6.1
Former smoker	1264	31.7	949	31.9	294	31.1
Never smoker	2203	55.2	1680	56.4	495	52.4
Missing	293	7.3	179	6.0	98	10.4
Comorbidities:	n = 3965		n = 2960		n = 938	
Acute myocardial infarction	425	10.7	302	10.2	123	13.1
Congestive heart failure	782	19.7	576	19.5	197	21.0
Hypertension, uncomplicated	1698	42.8	1240	41.9	440	46.9
Hypertension, complicated	1167	29.4	854	28.9	296	31.6
COPD	924	23.3	685	23.1	225	24.0
Diabetes without complications	1304	32.9	953	32.2	339	36.1
Diabetes with complications	770	19.4	559	18.9	203	21.6
Renal disease	916	23.1	666	22.5	234	24.9
Cancer (any malignancy)	237	6.0	171	5.8	63	6.7
Liver disease	241	6.1	171	5.8	64	6.8
Coagulopathy	702	17.7	506	17.1	180	19.2
Obesity	1138	28.7	847	28.6	276	29.4
Charlson Comorbidity Score						
Median (IQR)	1 (0–3)		1 (0–2)		1 (1–3)	
0	1090	27.5	842	28.4	230	24.5
1–2	1874	47.3	1391	47.0	442	47.1
3–4	822	20.7	596	20.1	219	23.3
> = 5	179	4.5	131	4.4	47	5.0
Elixhauser Score						
Median (IQR)	4 (2–6)		4 (2–6)		4 (2–6)	
0	308	7.8	225	7.6	77	8.2
1–4	2027	51.1	1563	52.8	429	45.7
> = 5	1630	41.1	1172	39.6	432	46.1

IQR = interquartile range; NH = non-Hispanic; COPD = chronic obstructive pulmonary disease

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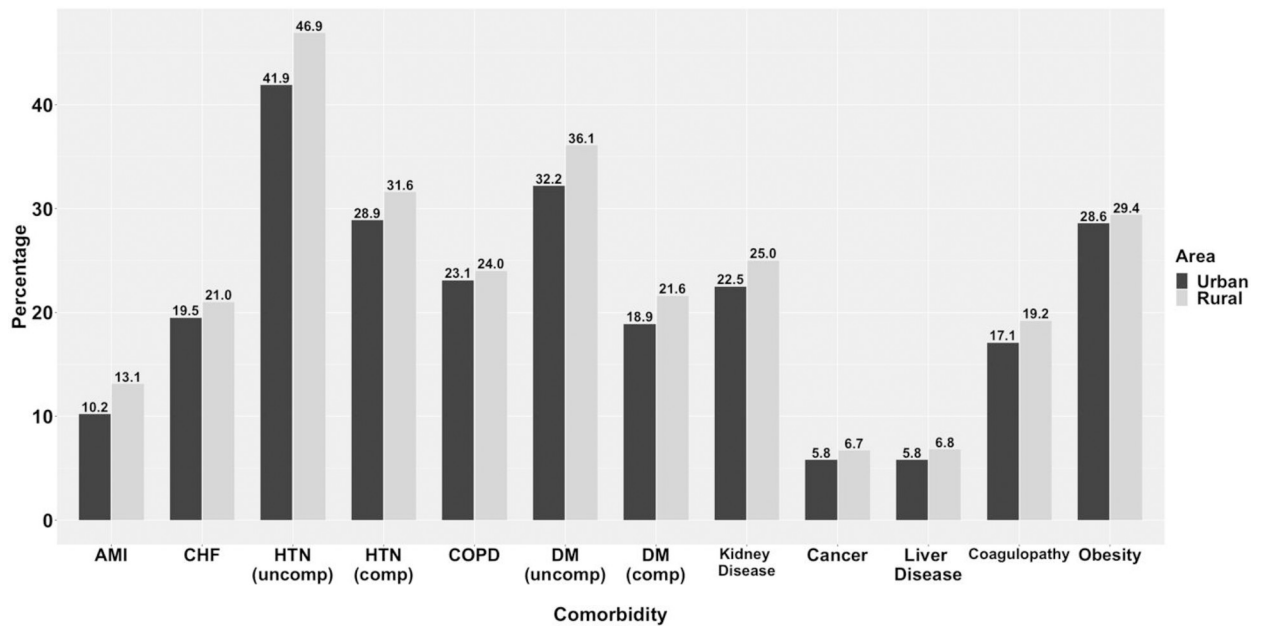


Fig 2. Comparison of rural and urban areas by comorbidity. Comparison of unadjusted comorbidity incidence between rural and urban residents hospitalized in North Carolina for COVID-19. AMI: Acute Myocardial Infarction, CHF: Congestive Heart Failure, HTN: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus.

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Table 2. Demographics, characteristics and comorbidities and percentage of death/hospice discharge for patients hospitalized with a SARS-CoV-2 infection or COVID-19 diagnosis.

	n	n death/hospice	stratum (row) %	percentage point difference (95% CI)	relative ratio (95% CI)
Rural*					
yes	945	156	16.5%	3.2 (0.6, 5.9)	1.2 (1.0, 1.5)
no	2978	395	13.3%	0 (ref)	1 (ref)
Age category					
0 to 17	114	<10	ns	-	-
18 to 34	426	<10	ns	-	-
35 to 44	370	11	3.0%	0 (ref)	1 (ref)
45 to 54	520	33	6.3%	3.4 (0.7, 6.1)	2.1 (1.1, 4.2)
55 to 64	795	79	9.9%	7.0 (4.3, 9.7)	3.3 (1.8, 6.2)
65 to 74	843	151	17.9%	14.9 (11.8, 18.1)	6.0 (3.3, 11.0)
75+	922	290	31.5%	28.5 (25.0, 31.9)	10.6 (5.9, 19.1)
Sex					
Female	2037	250	12.3%	0 (ref)	1 (ref)
Male	1953	318	16.3%	4.0 (1.8, 6.2)	1.3 (1.1, 1.5)
Race/Ethnicity					
Black, NH	1365	193	14.1%	-4.1 (-6.8, -1.4)	0.8 (0.7, 0.9)
Hispanic	903	63	7.0%	-11.3 (-13.9, -8.7)	0.4 (0.3, 0.5)
White, NH	1489	272	18.3%	0 (ref)	1 (ref)
Other, NH	166	22	13.3%	-5.0 (-10.5, 0.5)	0.7 (0.5, 1.1)
Unknown, NH	68	18	26.5%	8.2 (-2.5, 18.9)	1.4 (1.0, 2.2)
Insurance Status					
Commercial	492	27	5.5%	0 (ref)	1 (ref)

(Continued)

Table 2. (Continued)

	n	n death/hospice	stratum (row) %	percentage point difference (95% CI)	relative ratio (95% CI)
Medicaid	595	32	5.4%	-0.1 (-2.8, 2.6)	1.0 (0.6, 1.6)
Medicare	1962	459	23.4%	17.9 (15.2, 20.7)	4.3 (2.9, 6.2)
Self-pay	192	<10	ns	-	-
Smoking					
Current smoker	231	26	11.3%	-0.5 (-4.8, 3.8)	1.0 (0.7, 1.4)
Former smoker	1264	208	16.5%	4.7 (2.3, 7.2)	1.4 (1.2, 1.7)
Never smoker	2203	258	11.7%	0 (ref)	1 (ref)
Comorbidities:					
Acute myocardial infarction	425	124	29.2%	16.7 (12.2, 21.2)	2.3 (2.0, 2.8)
Congestive heart failure	782	198	25.3%	13.8 (10.5, 17.0)	2.2 (1.9, 2.6)
Hypertension, uncomplicated	1698	243	14.3%	0 (-2.1, 2.3)	1.0 (0.9, 1.2)
Hypertension, complicated	1167	273	23.4%	12.9 (10.2, 15.6)	2.2 (1.9, 2.6)
COPD	924	164	17.7%	4.5 (1.8, 7.3)	1.3 (1.1, 1.6)
Diabetes without complications	1304	215	16.5%	3.3 (0.9, 5.7)	1.3 (1.1, 1.5)
Diabetes with complications	770	167	21.7%	9.2 (6.1, 12.3)	1.7 (1.5, 2.0)
Renal disease	916	215	23.5%	12.0 (9.0, 14.9)	2.0 (1.7, 2.4)
Cancer (any malignancy)	237	61	25.7%	12.2 (6.5, 17.9)	1.9 (1.5, 2.4)
Liver disease	241	61	25.3%	11.8 (6.2, 17.4)	1.9 (1.5, 2.4)
Coagulopathy	702	199	28.3%	17.1 (13.6, 20.6)	2.5 (2.2, 2.9)
Obesity	1138	154	13.5%	-1.0 (-3.4, 1.3)	0.9 (0.8, 1.1)
Charlson Comorbidity Score					
0	1090	42	3.9%	0 (ref)	1 (ref)
1–2	1874	264	14.1%	10.2 (8.3, 12.2)	3.7 (2.7, 5.0)
3–4	822	193	23.5%	19.6 (16.5, 22.7)	6.1 (4.4, 8.4)
> = 5	179	67	37.4%	33.6 (26.4, 40.8)	9.7 (6.8, 13.8)
Elixhauser Score					
0	308	<10	ns	-	-
1–4	2027	145	7.2%	0 (ref)	1 (ref)
> = 5	1630	420	25.8%	18.6 (16.2, 21.0)	3.6 (3.0, 4.3)

CI = confidence interval; ns = not shown; NH = non-Hispanic; COPD = chronic obstructive pulmonary disease

*Zip code was missing for 68 patients; patient number does not add up to 3991 and death/hospice does not add up to 505

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with acute myocardial infarction and coagulopathy had the highest percentage of death/hospice discharge, each at 29%. Further, patient groups with higher Charlson and Elixhauser comorbidity scores had higher percentages of death/hospice discharge.

The majority of patients presented without fever (<100.4F), and 22% of patients had initial oxygen saturations below 93% (Table 3). Low oxygen saturation was more common in the rural patient population as compared to the urban patient population (24% versus 21%). Median BMI was 30 and was similar across both urban and rural populations. Rural patients more commonly had lower lymphocyte counts and more commonly showed signs of hyperinflammation via markers including C-reactive protein, D-dimer, and Procalcitonin.

The percentage of patients who died/were discharged to hospice was higher in those with lower initial oxygen saturation values (Table 4). Death/discharge to hospice was less common for patients with increasingly higher BMI. Patient groups with lower lymphocyte counts had higher percentages of death/hospice discharge. For markers of a hyperinflammatory response,

Table 3. Initial vitals and labs of patients hospitalized with a SARS-CoV-2 infection or COVID-19 diagnosis, total and stratified by rural/urban zip codes.

	Total		Urban		Rural	
	n	Column %	n	Column %	n	Column %
Temperature, °F	n = 3792		n = 2819		n = 912	
Median (IQR)	99 (98–100)		99 (98–100)		99 (98–100)	
< 100.4	3064	80.8	2239	79.4	773	84.8
100.4–102.2	491	12.9	389	13.8	96	10.5
>102.2	237	6.3	191	6.8	43	4.7
Oxygen saturation, %	n = 3978		n = 2967		n = 943	
Median (IQR)	96 (93–98)		96 (93–98)		96 (93–98)	
93–100	3114	78.3	2338	78.8	720	76.4
89–92	503	12.6	371	12.5	126	13.4
< = 88	361	9.1	258	8.7	97	10.3
BMI	n = 3149		n = 2368		n = 730	
Median (IQR)	30 (25–36)		30 (25–36)		30 (25–36)	
<18.5	100	3.2	68	2.9	30	4.1
18.5–24.9	631	20.0	482	20.4	136	18.6
25–29.9	827	26.3	620	26.2	191	26.2
30–39.9	1150	36.5	858	36.2	277	37.9
40+	441	14.0	340	14.4	96	13.2
Lymphocyte, (10 ³ /ul)	n = 3600		n = 2699		n = 838	
Median (IQR)	0.9 (0.6–1.4)		1.0 (0.7–1.4)		0.9 (0.6–1.3)	
>1.2	1100	30.6	846	31.3	236	28.2
>0.8–1.2	989	27.5	768	28.5	206	24.6
0.5–0.8	1113	30.9	805	29.8	287	34.2
<0.5	398	11.1	280	10.4	109	13.0
Aspartate aminotransferase, U/L	n = 3665		n = 2732		n = 868	
Median (IQR)	37 (26–58)		37 (26–57)		39 (27–61)	
< = 33	1530	41.7	1150	42.1	356	41.0
>33	2135	58.3	1582	57.9	512	59.0
Alanine aminotransferase, U/L	n = 3667		n = 2735		n = 868	
Median (IQR)	27 (18–45)		27 (18–45)		27 (18–46)	
< = 34	2318	63.2	1730	63.3	548	63.1
>34	1349	36.8	1005	36.7	320	36.9
Creatinine, mg/dL	n = 3800		n = 2837		n = 895	
Median (IQR)	1.0 (0.8–1.5)		1.0 (0.8–1.4)		1.0 (0.8–1.6)	
0–1.1	2313	60.9	1761	62.1	517	57.8
> 1.1–2	912	24.0	674	23.8	221	24.7
>2	575	15.1	402	14.2	157	17.5
Troponin, ng/mL	n = 2248		n = 1675		n = 549	
Median (IQR)	0.03 (0.02–0.10)		0.03 (0.01–0.11)		0.03 (0.02–0.09)	
<0.1	1681	74.8	1244	74.3	416	75.8
0.1–1	507	22.6	390	23.3	114	20.8
>1	60	2.7	41	2.5	19	3.5
Procalcitonin, ng/mL	n = 1619		n = 1313		n = 292	
Median (IQR)	0.2 (0.1–0.4)		0.2 (0.1–0.4)		0.2 (0.1–0.5)	
0–0.5	1267	78.3	1035	78.8	223	76.4
>0.5	352	21.7	278	21.2	69	23.6
D-Dimer, ng/mL	n = 514		n = 285		n = 229	

(Continued)

Table 3. (Continued)

	Total		Urban		Rural	
	n	Column %	n	Column %	n	Column %
median (IQR)	474 (249–1066)		422 (236–955)		540 (264–1194)	
< = 500	265	51.6	159	55.8	106	46.3
501–1000	111	21.6	56	19.6	55	24.0
>1000	138	26.8	70	24.6	68	29.7
Ferritin, ng/mL	n = 2329		n = 1687		n = 598	
Median (IQR)	439 (200–877)		434 (199–869)		462 (199–900)	
0–250	713	30.6	518	30.7	182	30.4
>250–500	567	24.3	419	24.8	134	22.4
>500–1000	545	23.4	383	22.7	152	25.4
>1000–2500	382	16.4	281	16.7	96	16.1
>2500	122	5.2	86	5.1	34	5.7
C-reactive protein, mg/L	n = 2227		n = 1624		n = 564	
Median (IQR)	71 (24–155)		68 (21–148)		79 (32–172)	
0–15	411	18.5	324	20.0	81	14.4
>15–100	949	42.6	697	42.9	242	42.9
>100–200	533	23.9	378	23.3	139	24.6
>200	334	15	225	13.9	102	18.1

IQR = interquartile range; BMI = body mass index

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except for alanine aminotransferase, patient groups with higher values had a larger percentage of death/discharge to hospice.

Further evaluation of rurality with the composite outcome of odds of death/hospice discharge using logistic regression demonstrated that rural patients had 1.3 times the odds of dying/hospice discharge as compared to urban patients (crude model: 95% CI 1.1, 1.6). The estimate decreased minimally when adjusted for age, sex, race/ethnicity, payer, disease comorbidities, presenting oxygen levels and cytokine levels, and hospital system (adjusted model OR 1.2, 95% CI 1.0, 1.5).

Discussion

This study described the characteristics of adults hospitalized with COVID-19 (identified through laboratory-confirmed SARS-CoV-2 infection and/or a COVID-19 diagnosis) in three large healthcare systems (17 total hospitals) in North Carolina from the time of COVID-19 pandemic onset through September, 2020. Of the 3,991 patients included in this study during that time period, 13% died and 2% were admitted to hospice care. The overall mortality rate observed here was lower than that observed in other large populations [5], despite higher prevalence of most measured comorbidities in our population. Notably, these hospital-level data revealed several urban-rural differences. Urban hospitalized patients were more likely to be female, with the opposite true in rural areas. Patients from urban areas were more often insured by Medicaid, while those from rural areas were more often insured by commercial insurers or Medicare. However, ages were similar for rural and urban patients.

Most importantly, patients from rural areas were slightly more likely to die from COVID-19 or be discharged to hospice than those from urban areas (death/hospice discharge percentage: 16.5% in rural vs 13.3% in urban). We found that even after adjustment for individual characteristics, such as age, sex, race, ethnicity, insurance provider, smoking status,

Table 4. Initial vitals and labs and percentage of death/hospice discharge for patients hospitalized with a SARS-CoV-2 infection or COVID-19 diagnosis.

	N	N death/hospice	stratum %	bar graph of stratum %	% point difference	RR
Temperature °F						
< 100.4°F (<38°C)	3064	430	14.0	14.0	0 (ref)	1 (ref)
100.4°F-102.2°F (38–39°C)	491	73	14.9	14.9	0.8 (-2.5, 4.2)	1.1 (0.8, 1.3)
>102.2°F (>39°C)	237	41	17.3	17.3	3.3 (-1.7, 8.2)	1.2 (0.9, 1.7)
Oxygen saturation						
93–100%	3114	366	11.8	11.8	0 (ref)	1 (ref)
89–92%	503	89	17.7	17.7	5.9 (2.4, 9.5)	1.5 (1.2, 1.9)
< = 88%	361	111	30.7	30.7	19.0 (14.1, 23.9)	2.6 (2.2, 3.1)
BMI						
<18.5	100	23	23.0	23.0	5.3 (-3.5, 14.0)	1.3 (0.9, 1.9)
18.5–24.9	631	112	17.7	17.7	0 (ref)	1 (ref)
25–29.9	827	115	13.9	13.9	-3.8 (-7.7, 0)	0.8 (0.6, 1.0)
30–39.9	1150	137	11.9	11.9	-5.8 (-9.4, -2.3)	0.7 (0.5, 0.8)
40+	441	47	10.7	10.7	-7.1 (-11.2, -3.0)	0.6 (0.4, 0.8)
Lymphocyte, (10³/ul) (732–8, 731–0, 26474–7)						
>1.2	1100	94	8.5	8.5	0 (ref)	1 (ref)
>0.8–1.2	989	120	12.1	12.1	3.6 (1.0, 6.2)	1.4 (1.1, 1.8)
0.5–0.8	1113	205	18.4	18.4	9.9 (7.1, 12.7)	2.2 (1.7, 2.7)
<0.5	398	124	31.2	31.2	22.6 (17.8, 27.5)	3.6 (2.9, 4.6)
Aspartate aminotransferase, U/L (1920–8)						
< = 33	1530	157	10.3	10.3	0 (ref)	1 (ref)
>33	2135	398	18.6	18.6	8.4 (6.1, 10.6)	1.8 (1.5, 2.2)
Alanine aminotransferase, U/L (1742–6)						
< = 34	2318	341	14.7	14.7	0 (ref)	1 (ref)
>34	1349	213	15.8	15.8	1.1 (-1.3, 3.5)	1.1 (0.9, 1.3)
CRP_cat						
0–1.1	2313	217	9.4	9.4	0 (ref)	1 (ref)
> 1.1–2	912	169	18.5	18.5	9.2 (6.4, 11.9)	2.0 (1.6, 2.4)
>2	575	175	30.4	30.4	21.1 (17.1, 25.0)	3.2 (2.7, 3.9)
Troponin, ng/mL (10839–9, 42757–5)						
<0.1	1681	229	13.6	13.6	0 (ref)	1 (ref)
0.1–1	507	141	27.8	27.8	14.2 (10.0, 18.4)	2.0 (1.7, 2.5)
>1	60	26	43.3	43.3	29.7 (17.1, 42.4)	3.2 (2.3, 4.4)
Procalcitonin, ng/ml (75241–0, null)						
0–0.5 ng/ml	1267	163	12.9	12.9	0 (ref)	1 (ref)
>0.5	352	105	29.8	29.8	17.0 (11.8, 22.1)	2.3 (1.9, 2.9)
D-Dimer, ng/mL (48066–5 *UNC only)						
< = 500 ng/ml	265	22	8.3	8.3	0 (ref)	1 (ref)
501–1000	111	25	22.5	22.5	14.2 (5.8, 22.7)	2.7 (1.6, 4.6)
>1000	138	46	33.3	33.3	25.0 (16.5, 33.6)	4.0 (2.5, 6.4)
Ferritin, ng/mL (2276–4)						
0–250	713	58	8.1	8.1	0 (ref)	1 (ref)
>250–500	567	95	16.8	16.8	8.6 (5.0, 12.3)	2.1 (1.5, 2.8)
>500–1000	545	103	18.9	18.9	10.8 (6.9, 14.6)	2.3 (1.7, 3.1)
>1000–2500	382	81	21.2	21.2	13.1 (8.5, 17.6)	2.6 (1.9, 3.6)
>2500	122	31	25.4	25.4	17.3 (9.3, 25.3)	3.1 (2.1, 4.6)
C-reactive protein, mg/L (1988–5, 30522–7)						

(Continued)

Table 4. (Continued)

	N	N death/hospice	stratum %	bar graph of stratum %	% point difference	RR
0–15	411	35	8.5	8.5	0 (ref)	1 (ref)
>15–100	949	114	12.0	12	3.5 (0.1, 6.9)	1.4 (1.0, 2.0)
>100–200	533	101	18.9	18.9	10.4 (6.2, 14.7)	2.2 (1.5, 3.2)
>200	334	99	29.6	29.6	21.1 (15.5, 26.7)	3.5 (2.4, 5.0)

BMI = body mass index

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comorbidities, hypoxia, and level of inflammation, rural patients with COVID-19 were more likely than urban patients to die or to be discharged to hospice. Although our analysis did not elucidate causal reasons for this difference in mortality, the rural health outcome disparities observed are consistent with the literature describing increasing rural-urban disparities in other states and regions [37]. Several studies reported higher COVID-19 infection rates, case fatality rates, and mortality in rural US counties [6–8]. Rural Americans encounter well-documented obstacles to health care access [37–40], which contribute to disparities between rural and urban residents in chronic disease risk factors [41, 42], life expectancy [43], COVID-19 testing [19], and health [44, 45].

Our data showed that rural patients had higher rates of all assessed comorbidities than urban patients. Furthermore, patients with comorbidities had higher rates of death or discharge to hospice compared to patients without comorbidities. In particular, patients in this study with acute myocardial infarction or coagulopathy had the highest percentage of death (29%), which was consistent with previous reports [46]. In addition, a higher percentage of patients from rural areas had multiple comorbidities, as indicated by greater Charlson Comorbidity Index (≥ 3) and Elixhauser scores (≥ 5). Both a higher percentage of people with comorbidities and a higher number of comorbidities per person in rural areas match previous reports, that compared to urban residents, people living in rural areas, across all racial and ethnic groups, have higher risks of the five leading causes of death: heart disease, cancer, unintentional injury, chronic lower respiratory disease, and stroke [47–50]. Rural Americans are also more likely than urban residents to have factors linked with hypertension, COPD, and diabetes, such as obesity, poor nutrition, smoking, and alcohol consumption [51, 52]. Several studies have linked hypertension, COPD, and diabetes with a more severe COVID-19 course, ventilation, and death [5, 53, 54]. In our study, all assessed comorbidities, except for uncomplicated hypertension and obesity, were associated with an increased risk of death or hospital discharge.

Patients from rural areas were also more likely to enter the hospital with laboratory evidence indicating hyperinflammation, such as elevated C-reactive protein and lymphopenia, compared to patients from urban areas. These findings suggest that rural patients may have had more severe COVID-19 illness and greater immune dysfunction possibly as a result of greater chronic disease burden, upon hospital admission. Other studies have shown that patients with laboratory markers of hyperinflammation disproportionately developed critical illness compared to those without these markers [46, 55–58].

Although in the United States, the COVID-19 pandemic initially impacted coastal urban areas with the greatest population densities [5, 59], the initial instances of community spread in North Carolina occurred in rural counties [20, 60]. The subsequent rural-urban differences in COVID-19 outcomes in NC are consistent with observations from other states in the Southeast United States. A study of hospitalized COVID-19 patients in Southwest Georgia found that rural populations had a higher prevalence of comorbidities than those described in reports

on urban populations [61]. Huang et al [47] found a higher infection rate and mortality rate in rural counties in South Carolina. Importantly, this latter study also demonstrated a correlation between COVID-19 mortality rates and socioeconomic vulnerability in rural counties [47]. Some of the acceleration in infection rates observed in rural counties may be due to institutional settings with increased transmission risk, including meat and poultry processing facilities, and assisted living centers [59].

This study contributes to the existing literature on health disparities in the United States by providing evidence of rural-urban health outcome differences related to COVID-19. Health inequalities for each of these groups with disproportionate disease burdens may be due to differences in socioeconomic status (SES) [62]. People with lower SES are more likely to have higher rates of comorbidities and limited access to health care resources [62–64]. Taken together, the rural-urban differences in SES and healthcare resources, which elsewhere have been called structural urbanism [20], should be viewed as important predictors of COVID-19 outcomes and evidence for policy changes addressing these differences.

Strengths and limitations

The primary strength of this study was its analysis of hospital-level data. However, these findings should be interpreted with several limitations in mind. Our data only included patients hospitalized with COVID-19 and did not include those who were ill, but not hospitalized or those who died without a hospital admission (e.g., at home or assisted living facility). Therefore, our data did not include the least and most severe COVID-19 cases. Another limitation in our analysis was that our data included cases only up to the end of September 30, 2020, the point when COVID-19 incidence rates began increasing and accelerating at a faster rate in rural regions than previously seen [65]. Thus, it is possible that our results would have demonstrated greater associations between rurality and death from COVID-19 had we included data beyond September 2020 as larger numbers of people from rural locations were succumbing to COVID-19. Additionally, the effects of subsequent genetic variants of the SARS-CoV-2 virus, including the Delta and Omicron variants of 2021 and 2022, on hospitalizations and deaths could not be determined with data from this time period. Differences in outcomes between rural and urban patients resulting from later variants should be investigated in subsequent research. Furthermore, we were unable to analyze the relationship between the COVID-19 outcome and the timeliness of rural and urban patients' hospitalization after the onset of symptoms because symptom onset was not an available variable in our health system data.

Policy implications

Several policy recommendations to decrease the rural-urban health outcome disparities for this and future pandemics can be drawn from this analysis. First, improved resources and preparedness for rural areas needs to be prioritized with federal and state funding. Remaining rural hospitals need resources and in areas where closures have occurred or no rural hospitals exist, alternative systems for emergency and acute care should be prioritized. Many rural hospitals were unequipped to manage surges in infectious patients [62, 66]. Relatedly, there needs to be efforts to speed transfer of severe cases to urban hospitals. Increased transportation time and perceived difficulty of travel to physician services are prohibitive to seeking healthcare [47, 67]. The cost (perceived and real) of transport for out-of-network or uninsured patients may also play a role [68] and may be addressed by changes in policy to make this transport free to patients in emergency or life-threatening situations [69].

Second, the COVID-19 pandemic has further revealed the disproportionately high prevalence and severity of chronic diseases in rural areas compared to urban areas. Since

comorbidities caused greater vulnerability to severe COVID-19 illness, improvements to education and public health programs and access to free or affordable health insurance, Medicaid or other, to reduce chronic conditions in rural areas are necessary. Policy makers in states such as North Carolina need a path forward to addressing the barriers to Medicaid expansion or an alternative model to support long-term health of their constituents. Other important components of public health programs would include reducing poverty, reducing the barriers to primary care in rural areas, decreasing mistrust of medical professionals and vaccines, and addressing other economic and social determinants of health resulting in rural-urban health disparities. Rural areas and small towns have lower vaccination rates (36% rural vs 46% urban) [70], and many are now hotspots for COVID-19 infection [71], underscoring the need for trust building and efforts to reduce vaccine hesitancy in rural areas. These policy changes are especially important given the economic challenges faced by rural hospitals, a quarter of which were at high risk of closure prior to the COVID-19 pandemic [66, 72, 73]. The US experienced 181 rural hospital closures in the 15 years prior to the pandemic [74]. Continued closure of rural hospitals would further concentrate health care facilities in large cities [62] and exacerbate existing barriers to healthcare access.

Conclusions

Rural North Carolina residents hospitalized for COVID-19 had a higher probability of dying or being discharged to hospice in this study. This research adds to the evidence of health disparities in the United States revealed by the COVID-19 pandemic: while many studies have shown racial, ethnic, and age-related disparities, this analysis provides evidence for rural-urban disparities as well. Policies to bolster intensive care units and other medical resources for rural healthcare systems, increase access to primary care, and improve education and public health to attenuate comorbidities in rural areas should be put in place to decrease the risk of death due to future pandemics in rural areas.

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