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Research Report

Disproportionate impact of COVID-19 severity and mortality on hospitalized American Indian/Alaska Native patients

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Abstract

Epidemiological data across the United States of America illustrate health disparities in COVID-19 infection, hospitalization, and mortality by race/ethnicity. However, limited information is available from prospective observational studies in hospitalized patients, particularly for American Indian or Alaska Native (AI/AN) populations. Here, we present risk factors associated with severe COVID-19 and mortality in patients (4/2020–12/2021, n = 475) at the University of New Mexico Hospital. Data were collected on patient demographics, infection duration, laboratory measures, comorbidities, treatment(s), major clinical events, and in-hospital mortality. Severe disease was defined by COVID-related intensive care unit requirements and/or death. The cohort was stratified by self-reported race/ethnicity: AI/AN (30.7%), Hispanic (47.0%), non-Hispanic White (NHW, 18.5%), and Other (4.0%, not included in statistical comparisons). Despite similar timing of infection and comparable comorbidities, admission characteristics for AI/AN patients included younger age ($P = 0.02$), higher invasive mechanical ventilation requirements ($P = 0.0001$), and laboratory values indicative of more severe disease. Throughout hospitalization, the AI/AN group also experienced elevated invasive mechanical ventilation ($P < 0.0001$), shock ($P = 0.01$), encephalopathy ($P = 0.02$), and severe COVID-19 ($P = 0.0002$), consistent with longer hospitalization ($P < 0.0001$). Self-reported AI/AN race/ethnicity emerged as the highest risk factor for severe COVID-19 (OR = 3.19; 95% CI = 1.70–6.01; $P = 0.0003$) and was a predictor of in-hospital mortality (OR = 2.35; 95% CI = 1.12–4.92; $P = 0.02$). Results from this study highlight the disproportionate impact of COVID-19 on hospitalized AI/AN patients, who experienced more severe illness and associated mortality, compared to Hispanic and NHW patients, even when accounting for symptom onset and comorbid conditions. These findings underscore the need for interventions and resources to address health disparities in the COVID-19 pandemic.

Keywords: COVID-19, race/ethnicity, hospitalization

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Significance Statement

This study fills an important gap in knowledge about the impact of COVID-19 on racial/ethnic minority groups, particularly American Indian/Alaska Native populations. This prospective observational study in hospitalized patients was conducted at the University of New Mexico Hospital, which serves a diverse patient population. Since 475 individuals were followed longitudinally, robust comparisons between different racial/ethnic groups with respect to disease progression were feasible. Factors including COVID-19 symptoms duration, days infected prior to hospitalization, comorbidities, and adverse clinical events in determining factors associated with disease severity and mortality were examined. This work provides insights into the disproportionate impact of COVID-19 on American Indian/Alaska Native patients and highlights the need for interventions and resources to address health disparities in the COVID-19 pandemic.

Introduction

Evidence shows that SARS-CoV-2 infections and mortality rates from COVID-19 are significantly higher in certain racial/ethnic minority groups relative to non-Hispanic Whites (NHW) (1–3). Despite American Indian/Alaska Native (AI/AN) populations being 1.6 times more likely to be infected by SARS-CoV-2, having 2.5 times more hospitalization, and 2.0-fold higher mortality than NHWs (4), the impact of SARS-CoV-2 infection on clinical outcomes in hospitalized AI/AN patients remains largely unreported. Historically, AI/AN communities have faced challenges in accessing quality healthcare due to geographic remoteness, limited healthcare infrastructure (5, 6), socioeconomic constraints (7, 8), historical trauma (9–12), and discriminatory policies (13). These barriers have been exacerbated during the COVID-19 pandemic, further intensifying health disparities, and hindering timely diagnosis, treatment, and management of the disease (5). As such, a multitude of factors contributes to the disproportionate burden of COVID-19 including social determinants of health (e.g. poverty, congregate living practices, household air pollution, and inadequate access to quality healthcare) (14, 15), as well as increased risk of chronic conditions [e.g. asthma, chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes, and obesity] (16–20).

The State of New Mexico (NM) is comprised of a diverse population consisting of the nation's highest percentage of Hispanics (50.1%) and the third-highest proportion of people of AI/AN ancestry (11.2%) (21). The Navajo Nation, which extends into Utah, Arizona, and NM, surpassed New York as the most COVID-19-affected US region per capita early in the pandemic (May 2020) (22). Within the same period, data from the National Indian Health Board showed that AI/AN individuals accounted for 43% of COVID-19 cases in NM (23). Throughout the pandemic, and particularly during the early phases, the University of New Mexico Hospital (UNMH) was one of the primary facilities providing patient care since it is a 618-bed tertiary care facility that serves as a referral center for the state and surrounding areas including Tribal lands.

In a previous investigation conducted in a subset of the patients (n = 94) presented here, the strongest predictor of severe COVID-19 was self-reported race/ethnicity as AI/AN (24). Based on the sample size and demographic distribution for the initial enrollees (n = 94), the cohort was stratified into two groups: AI/AN (n = 43) and all other races combined (non-AI/AN, n = 51) (24). To better understand the clinical course and pathogenesis of COVID-19, a prospective observational study was conducted on a larger cohort of hospitalized patients (n = 475) at UNMH who represent the primary demographic groups in NM (i.e. AI/AN, Hispanic, and NHW people). Data are presented on demographic characteristics, duration of SARS-CoV-2 infection prior to hospital admission, presenting clinical characteristics, comorbidities, major clinical events during hospitalization, disease outcomes, and predictors of severe disease and mortality. The study fills an important gap in knowledge by identifying risk factors associated with severe COVID-19 in a diverse cohort of hospitalized patients and highlights the disproportionate impact of COVID-19 on hospitalized AI/AN patients.

Results

Patient characteristics

The cohort (n = 475; 46.1% female) consisted of four self-reported race/ethnicity groups: American Indian/Alaska Native (AI/AN, n = 146, 30.7%), Hispanic (n = 222, 46.7%), Non-Hispanic White (NHW, n = 88, 18.5%) and Other [n = 19, 4.0%; Black/African American (n = 13), Asian (n = 5), and Pacific Islander (n = 1), Fig. 1A]. There was one individual in the Other group who identified as multiracial. Due to the limited sample size, the Other group was not included in the statistical analysis. The distribution of sex at birth was similar across the AI/AN, Hispanic, and NHW groups ($P = 0.81$, Fig. 1A). The median age for the cohort was 55 years (interquartile range [IQR] 42–65). Age distribution was stratified into three age tertiles (18–44, 45–64, and ≥65 years) to determine the likelihood of each race/ethnicity group being relatively younger or older compared to the other groups. Significant differences in age distribution were observed among younger (18–44 years, $P = 0.02$) and older (>65 years, $P = 0.045$) patients (Fig. 1B). The AI/AN group exhibited a higher proportion of younger individuals ($P = 0.01$) and a lower proportion of older individuals ($P = 0.02$) compared to the Hispanic group (Fig. 1B).

Timing of SARS-CoV-2 infection prior to admission

To determine the onset of SARS-CoV-2 infection and associated clinical features during the early stages of the disease (i.e. admission oxygen requirements) several admission characteristics were compared across the three groups. The mean (SEM) time of symptom onset prior to hospital admission for the cohort was 6.50 ± 0.22 days and did not differ across the groups ($P = 0.54$, Fig. 1C). Moreover, none of the COVID-19-related symptoms prior to hospitalization differed across the groups (Table S1). The average time from the patients' first SARS-CoV-2 PCR(+) test to admission was 3.10 ± 0.21 days (Fig. 1D). Although there was a slightly longer illness in the AI/AN (3.94 ± 0.44) group relative to the Hispanic (2.88 ± 0.28) and NHW (2.77 ± 0.53) groups, the across group difference was not significant ($P = 0.07$, Fig. 1D).

Presenting clinical characteristics

Despite the timing of symptom onset ($P = 0.54$, Fig. 1C) and time since initial viral detection ($P = 0.07$, Fig. 1D) to admission being comparable between the three groups, requirements for invasive

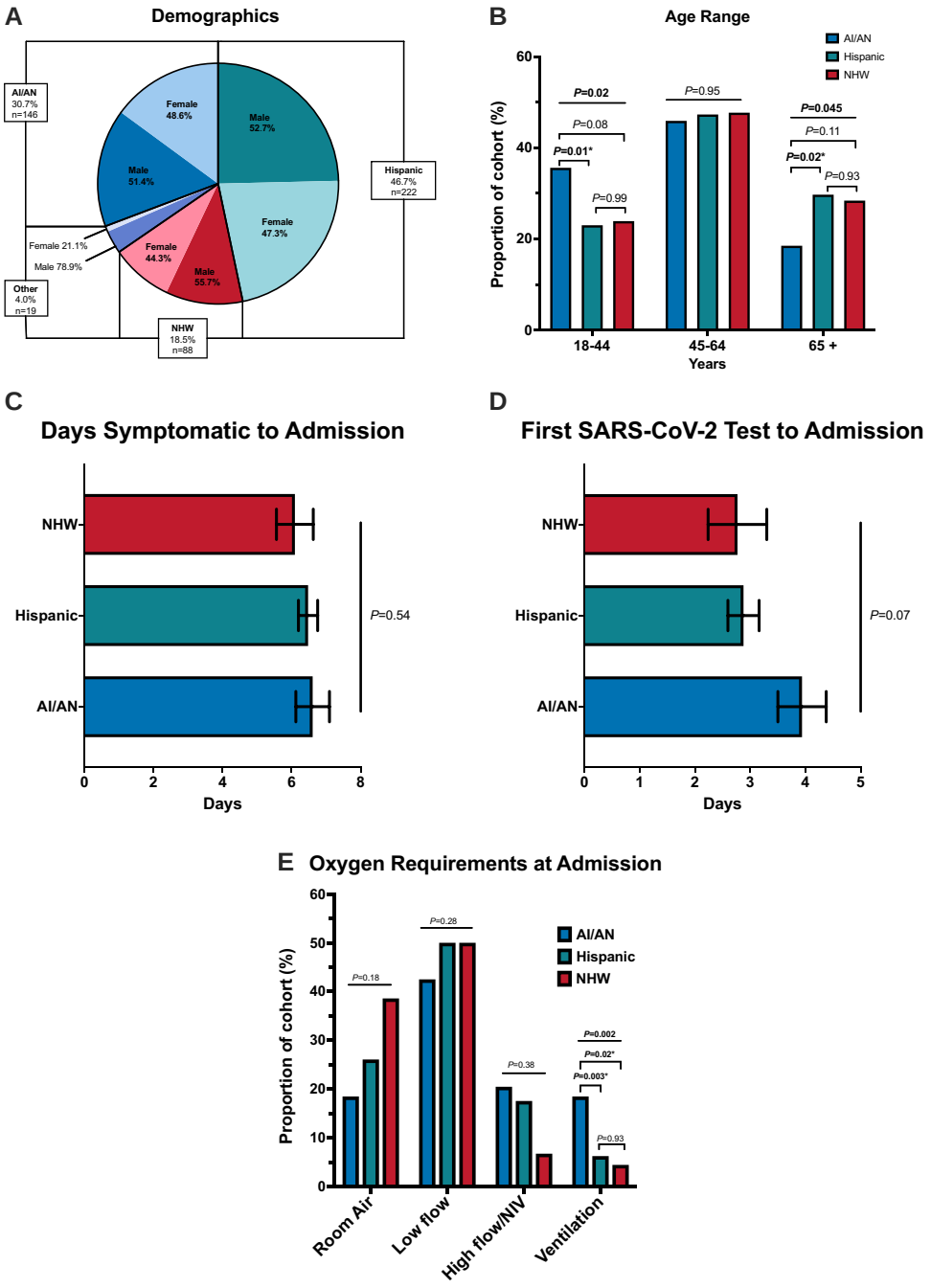

Fig. 1. Patient demographics, timing of SARS-CoV-2 infection, and admission oxygen requirements. (A) The cohort (n = 475; 46.1% female) consisted of four self-reported race/ethnicity groups: American Indian/Alaska Native (AI/AN, n = 146, 30.7%), Hispanic (n = 222, 46.7%), Non-Hispanic White (NHW, n = 88, 18.5%) and Other [n = 19, 4.0%; Black/African American (n = 13), Asian [n = 5), and Pacific Islander n = 1). There were 17 pregnant patients in the cohort, 14 were AI/AN (9.6%), 2 were Hispanic (0.9%), and 1 was NHW (1.1%, $P < 0.0001$). (B) When stratified into three age tertiles, there was a different proportion among the younger and older patients. The AI/AN group had a higher proportion of younger ($P = 0.01$) and a lower proportion of older ($P = 0.02$) individuals, relative to the Hispanic group. (C) Days symptomatic prior to hospital admission. (D) Days from first SARS-CoV-2(+) PCR test to admission. (E) Oxygen requirements upon admission (room air, low-flow nasal cannula, high-flow/noninvasive ventilation (NIV), and invasive mechanical ventilation). Differences in proportions across the groups were determined using a chi-square test. In case of significant differences, pairwise chi-square tests for equal proportions were performed using Holm's multiple test correction. Bold font indicates statistical significance at $P \leq 0.05$. *Indicates significant after Holm correction.

mechanical ventilation differed across the cohort ($P = 0.002$, Fig. 1E). The AI/AN group had the largest proportion of patients requiring invasive mechanical ventilation (18.5%), which was substantially greater than either the Hispanic (6.3%, $P = 0.003$) or NHW (4.5%, $P = 0.02$) groups (Fig. 1E), illustrating more severe disease upon admission.

To further characterize presenting features in the cohort, vital signs and clinical laboratory values were determined within the first 24 hours of admission (Table S2, Figs. S1 and S2). Although vital signs were comparable across the groups, several hematological measures differed including WBCs ($P < 0.0001$), neutrophil count ($P < 0.0001$) and percentage ($P < 0.0001$), and the neutrophil/

lymphocyte ratio (NLR) for the count ($P < 0.0001$) and percentage ($P < 0.0001$) with all the hematological variables elevated in the AI/AN group (Table S2 and Fig. S1). The lymphocyte percentage also differed in the overall cohort ($P = 0.002$) and was lowest in patients who self-identified as AI/AN group.

Procalcitonin, a biomarker for inflammation, differed across the cohort ($P = 0.02$), with AI/AN patients having the highest levels (Table S2 and Fig. S2). Additionally, differences were witnessed for markers of kidney function [i.e. BUN ($P = 0.003$) and eGFR ($P = 0.02$)] with the AI/AN group having the lowest BUN and highest eGFR. Serum bicarbonate levels were altered in the cohort ($P < 0.0001$) and lowest in the AI/AN group. Measures of hepatic function were also distinct among the cohort including albumin ($P < 0.0001$), T-bilirubin ($P = 0.02$), and ALP ($P < 0.0001$). Levels of albumin were lowest in the AI/AN patients, while ALP was substantially elevated.

Patient comorbidities upon admission

Since COVID-19 disease severity is strongly influenced by certain comorbid conditions, past medical conditions were extensively cataloged for the cohort (Table 1 and Fig. S3). Several chronic respiratory diseases differed across the groups including COPD ($P < 0.0001$) and sleep apnea ($P = 0.0003$). Metabolic disorders, specifically hyperlipidemia ($P = 0.04$) and hypothyroidism ($P = 0.04$), showed such a similar pattern. There were also differences in the proportion of past smokers ($P = 0.01$). For all these comorbid conditions, the proportion was lowest in AI/AN patients and highest in the NHW group. In addition, to capture the comorbidities as a composite score, the age-adjusted Charlson Comorbidity Index (CCI) was calculated (25). The number of patients with low (0–3), medium (4–7), and high (8–10) CCI were similar between the stratified groups.

Major clinical events related to COVID-19 during hospitalization

To gain an improved understanding of COVID-19 pathogenesis in a diverse patient population, major clinical events during hospitalization were compared among the cohort (Table 2). Requirements for invasive mechanical ventilation varied in the cohort ($P < 0.0001$) with the AI/AN group experiencing 2-fold higher proportion than Hispanics ($P < 0.0001$) and 1.8-fold higher than NHWs ($P = 0.01$). In addition, there were differences in the development of shock ($P = 0.01$) and encephalopathy ($P = 0.02$). Shock was 1.6 times higher in AI/AN versus Hispanics ($P = 0.006$) and 1.5 times greater than NHWs ($P = 0.08$). The proportion of encephalopathy was different ($P = 0.007$) and 2.1 times higher in AI/AN versus Hispanics. However, while the incidence of encephalopathy was 1.7 times higher, the proportion was not different ($P = 0.17$) in AI/AN versus NHWs.

COVID-19 disease outcomes

Further characterization of the disease course was determined by comparing the number of patients who developed severe disease (required ICU support), length of hospitalization (days), and in-hospital mortality. Throughout hospitalization, severe disease occurred in 40.6% of the overall cohort and varied amongst the groups ($P = 0.0002$, Fig. 2A). Consistent with an elevated number of major clinical events, 54.1% of the AI/AN group developed severe disease compared to 35.6% of the Hispanic ($P = 0.0007$) and 30.7% of the NHW ($P = 0.0008$) groups. The length of hospitalization was also different across the groups ($P < 0.0001$) with an average length of stay in the overall cohort of 14.05 ± 0.89 days (Fig. 2B). AI/AN patients had the lengthiest duration of hospitalization (20.07 ± 2.40 days), which was 1.7-fold longer than Hispanic (12.16 ± 0.90 days, $P < 0.0001$) and 2-fold longer than NHW (9.91 ± 1.08 days, $P < 0.0001$) patients. In-hospital mortality in the overall cohort was 17.7%. Although in-hospital mortality was higher in the AI/AN group (22.6%) versus the Hispanic (15.8%) and NHW (15.9%) groups, univariate analysis did not indicate a significant difference ($P = 0.21$, Fig. 2C). However, AI/AN patients who died due to COVID-19 complications were younger (55.88 ± 2.23 years) compared to Hispanics (60.03 ± 2.26 years) and NHWs (60.93 ± 2.72 years).

Predictors of COVID-19 disease severity and mortality

Logistic regression models were fit to determine factors that predict the development of severe disease and mortality. The highest risk for the severe disease was self-reported race/ethnicity as AI/AN (OR = 3.19; 95% CI = 1.70–6.01; $P = 0.0003$), being male (OR = 2.73; 95% CI = 1.76–4.24; $P < 0.0001$), and each additional year in age (OR = 1.02; 95% CI = 1.01–1.04; $P = 0.001$), all of which remained significant after multiple test correction (Fig. 3A). Performing an identical model in which individual comorbidities were replaced by the CCI revealed that those who self-reported as AN/AI (OR = 3.66; 95% CI = 2.01–6.68; $P < 0.0001$), being male (OR = 2.28; 95% CI = 1.52–3.42; $P < 0.0001$) and a higher CCI (OR = 1.22; 95% CI = 1.13–1.32; $P < 0.0001$) remained strong predictors of severe disease after correcting for multiple comparisons (Fig. 3B).

There was an increased risk of mortality, after adjusting for multiple comparisons, in males (OR = 2.16; 95% CI = 1.23–3.77; $P = 0.007$), patients with chronic kidney disease (CKD) (OR = 2.48; 95% CI = 1.32–4.62; $P = 0.004$), and patients who were treated with steroids (OR = 6.96; 95% CI = 2.01–24.14; $P = 0.002$, Fig. 3C). Regressing on mortality with the CCI as a covariate revealed enhanced risk associated with self-reporting as AI/AN (OR = 2.35; 95% CI = 1.12–4.92; $P = 0.02$), being male (OR = 2.06; 95% CI = 1.22–3.51; $P = 0.007$), steroid treatment (OR = 6.62; 95% CI = 1.95–22.50; $P = 0.002$), and a higher CCI (OR = 1.23; 95% CI = 1.12–1.36; $P < 0.0001$), after multiple test correction (Fig. 3D).

Discussion

From the start of the pandemic onward, New Mexico statewide data indicated a disproportionate rate of hospitalizations from COVID-19 in AI/AN people, which parallels race/ethnicity data across the country (26). Although the national databases include the American Indian and Alaska Native populations as one reporting group, the cohort described here are individuals from the multitude of American Indian communities in the Southwest. While robust population-level data are available for the different races/ethnicities in the United States of America, studies describing the clinical course and disease outcomes in a diverse cohort of hospitalized patients who self-report as AI/AN, Hispanic, or NHW remain largely unreported. As such, we conducted a single-site, prospective observational study at the UNMH, a large tertiary care facility that serves the diverse population of NM. In addition, the inpatient population at UNMH has been further enriched with AI/AN patients since 1952 when a federal contract between the Bureau of Indian Affairs, the Indian Health Service, and the local government established UNMH as the referral center for the AI/AN people of NM (27).

Table 1. Patient comorbidities and adverse clinical events.

Patient characteristics	All patients (n = 475)	AI/AN (n = 146)	Hispanic (n = 222)	NHW (n = 88)	Other (n = 19)	*P*
Cancer	52 (10.9)	12 (8.2)	23 (10.4)	13 (14.8)	4 (21.1)	0.28
Cardiovascular disease						
Hypertension	220 (46.3)	59 (40.4)	105 (47.3)	43 (48.9)	13.0 (68.4)	0.33
Coronary artery disease	34 (7.2)	7.0 (4.8)	15.0 (6.8)	10 (11.4)	2 (10.5)	0.16
Heart failure[a]	43 (9.1)	9 (6.2)	19 (8.6)	12 (13.6)	3 (15.8)	0.15
Stroke	19 (4.0)	5 (3.4)	8 (3.6)	4 (4.5)	2 (10.5)	0.90
Chronic respiratory disease						
Asthma	60 (12.6)	25 (17.1)	24 (10.8)	10 (11.4)	1 (5.3)	0.19
COPD	27 (5.7)	2 (1.4)	9 (4.1)	15 (17.0)	1 (5.3)	**<0.0001**[b,c]
Sleep apnea	46 (9.7)	4 (2.7)	23 (10.4)	16 (18.2)	3 (15.8)	**0.0003**[c,d]
Immunosuppression						
Solid organ transplant	9 (1.9)	2 (1.4)	6 (2.7)	1 (1.1)	0 (0.0)	0.55
Autoimmune disease[e]	75 (15.8)	24 (16.4)	32 (14.4)	16 (18.2)	3 (15.8)	0.69
Kidney disease						
CKD stage 3b	32 (6.7)	6 (4.1)	16 (7.2)	9 (10.2)	1 (5.3)	0.19
CKD stage 4	26 (5.5)	7 (4.8)	13 (5.9)	4 (4.5)	2 (10.5)	0.86
CKD stage 5	26 (5.5)	11 (7.5)	13 (5.9)	2 (2.3)	0 (0.0)	0.24
Liver disease						
Cirrhosis	20 (4.2)	11 (7.6)	6 (2.7)	3 (3.4)	0 (0.0)	0.08
Other[f]	13 (2.3)	6 (4.1)	4 (1.8)	2 (2.3)	1 (5.3)	0.40
Metabolic disease						
BMI, median (IQR)	32.1 (10.3)	32.4 (8.6)	32.0 (10.6)	32.1 (11.4)	29.2 (19.1)	0.93
Obesity class I[g]	115 (24.2)	38 (26.0)	48 (21.6)	26 (29.5)	3 (15.8)	0.30
Obesity class II[g]	69 (14.5)	26 (17.8)	35 (15.8)	8 (9.1)	0 (0.0)	0.18
Obesity class III[g]	93 (19.6)	23 (15.8)	45 (20.3)	19 (21.6)	6 (31.6)	0.45
Diabetes[h]						
Controlled	80 (16.8)	24 (16.4)	35 (15.8)	19 (21.6)	2 (10.5)	0.46
Uncontrolled	145 (30.5)	49 (33.6)	71 (32.0)	19 (21.6)	6 (31.6)	0.12
Hyperlipidemia	119 (25.1)	28 (19.2)	55 (24.8)	30 (34.1)	6 (31.6)	**0.04**[c,i]
Hypothyroidism	51 (10.8)	11 (7.5)	24 (10.9)	16 (18.6)	0 (0.0)	**0.04**[i]
Smoker						
Past	99 (22.7)	20 (14.3)	53 (25.7)	22 (30.1)	4 (22.2)	**0.01**[c,d]
Current	47 (10.7)	10 (7.1)	20 (9.7)	11 (15.1)	6 (31.6)	0.18
CCI score						
0–3	255 (53.7)	86 (58.9)	119 (53.6)	40 (45.5)	10 (52.6)	0.14
4–7	178 (37.5)	48 (32.9)	84 (37.8)	38 (43.2)	8 (42.1)	0.28
8–10	42 (8.8)	12 (8.2)	19 (8.6)	10 (11.4)	1 (5.3)	0.68

Data are presented as the number of patients (n) and percentage (%) in each category unless otherwise noted. The history of comorbidities prior to admission was determined by medical chart review and verbal interview with the patient or LAR. Adverse clinical events were recorded throughout hospitalization. Differences in proportions across categorical variables were determined using a chi-square test with Yates continuity correction. In case of significant differences, pairwise analysis was performed with the same test. Holm correction for multiple testing was then applied. Bold indicated statistical significance at $P \leq 0.05$.
COPD: chronic obstructive pulmonary disease; BMI: body mass index.
[a]Defined by a prior diagnosis of heart failure (preserved ejection fraction and reduced ejection fraction) and cardiomyopathy (ischemic and nonischemic).
[b]Pairwise comparison showed significant differences between NHW versus AI/AN and NHW versus Hispanic.
[c]Indicates significant after Holm correction.
[d]Pairwise comparison showed significant differences between AI/AN versus Hispanic and AI/AN versus NHW.
[e]Defined by a prior diagnosis of either lupus or rheumatoid arthritis. Other autoimmune diseases are not reported in the population.
[f]Defined by a prior diagnosis of chronic hepatitis C or nonalcoholic fatty liver disease.
[g]Obesity classifications were defined by BMI, where class I: BMI of 30 to <35, class II: BMI of 35 to <40, and class III: BMI of 40 or higher.
[h]Controlled versus uncontrolled diabetes was defined by Hb A1C levels: controlled (<7.0%) and uncontrolled (≥7.0%).
[i]Pairwise comparison showed significant differences between AI/AN versus NHW.

Previous studies in NM populations, including one on COVID-19 disease severity in a subset of the patients reported here, showed that ancestry informative markers (AIMs) reveal high concordance between self-identified race/ethnicity and genetic ancestry estimates, thus providing confidence in the self-reporting data (24, 28). However, without determining AIMs for the entire cohort, racial misclassification could be a limitation of the study (29).

Important considerations for determining factors associated with disease severity and mortality are how long the patients have been ill (symptomatic) and how long individuals have had a SARS-CoV-2 infection prior to hospitalization. Neither the duration of COVID-19 symptoms nor the days infected prior to admission differed across the groups. However, the ~1 day longer infection in the AI/AN group may have contributed to more advanced disease upon admission, including oxygen requirements.

Despite comparable infection duration, the AI/AN group hospital was significantly younger (i.e. higher proportion in the 18–44 age group) and more severely ill, as indicated by higher oxygen requirements for supportive care. Although these findings potentially indicate increased susceptibility to COVID-19 hospitalizations in the AI/AN population in NM, the underlying cause for such remains undefined. The AI/AN group also had hematological features indicative of severe COVID-19 at admission, such as elevated WBCs, neutrophils, and NLR, in the context of reduced lymphocytes (30). Additional indices of severe disease were also pronounced in the AI/AN group within the first 24 hours of admission including inflammatory markers (elevated procalcitonin and reduced albumin), renal dysfunction (reduced BUN and increased eGFR), and signs of hepatic damage (reduced albumin and elevated ALP) (30–32). Given the increased WBCs and NLR in the AI/AN group, these results suggest that hypoalbuminemia may be a result of systemic inflammation from COVID-19. Collectively, the admission characteristics indicate a more

Table 2. Clinical events during hospitalization.

Clinical events	All patients (n = 475)	AI/AN (n = 146)	Hispanic (n = 222)	NHW (n = 88)	Other (n = 19)	P
Invasive Mechanical ventilation	128 (26.9)	59 (40.4)	45 (20.3)	20 (22.7)	4 (21.1)	**<0.0001**[a,b]
RRT[c]	19 (4.0)	8 (5.5)	7 (3.2)	4 (4.5)	0 (0.0)	0.54
Acute hepatic injury[d]	364 (76.6)	115 (78.8)	164 (73.9)	67 (76.1)	18 (94.7)	0.56
Heart failure	30 (6.3)	8 (5.5)	15 (6.8)	7 (8.0)	0 (0.0)	0.75
Thrombotic events						
Stroke	6 (1.3)	2 (1.4)	1 (0.5)	3 (3.4)	0 (0.0)	0.12
VTE[e]	40 (8.4)	16 (11.0)	18 (8.1)	6 (6.8)	0 (0.0)	0.49
Shock[f]	125 (26.3)	52 (35.6)	49 (22.1)	21 (23.9)	3 (15.8)	**0.01**[g,b]
Encephalopathy	60 (12.6)	28 (19.2)	20 (9.0)	10 (11.4)	2 (10.5)	**0.02**[g,b]

Adverse clinical events that occurred during hospitalization were included on this table. Categorical data are presented as the number of patients (n) and percentage (%). Differences in proportions across categorical variables were determined using a chi-square test with Yates continuity correction. In case of significant differences, pairwise analysis was performed with the same test. Holm correction for multiple testing was then applied. Bold indicated statistical significance at $P \leq 0.05$.
RRT: renal replacement therapy; VTE: venous thromboembolism.
[a]Pairwise comparisons demonstrated significant differences between AI/AN versus Hispanic and AI/AN versus NHW.
[b]Indicates significant after Holm correction.
[c]Only patients with no history of RRT prior to hospitalization were included. RRT was defined by continuous renal replacement therapy and intermittent hemodialysis.
[d]Defined as aspartate transaminase >5x upper limit of normal (ULN) and alanine transaminase >5x ULN. ULN was defined as ≤40 U/L for both laboratory measures.
[e]Defined as deep vein thrombosis and/or pulmonary embolism events.
[f]Defined as mean arterial pressure ≤65 mmHg, obtained from cuff and intra-arterial measurements.
[g]Pairwise comparisons demonstrated significant differences between AI/AN versus Hispanic.

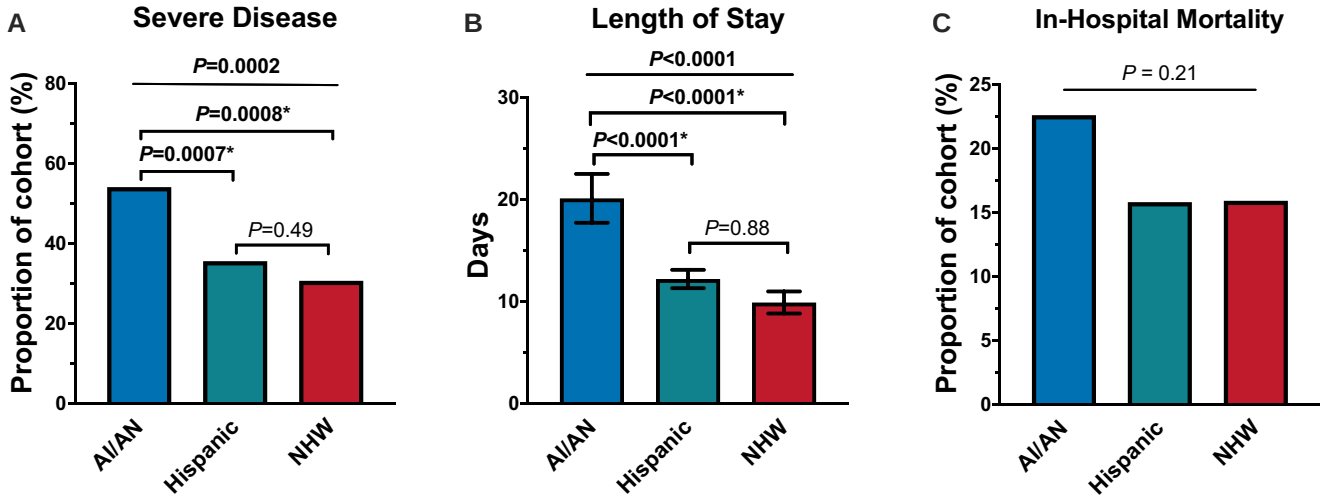

Fig. 2. COVID-19 disease outcomes during hospitalization. Patients were stratified into AI/AN, Hispanic, and NHW for comparisons of disease outcomes. Data are presented as proportions (%) and mean (SEM). Kruskal–Wallis tests were utilized to compare differences between days across the groups. Pairwise comparisons were performed for significant across-group differences using Mann–Whitney *U* analysis. Differences in proportions across the groups were determined using a chi-square test for equal proportions. In case of significant differences, pairwise chi-square tests for equal proportions were performed using Holm's multiple test correction. Bold font indicates statistical significance at $P \leq 0.05$. *Indicates significant after Holm correction. (A) Severe disease is defined as requiring ICU support during hospitalization. (B) Length of stay (days). (C) In-hospital mortality.

rapid onset of severe disease in the AI/AN group and a clinical presentation of such in younger individuals.

A comprehensive investigation of comorbid conditions known to influence disease outcomes for COVID-19 revealed that COPD, sleep apnea, hyperlipidemia, hypothyroidism, and history of past smoking differed among the groups and was lowest in AI/AN patients (16). Additional analysis of comorbidities using the CCI did not show any categorical differences across the groups. Taken together, these findings suggest that comorbid conditions may not be a driver of the enhanced disease severity witnessed in AI/AN.

After defining the admission characteristics, we determined major clinical events associated with COVID-19 throughout the course of hospitalization. The AI/AN group had a markedly higher proportion of invasive mechanical ventilation and was more prone to develop shock and encephalopathy. The elevated degree of major clinical events across hospitalization is consistent with the pronounced development of severe disease that was experienced by 54.1% of the AI/AN group. A greater burden of severe disease in individuals who self-reported as AI/AN is a strong contributing factor to an extended duration of hospital stay that was 1.7 and 2.0 times longer in the AI/AN group than the Hispanic and NHW groups, respectively.

To determine predictors of disease outcomes, logistic regression models were generated for severe COVID-19 and mortality. For the severe disease and mortality models, demographic variables were included as covariates in the context of individually indexed comorbidities, as well as separate models in which comorbidities were replaced by the CCI scores. The strongest predictor of severe disease was self-reporting as AI/AN followed by

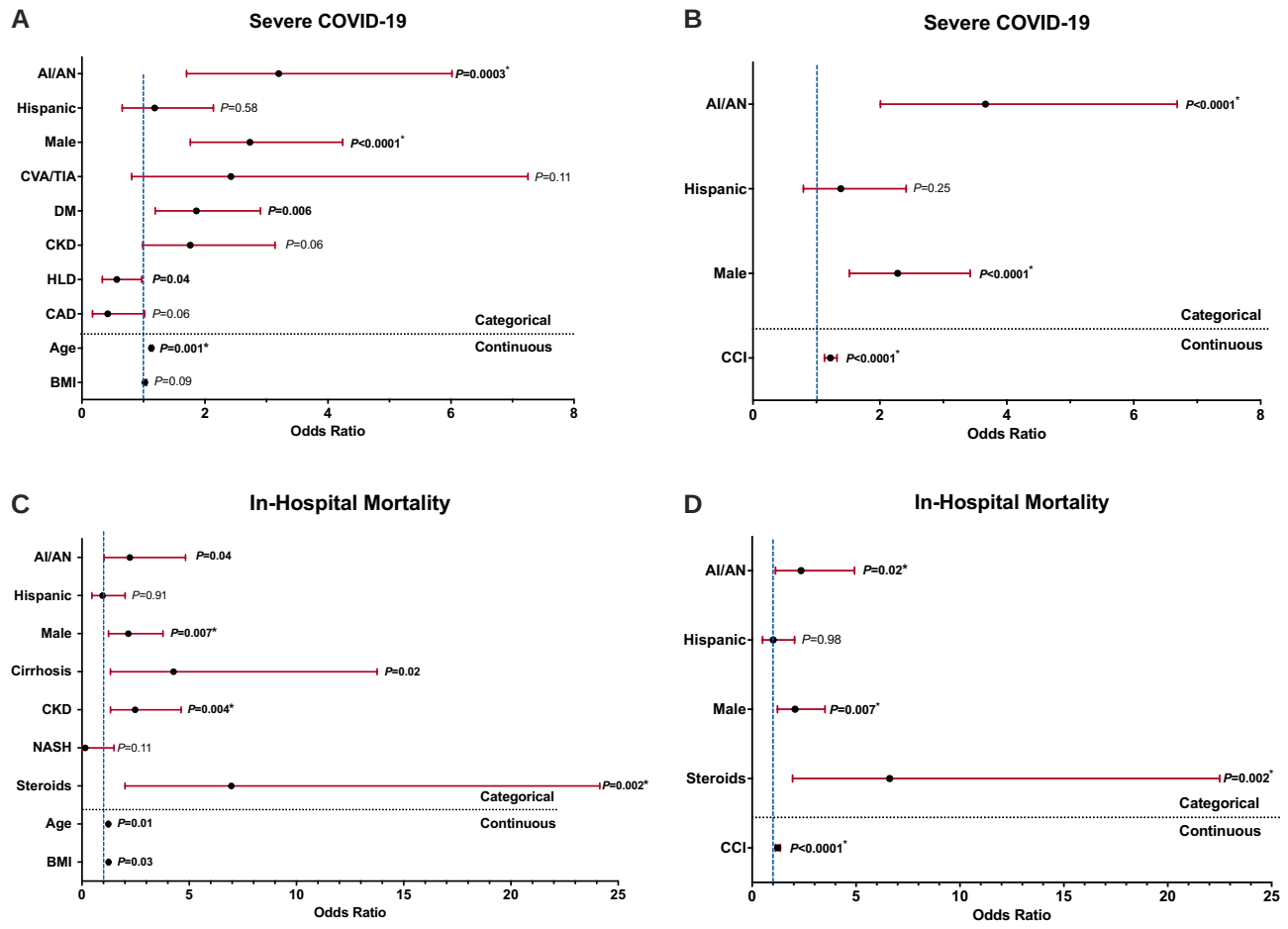

Fig. 3. Predictors of severe COVID-19 and mortality. Data are presented as OR and 95% CI as determined by logistic regression modeling. Bold font indicates statistical significance at $P \leq 0.05$. *Indicates significance after Holm adjustment for multiple comparisons. (A) Development of severe disease throughout hospitalization as the outcome variable. Covariates in the model were race/ethnicity (NHW set as reference), age, sex at birth, days symptomatic before enrollment, BMI, treatment, and all comorbid conditions that occurred in >5 patients. (B) Development of severe disease throughout hospitalization as the outcome variable with the same covariates, except individual comorbidities and age were represented by the Charlson Comorbidity Index (CCI). C) In-hospital mortality as the outcome variable with the following covariates in the model: race/ethnicity (NHW set as reference), age, sex at birth, days symptomatic before enrollment, BMI, treatment, and all comorbid conditions that occurred in >5 patients. D) In-hospital mortality as the outcome variable with the same covariates, except individual comorbidities and age were represented by the CCI. AI/AN, American Indian/Alaska Native; CVA/TIA, cerebral vascular accidents/transient ischemic attack; DM, diabetes mellitus; CKD, chronic kidney disease; HLD, hyperlipidemia; CAD, coronary artery disease; BMI, body mass index; CCI, Charlson Comorbidity Index; NASH, nonalcoholic steatohepatitis.

being male in both the individual comorbidities and CCI models. In addition, increasing age emerged as a predictor of severe COVID-19 in the model that included all comorbidities. Since age is one of the variables captured in the CCI algorithm, it did not emerge as an individual predictor of severe disease; however, a higher CCI score was associated with an increased risk of severe COVID-19.

Additional regression models exploring in-hospital mortality revealed that being male, having CKD, and steroid treatment were all associated with an increased risk of death. These results align with previous research highlighting the higher susceptibility of males and individuals with underlying renal conditions to severe COVID-19 outcomes (33, 34). The identification of CKD as a risk factor underscores the importance of monitoring and managing kidney health in COVID-19 patients, as these individuals may be more vulnerable to adverse clinical outcomes. Furthermore, our analysis indicated that steroid treatment was associated with an increased risk of mortality. This finding warrants careful interpretation as it may reflect the severity of illness, as patients with more severe symptoms are more likely to receive steroid therapy. It is important to note that the decision to administer steroids is based on clinical judgment and individual patient characteristics, and further research is needed to understand the precise impact of steroid treatment on mortality risk in COVID-19 patients. In addition, when examining treatment with remdesivir and/or steroids, no treatment disparities were observed ($P > 0.05$) for each treatment and their combination. Self-reporting as AI/AN emerged as a significant risk factor for mortality in the model that contained individual comorbidities but was not significant after correction for multiple comparisons. However, when utilizing the CCI instead of individual comorbidities in the model, self-reporting as AI/AN emerged as the strongest risk factor for mortality. This suggests that the aggregated measure of comorbidity burden captured by CCI, in combination with self-reporting as AI/AN, provides a more robust prediction of mortality risk in the cohort. This finding also highlights the nature of regression models in which reduced degrees of freedom (i.e. predictor variables) when incorporating the CCI offers more robust models.

Results presented here in a diverse demographic group of hospitalized patients clearly demonstrate a higher burden of severe

COVID-19 and mortality in AI/AN people in New Mexico and surrounding region, despite a comparable duration of infection and having fewer comorbidities than the Hispanic and NHW patients. Due to the low proportion of Asian and Black/African American individuals living in New Mexico, these populations were not included in the statistical comparisons with the other three race/ethnicity groups, limiting our ability to obtain important information for those groups. While a limitation of the study is the single-site analysis in the Southwestern United States of America and lack of representation from several racial/ethnic groups, this prospective longitudinal study is consistent with retrospective studies examining in-hospital mortality in Mississippi, and a retrospective cohort study among Medicare beneficiaries in the United States of America, all of which focused on the early phase of the pandemic (35–37). Findings from those studies also showed the highest level of mortality among AI/AN people relative to other racial/ethnic groups. While vaccination certainly impacts disease severity, this information was not included in the models due to incomplete/inconsistent information in the reporting structure. However, vaccination does not likely explain our results since the AI/AN population has the highest level of vaccination during the recruitment period in New Mexico and Nationally (38).

As with the disproportionate burden of COVID-19 morbidity and mortality seen in AI/AN populations, similar historical patterns are documented for other respiratory infections such as the 1918 influenza pandemic, tuberculosis, and the 2009 H1N1 influenza pandemic (39–42). The underlying etiology for the disproportionate burden of severe COVID-19 and mortality in the AI/AN people is almost certainly multifactorial and may include social determinants of health, as well as potential immunological responses to the virus, among many other nonmedical and medical factors. Our previous study from the early phases of the pandemic (pre-Delta) showed that AI/AN patients had significantly higher and protracted SARS-CoV-2 viral loads in peripheral blood which was a strong predictor of severe COVID-19 (24). Viral sequencing efforts in a subgroup of the patients presented here revealed infection with SARS-CoV-2 from viral clades 20A, 20B, 20C, 20G, Alpha, and Delta that were equally distributed across the groups. While findings from our studies can provide valuable insights into the general understanding of COVID-19 and its management, they may not directly reflect the situation of the Omicron and forthcoming waves. Therefore, it is crucial to interpret and apply our findings cautiously, considering the evolving nature of the pandemic.

In summary, these findings emphasize the need for addressing health disparities in the COVID-19 pandemic for racial and ethnic minority groups. Collaborative partnerships between tribal authorities, healthcare providers, and public health agencies are also essential in developing and implementing effective strategies to address access barriers and improve health outcomes (43).

The large sample size in this study provides robust comparisons between different racial and ethnic groups which reflects the diverse population in the Southwest. The single-site study has a robust database that allowed us to account for important factors such as the duration of COVID-19 symptoms and days infected prior to hospitalization, as well as comorbidities, in determining factors associated with disease severity and mortality. To identify potential therapeutic targets for improved patient outcomes, particularly in populations who are most susceptible, we are currently investigating the entire expressed transcriptome in individuals representing different races/ethnicities with nonsevere and severe COVID-19.

Methods

Study participants

In this prospective observational study, eligible hospitalized patients with quantitative reverse transcription polymerase chain reaction confirmed (RT-qPCR) SARS-CoV-2 infections were recruited from UNMH. Exclusion criteria for this study included patients younger than 18 years of age, receiving extracorporeal membrane oxygenation treatment upon admission, or inability/unwillingness of either the patient or legally authorized representative (LAR) to provide informed consent. Admission dates in the cohort ranged from April 23, 2020 to December 14, 2021. The study was approved by the University of New Mexico Health Sciences Center Human Research Protection Office (protocol #20–194).

Data collection

Verbal interviews with the patient/LAR were conducted to determine patient demographics, past medical histories (including all comorbidities), and presenting COVID-19 symptoms. This information was also extracted from the electronic health records (EHR) for validation. Participants were provided the opportunity to self-identify their racial/ethnic identity. The choice of race included: Asian, AI/AN, Black, Native Hawaiian/Other Pacific Islander, White, unknown, or other (specify). A separate question encompassed ethnicity: Hispanic/Latino, Non-Hispanic Latino, Not specified, or other (specify). Using this information, we came up with the primary comparison groups representative of the demographics for the State of New Mexico: AI/AN, Hispanic/Latino, Non-Hispanic White, and Other.

The burden of multiple comorbid conditions was assessed using the 17-item age-adjusted CCI (25). The CCI is a widely used method to categorize comorbidities of patients based on the International Classification of Diseases diagnosis codes. The index is calculated from a weighted index of age, plus an associated weight (from 1 to 6) for each comorbidity category based on the adjusted risk of mortality or resource use. The sum of all the weights results in a single comorbidity score for a patient. A higher score indicates a greater burden of comorbidities and a higher likelihood of mortality. Additional information extracted from the EHR for the hospitalized encounter included: laboratory values (see Table S1), oxygen requirements (i.e. room air, low-flow, high-flow/noninvasive ventilation (NIV), or invasive mechanical ventilation), treatment (i.e. remdesivir and/or steroids), acute clinical events related to COVID-19 [i.e. invasive mechanical ventilation, kidney replacement therapy, acute hepatic injury, heart failure, stroke, venous thromboembolism (VTE), shock, and encephalopathy], length of hospitalization (days), and in-hospital mortality. Severe disease was defined as COVID-19-related admission to the intensive care unit (ICU) and/or death during hospitalization, while nonsevere disease was defined as not requiring ICU support and survival throughout hospitalization.

Statistical analyses

Statistical comparisons were performed using SPSS (version 28.0, IBM) and R (version 4.2.2). Patient demographics, comorbidities, clinical measures, laboratory values, therapeutic treatments, and disease outcomes were analyzed between the AI/AN, Hispanic, and NHW groups. Categorical data (e.g. sex at birth, comorbidities, etc.) were reported as the count of individuals and their corresponding proportion (%). Differences in proportions across the groups were determined using a chi-square test for

equal proportions with Yates continuity correction. In cases of significant differences, pairwise analysis was performed using the same test. Continuous variables [e.g. age, body mass index (BMI), laboratory values, etc.] were described as the median and IQR values or means and standard error of the mean (SEM) as appropriate. The Kruskal–Wallis test or one-way ANOVA was used to compare data among the three groups. Pairwise comparisons were performed for significant across-group differences using the Mann–Whitney *U* test. The Holm correction was used to adjust for multiple comparisons. Significance was established as $P \leq 0.05$. By using these statistical methods and criteria, we aimed to comprehensively analyze and compare the various variables across the AI/AN, Hispanic, and NHW groups in our study.

Logistic regression models were used to examine the associations between various factors and disease severity or mortality outcomes in COVID-19 patients. These analyses were conducted with either disease severity or mortality as the dependent variables and race/ethnicity (NHW set as reference), age, sex at birth, days symptomatic before enrollment, BMI, treatment (remdesivir and/or steroids), comorbid conditions, and major clinical events as covariates. In the models, treatment with remdesivir and steroids was coded as 0 = no treatment and 1 = treatment for each of the treatments. This allowed for the individual and combined effects of treatment on the outcome variables. NHW was selected as the reference group since they represent the socioeconomically advantaged racial/ethnic group, thus offering the ability to detect potential health disparities among minority groups. Relevant factors were identified by forward–backward selection minimizing the Akaike information criterion. This method was utilized to determine the most relevant factors influencing the outcome, and to create a model that is neither too simple (missing important predictors) nor too complex (including irrelevant predictors) (44). In separate models with the same criteria, CCI was used instead of individual comorbidities to capture the cumulative impact of multiple comorbidities in a single, standardized measure, which can be particularly beneficial when analyzing outcomes influenced by the overall health status, such as in our case. This can help to avoid potential issues related to multicollinearity that may arise when including multiple related variables (individual comorbidities) in the model. Further, the CCI has been widely validated and used in numerous studies, providing a common metric that allows for comparability across studies and populations. Holm correction for multiple testing was applied for all models.

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Supplementary material

Supplementary material is available at *PNAS Nexus* online.

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Author Contributions

D.J.P. and I.H. conceived and designed the study; G.M., I.H., and D.J.P. wrote the protocol, obtained ethics approval and authorization for the study; J.P.T., M.H., M.U., P.S., and J.O.L. provided clinical input; I.H., J.P.T., M.H., and D.J.P. enrolled participants; I.H., A.V.Y., T.A., A.C., J.J.K., A.D., D.K.L., Q.C., A.W., J.O.L., and D.J.P. gathered study data; I.H., T.A., O.B., C.G.L., A.F., C.O., S.B.A., S.L., K.A.S., and D.J.P. analyzed the data; K.A.S. provided statistical advice and support for quantitative and regression analysis; I.H. and D.J.P. wrote the manuscript; I.H. and D.J.P. have directly accessed and verified the underlying data reported in the manuscript. All authors contributed to revising the manuscript and agree on the final version.

Data availability

The datasets supporting the current study have not been deposited because they contain personally identifiable information from human subjects. These data may be made available from the corresponding author on request (Douglas J. Perkins; DPerkins@salud.unm.edu). A proposal with a detailed description of the study objectives and statistical analysis plan will be needed to evaluate the reasonability of the requests. Deidentified data will be provided after approval from the lead contact and the University of New Mexico standard IRB process for such requests.

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