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Complete List of Authors:	Cai, Miao; Saint Louis University, Department of Epidemiology & Biostatistics Bowe, Benjamin; Saint Louis University, Epidemiology and Biostatistics Xie, Yan; VA Saint Louis Health Care System, Clinical Epidemiology Center Al-Aly, Ziyad; VA Saint Louis Health Care System, Clinical Epidemiology Center

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Temporal Trends of COVID-19 Mortality and Hospitalization Rates: An observational cohort study from the US Department of Veterans Affairs

Miao Cai[a,b], PhD; Benjamin Bowe[a,b,c], MPH; Yan Xie[a,b,c], MPH; and Ziyad Al-Aly[a,b,d,e,f] MD

[a] Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[b] Veterans Research & Education Foundation of St. Louis, Saint Louis, Missouri

[c] Department of Epidemiology and Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri

[d] Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

[e] Nephrology Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[f] Institute for Public Health, Washington University in Saint Louis, Saint Louis, Missouri

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Corresponding Author:
Ziyad Al-Aly, M.D.
VA Saint Louis Health Care System
915 North Grand Boulevard, 151-JC
Saint Louis, MO 63106
Telephone: (314) 289-6333
Twitter @zalaly
Email: zalaly@gmail.com

Abstract

Objective: To investigate the temporal trends of 30-day mortality and hospitalization in United States Veterans with COVID-19 and 30-day mortality in hospitalized Veterans with COVID-19; and to decompose the contribution of changes in the underlying characteristics of affected populations to these temporal changes.

Design: Observational cohort study.

Setting: US Department of Veteran Affairs.

Participants: 49 238 United States Veterans with a positive COVID-19 test between March 20, 2020 and September 19, 2020; and 9 428 United States Veterans hospitalized with a positive COVID-19 test during the same period.

Outcome measures: 30-day mortality rate and hospitalization rate.

Results: Between March 20, 2020 and September 19, 2020 and in COVID-19 positive individuals, 30-day mortality rate dropped by 9.2% from 13.6% to 4.4%; hospitalization rate dropped by 16.8% from 33.8% to 17.0%. In hospitalized COVID-19 individuals, 30-day mortality rate dropped by 12.7% from 23.5% to 10.8%. Among COVID-19 positive individuals, decomposition analyses suggested that changes in demographic, health and contextual characteristics, COVID-19 testing capacity, and hospital occupancy accounted for 40.2% and 33.3% of the decline in 30-day mortality and hospitalization, respectively. Changes in the underlying characteristics of hospitalized COVID-19 individuals accounted for 29.9% of the decline in 30-day mortality.

Conclusion: Between March and September 2020, changes in demographic and health characteristics of people infected with COVID-19 contributed measurably to the substantial decline in 30-day mortality and hospitalization.

Strengths and limitations of the study

- National large-scale individual-level data from the US Department of Veterans Affairs which operated the largest integrated health care system in the United States.
- Advanced decomposition methods disentangle the influence of changes in demographics and health characteristics on temporal trends of 30-day mortality and hospital rates.
- The study accounted for important but less studied drivers of change in mortality and hospitalization including contextual variables, testing capacity, and hospital occupancy rates.
- The Veteran population includes mostly older White males, which may limit the generalizability.

Introduction

Reports from regional health systems and the Center of Disease Control suggest substantial temporal variations in COVID-19 mortality rates[1-3]; however, a national temporal analysis of mortality and hospitalization rates accounting for individual-level characteristics is lacking and the relative contribution of changes in demographic and health characteristics of people infected with COVID-19 to temporal differences in mortality rates is not clear.

A deeper understanding of the changes in hospitalization and mortality rates and the drivers of such changes in the first wave of the pandemic will aid effort to optimize management of future waves of this global pandemic.

In this work, we leveraged the breadth and depth of the United States Department of Veterans Affairs electronic health care databases to describe temporal changes in mortality rates and hospitalization among COVID-19 positive Veterans, and temporal changes in mortality rates of hospitalized veterans with COVID-19. We then decomposed the contribution of changes in demographic, health, contextual characteristics to these temporal changes.

Methods

Identification of COVID-19 test positive individuals

Using the comprehensive COVID-19 Shared Data Resource (CSDR) [4] developed by the Department of Veterans Affairs (VA), we identified unique US Veterans with their first laboratory confirmed COVID-19 positive test between March 20, 2020 and September 19, 2020. The CSDR captures COVID-19 cases based on laboratory results that comply with

Centers for Disease Control and Prevention standards, including 2019-nCOV RT-PCR (reverse transcription-polymerase chain reaction) Diagnostic Panel and the SARS-CoV-2 Multiplex Assay, or human-confirmed case review[4]. The VA had its first COVID-19 positive patient on March 02, 2020. In this study, March 20, 2020 was selected as the first day of observation where it was the first day that VA had more than 100 COVID-19 positive patients nationally, facilitating stabilization of rate calculations. September 19, 2020 was selected as the last day of observation to ensure 30 days of follow-up for observation of outcomes.

Data sources

Data were obtained from the VA CSDR[4] and Corporate Data Warehouse (CDW) [5-17], which provides electronic health record information during routine healthcare. Demographic information and dates of death were collected from the CDW SPatient domain. Patient clinical diagnoses, procedures, and hospitalization characteristics were obtained from the CDW Outpatient Encounter and Inpatient Encounter domains. Smoking status was obtained from the CDA Health Factors domain. Laboratory results, including serum creatinine, were obtained from the CDW Patient Laboratory Chemistry domain. Data on height, weight, and blood pressure were procured from the CDW Vital Signs domain. The CDW Outpatient Pharmacy domain was used to obtain diabetes medication data. The Planning System Support Group Enrollee provided the Federal Information Processing Standard (FIPS) code of residence. The 2015 Area Deprivation Index (ADI) were obtained from the University of Wisconsin. The ADI is a composite measure of a census block group's socio-economic disadvantage, and is constructed from data elements including education, employment, housing quality, and poverty measures[18].

Outcomes

We examined the temporal trends in a) rates of 30-day mortality and hospitalization among those with a positive COVID-19 test, and b) rates of 30-day mortality among those hospitalized with COVID-19. 30-day mortality was defined as all-cause mortality occurring within the 30 days after the participant's first COVID-19 positive test. Hospitalization is defined by a hospital admission between 5 days before and 30 days after the first COVID-19 positive test.

Participant characteristics

Race was categorized as White, Black, and other. Health features included body weight index (BMI) and smoking status. BMI was computed from the last measurements of the participant's height and weight prior and closest to the first COVID-19 positive test date. Smoking status was categorized as never smoker, former smoker, and current smoker, based on the most recent record prior to the first COVID-19 positive test. Comorbidities included cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), dementia, diabetes mellitus, human immunodeficiency virus (HIV), hypertension, peripheral artery disease, and pneumonia. Cancer, cardiovascular disease, cerebrovascular disease, dementia, HIV, peripheral artery disease, pneumonia, and COPD were identified in the two years prior to testing positive for COVID-19 through International Classification of Diseases Tenth Version Clinical Modification diagnosis codes. Chronic kidney disease was defined as baseline estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73m^2. Baseline eGFR was calculated using the CKD-EPI equation[19] and was assessed as the Veteran's last outpatient value prior to the date of first COVID-19 test positive. Participants who had no measurement of baseline eGFR (N=5 447, 11.1% for Veterans with COVID-19; N=717, 7.6% for hospitalized Veterans with COVID-19) were assumed to have no chronic kidney disease. Diabetes was defined as any use of antihyperglycemic medications[20-23] or incidence of hemoglobin A1C greater or equal to 6.5%.[24] Hypertension was defined as median systolic blood pressure greater than or equal to 130 mmHg or median diastolic blood pressure greater than or equal to 80 mmHg in one year.[25] Participants who had no measurement of blood pressure (N=2 699, 5.5% for Veterans with COVID-19; N=235, 2.5% for hospitalized Veterans with COVID-19) were assumed to have no chronic kidney disease. ADI is a composite measure of a geographic location's socio-economic disadvantage, and ranges from 0 (low disadvantage) to 100 (high disadvantage). County level ADI of the participants was assigned based on the participant's FIPS code of residence location at the first COVID-19 positive test date. Mean imputation was applied to missing values of covariates including BMI (missing = 111, 0.2% of Veterans with COVID-19; missing = 11, 0.1% of hospitalized Veterans with COVID-19) and ADI (missing = 1303, 2.6% of Veterans with COVID-19; missing = 88, 1.0% of hospitalized Veterans with COVID-19). COVID-19 testing capacity was calculated as 7-day averages of the number of COVID-19 tests conducted in a hospital system divided by the total number of veterans served in that hospital system in the last calendar year. Hospital occupancy was defined as the percentage of beds occupied by hospitalized patients in a hospital system within a calendar week. COVID-19 testing capacity and hospital occupancy were linked to the Veterans by the hospital system in which the individuals had their first positive COVID-19 test.

Statistical analyses

We calculated and plotted 7-day moving averages of crude and standardized 30-day mortality and hospitalization rates in COVID-19 positive participants, as well as 30-day mortality rates in hospitalized COVID-19 positive participants. The 7-day range included the current day, and the three days before and after. Standardized rates were adjusted for age, race, gender, health behaviors (smoking status and BMI), comorbidities, and ADI through indirect standardization [26]. The standardization was based on the ratio difference between expected and observed number of outcomes, where expected number of outcomes were estimated from individual-level logistic regressions.

To understand driving factors of the temporal tends in the outcomes, we decomposed the contribution of the changes in key participant characteristics to changes in the observed rates of outcomes over time. We first constructed individual-level logistic regression models for the different outcomes using four sets of factor domains: demographics (age, race, gender), health characteristics (BMI, diabetes, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, dementia, HIV, hypertension, peripheral artery disease, pneumonia, and smoking status), contextual factors (ADI), COVID-19 testing capacity, and hospital occupancy. Hospital occupancy rate was not included as a predictor of hospitalization since they are measuring the same variable. For each individual, we then computed the expected probabilities of the outcome based on a participants observed characteristics and under a reference characteristics set, where probability of the outcome was minimized (age was set as zero, and other categorical variables were set to be the reference group). We estimated the additive contribution of the six set of factor domains to the estimated rates of the outcome using decomposition analysis[27]. Then the change in outcome rates between the first (March 20 to April 19) and the last (August 20 to September 19) 30 day periods associated with each domain were calculated by taking the difference of the contributions between the two periods.

All statistical tests were two sided, and a p-value less than 0.05 or a 95% confidence interval that did not contain unity was considered statistically significant. Statistical analyses and data visualization were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC) and R 4.0.2[28]. The participants were not involved in the design, or conduct, or reporting, or dissemination plans of the study. The study was approved by the Institutional Review Board of the Department of Veterans Affairs St Louis Health Care System, St Louis, MO.

Patient and public involvement

This research was done without patient and public involvement.

Results

Between March 20, 2020 and September 19, 2020, we identified 49 238 US Veterans who tested positive for COVID-19 and 9 428 US Veterans hospitalized with COVID-19. Characteristics of the two cohorts are reported in Table 1. Among individuals with COVID-19, the median age was 63.3 years (interquartile range [IQR], 49.8 to 73.1 years); 60.6% were White, 33.9% were Black, and 11.5% were women. Among hospitalized individuals, the median age was 70.6 years (IQR 61.2 to 76.8 years), 53.6% were White, 40.4% were Black, and 6.0% were women.

Temporal trends in 30-day mortality and hospitalization rates

Between March 20, 2020 and September 19, 2020 and among individuals with a COVID-19 positive test the 30-day mortality rate dropped by 9.2% from 13.6% to 4.4%; the hospitalization rate dropped by 16.8% from 33.8% to 17.0% (Table 2 and Figure 1). Among hospitalized individuals with COVID-19, the 30-day mortality rate dropped by 12.7% from 23.5% to 10.8% (Table 2 and Figure 1). After accounting for demographics, contextual factors, health characteristics, COVID-19 testing capacity, and hospital occupancy, standardized rates showed consistent decline during the period (Figure 1).

Between March 20, 2020 and September 19, 2020 and among hospitalized individuals with COVID-19, we observed consistent decline in healthcare resource utilization including decline in rates of intensive care unit (ICU) admission, mechanical ventilator use, and length of hospital stay (Supplemental Table 1). The rate of ICU stay dropped by 4% from 35.6% to 31.6%; the rate of mechanical ventilator use dropped by 11.3% from 20.6% to 9.3%; the mean length of stay dropped by 4.2 days from 13.8 to 9.6 days.

Predictors of 30-day mortality and hospitalization

Adjusted odds ratios for the association between potential predictors and risk of 30-day mortality and hospitalization among Veterans with COVID-19, as well as risk of 30-day mortality among hospitalized Veterans with COVID-19 are presented in Table 3. Among Veterans with COVID-19, older age, Black and other race, male gender, current smoker, diabetes, cancer, cardiovascular disease, dementia, chronic kidney disease, pneumonia, COPD, and higher hospital occupancy rate were associated with higher risk of 30-day mortality and hospitalization; higher COVID-19 testing capacity was associated with lower risk of 30-day mortality and hospitalization. Among hospitalized Veterans with COVID-19, older age, male gender, obesity, current smoker, diabetes, cardiovascular disease, chronic kidney disease, dementia, and higher hospital occupancy rate were associated with higher risk of 30-day mortality; higher COVID-19 testing capacity was associated with lower risk of 30-day mortality. The models for 30-day mortality and hospitalization among those who tested positive, and the model for 30-day mortality among hospitalized achieved reasonably good predictive performance, with the c-statistics of 0.834, 0.718, and 0.746, respectively. The c-statistics for nested models, showing the predictive performance improvement when adding different variable sets, are included in Supplemental Table 2.

Temporal change of predictors of 30-day mortality and hospitalization

The demographic, health, and contextual characteristics as well as hospital occupancy and testing capacity in each 30-day interval between March 20, 2020 and September 19, 2020 are described in Figure 2A and 2B and Supplemental Table 3A and 3B. We observed substantial decline in percent of Black patients over time in both individuals with COVID-19 (from 47.2% to 25.5%, dropping by 21.7%) and hospitalized individuals with COVID-19 (from 54.4% to 28.2%, dropping by 26.3%). The prevalence of comorbidities was consistently dropping between the two period in individuals with COVID-19; the overall trend of comorbidity prevalence was still declining while less consistent in hospitalized individuals with COVID-19. In both of two cohorts over time, the percent of individuals living in disadvantaged neighborhood (higher ADI) and COVID-19 testing capacity were increasing, while hospital occupancy was decreasing.

The contribution of changes in predictors to temporal changes in 30-day mortality and hospitalization rates

Decomposition analyses showed that from March 20, 2020 to September 19, 2020 and among COVID-19 positive individuals, changes in demographics, health characteristics, and contextual characteristics, expansion of testing capacity, and decreasing hospital occupancy contributed to 26.1%, 7.6%, 5.4%, -1.1%, and 2.2% of the decline in 30-day mortality rates respectively. Altogether, these predictors accounted for 40.2% of the decline in 30-day mortality in Veterans with COVID-19 (Figure 3 and Supplemental Table 4).

Changes in demographics, health characteristics, and contextual characteristics, and expansion of testing capacity, and decreasing hospital occupancy contributed to 19.6%, 9.0%, -0.6%, and 5.4% of the decline in hospitalization rates. Altogether, they accounted for 33.3% of the decline in hospitalization rates in Veterans with COVID-19 (Figure 3 and Supplemental Table 4).

Among those hospitalized with COVID-19, changes in demographic, health characteristics, and contextual characteristics, expansion of testing capacity, and decreasing hospital occupancy accounted for 23.6%, 2.4%, -0.8%, 1.6%, and 3.1% of the decline in 30-day mortality rate respectively. All predictors collectively accounted for, 29.9% of the decline in 30-day mortality (Figure 3 and Supplemental Table 4).

Discussion

This analysis of temporal trends of COVID-19 hospitalization and mortality suggests substantial decline between March 2020 and September 2020. We also observed substantial shifts in the demographic and health characteristics of those who tested positive for COVID-19 and in those who were hospitalized with a positive COVID-19 test including substantial decline in the percentage of Black people and comorbidity burden as well as increase in testing capacity and reduction in hospital occupancy rates. Around 40.2% of the decline in mortality rates and 33.3% of decline in hospitalization rates were explained by changes in the underlying characteristics of people who tested positive for COVID-19. Around 29.9% of the decline in mortality rates among hospitalized individuals was explained by changes in their underlying characteristics.

Our analysis highlights the influence of individual-level demographic and health characteristics on hospitalization and mortality rates in COVID-19. The contribution of changes in testing capacity to these outcomes (albeit small) was measurable. The contribution of hospital occupancy rates to decline in mortality rates also highlights the importance of this variable as policy makers and health systems continue to optimize the public health response to this pandemic.

Slightly more than half of decline in rates was not predicted by the explanatory variables in our models and likely reflects the influence of factors that are not accounted for in our approach including improvement in medical care (to the extent that it may have influenced the outcomes), a putative seasonality effect, and the potential influence of the broader public health policy measures on these outcomes. In particular, it has been postulated that severity of COVID-19 may be proportionate to the viral inoculum which initiates the infection in the human host, and it is plausible that public health policies (e.g. physical distancing, masking, etc.) may have reduced the viral inoculum in some infected individuals and might have consequently resulted in less severe COVID-19 (and reduced hospitalization and mortality) – a hypothesis referred to as the variolation of coronavirus[29]. The COVID-19 pandemic has brought to prominence the complex interplay of several dynamic drivers including individual-level demographic and health characteristics, health system-level characteristics, the influence of socioeconomic factors, and the broader contextual reality in which people live (public health response, etc.) — all collectively shape the ultimate health outcomes of COVID-19. Continued effort to surveil temporal trends of key indicators of this global pandemic, and careful analysis of drivers of any temporal change is needed to inform ongoing effort to optimize the management of this so far unabated pandemic.

A key strength of this analysis is the use of individual level data from the US Department of Veterans Affairs which operates the largest nationally integrated health care system in the US, and use of advanced methods to decompose the influence of changes in demographics and health characteristics on temporal trends. In addition to accounting for individual-level demographic and health characteristics, our analyses also account for contextual variables, testing capacity, and measures of hospital occupancy rates — as important determinants of outcomes in this pandemic.

This analysis has several limitations. While the use of data from the Department of Veterans Affairs enabled the evaluation of national temporal trends using individual-level data, the Veteran population is comprised of older White males and the findings may not be generalisable to the general population. While we used validated definitions to identify covariates, we cannot completely rule out misclassification bias. While we accounted for known predictors, our analyses do not account for predictors that are not measured in the datasets including improvement in medical care as the pandemic progressed, and other unmeasured or unknown variables.

In sum, between March 2020 and September 2020, substantial decline in 30-day mortality and hospitalization among COVID-19 positive individuals and substantial decline in 30- day mortality among hospitalized Veterans with COVID-19. The temporal decline in these outcomes was partially explained by changes in underlying demographic, health, and contextual characteristics, and well as expansion of testing capacity, and reduction in hospital capacity. The results may be helpful in informing effort to optimize the collective public health response to this ongoing pandemic.

Author Contribution:

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Cai, Bowe, Xie.

Drafting of the manuscript: Cai, Al-Aly.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Cai, Bowe, Xie.

Supervision and funding: Al-Aly.

Conflict of Interest Disclosures: None reported.

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Table 1: Characteristics of the individuals with COVID-19 and hospitalized individuals with COVID-19

Characteristic	Veterans with COVID-19 (N = 49238)	Hospitalized Veterans with COVID-19 (N = 9428)
Demographics		
Age, median (IQR), year	63.3 (49.8-73.1)	70.6 (61.2-76.8)
Race, no. (%)		
White	29814 (60.6)	5054 (53.6)
Black	16714 (33.9)	3809 (40.4)
Other	2710 (5.5)	565 (6.0)
Sex, no. (%), women	5673 (11.5)	527 (5.6)
Health characteristics		
BMI category, no. (%)		
Underweight (<8.5 kg/m^2)	265 (0.5)	83 (0.9)
Normal weight (18.5 to <25 kg/m^2)	9939 (20.2)	1836 (19.5)
Overweight (25 to <30 kg/m^2)	15032 (30.5)	2922 (31.0)
Obesity (>18.5 kg/m^2)	24002 (48.7)	4587 (48.7)
Smoke, no. (%)		
Never smoker	27492 (55.8)	4713 (50.0)
Former smoker	13062 (26.5)	2956 (31.4)
Current smoker	8684 (17.6)	1759 (18.7)
Hypertension, no. (%)	30568 (62.1)	6347 (67.3)
Diabetes, no. (%)	13717 (27.9)	3695 (39.2)
Cancer, no. (%)	4558 (9.3)	1443 (15.3)
Cardiovascular disease, no. (%)	10399 (21.1)	3417 (36.2)
Cerebrovascular disease, no. (%)	5192 (10.5)	1836 (19.5)
Dementia, no. (%)	5350 (10.9)	1953 (20.7)
Chronic kidney disease, no. (%)	9573 (21.9)	3042 (34.9)
Peripheral artery disease, no. (%)	1411 (2.9)	543 (5.8)
HIV, no. (%)	504 (1.0)	141 (1.5)
Pneumonia, no. (%)	765 (1.6)	336 (3.6)
COPD, no. (%)	7666 (15.6)	2429 (25.8)
Contextual factors		
ADI rank category, no. (%)		
0 to 33.3	10248 (20.8)	1785 (18.9)
33.4 to 66.6	20861 (42.4)	3643 (38.6)
66.7 to 100	18129 (36.8)	4000 (42.4)
Testing capacity		
COVID-19 testing capacity, mean (SD), per 10000 people	3.1 (1.9)	2.8 (1.8)
Hospital occupancy		
Hospital occupancy, mean (SD), %	37.0 (10.8)	38.1 (10.5)

ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus; IQR: interquartile range; IQR: interquartile range; SD: standard deviation.

Table 2 30-day mortality and hospitalization rates in US veterans by 30-day periods, March 20, 2020 to September 19, 2020

Periods	Total number of COVID-19 patients	30-day mortality, n (%)	Hospitalization, n (%)	30-day mortality among hospitalized COVID-19 patients, n (%)
March 20 - April 19	5896	13.6%	33.8%	23.5%
April 20 - May 19	6685	12.3%	17.2%	17.0%
May 20 - June 19	4824	7.1%	20.0%	12.6%
June 20 - July 19	13084	4.9%	17.4%	11.8%
July 20 - August 19	11874	5.2%	15.8%	11.1%
August 20 - September 19	6875	4.4%	17.0%	10.8%
Overall	49238	7.2%	19.1%	14.8%

Table 3 Odd ratios (95% confidence intervals) of predictors associated with 30-day mortality and hospitalization among Veterans and hospitalized Veterans with COVID-19

Characteristics	**Veterans with COVID-19**		**Hospitalized Veterans with COVID-19**
	30-day mortality	**Hospitalization**	**30-day mortality**
Demographics			
Age	1.08 (1.07, 1.08)	1.02 (1.02, 1.02)	1.06 (1.06, 1.07)
Race (reference = white)			
Black	1.11 (1.01, 1.22)	1.64 (1.56, 1.74)	1.03 (0.90, 1.18)
Other	1.33 (1.12, 1.58)	1.58 (1.42, 1.76)	1.20 (0.92, 1.57)
Sex, women (reference = men)	0.52 (0.40, 0.67)	0.74 (0.67, 0.82)	0.72 (0.47, 1.06)
Health characteristics			
BMI category (reference = normal weight)			
Underweight (< 18.5 kg/m^2)	1.03 (0.64, 1.59)	1.26 (0.92, 1.71)	0.67 (0.29, 1.38)
Overweight (25 to < 30 kg/m^2)	0.89 (0.80, 1.00)	0.98 (0.91, 1.06)	1.07 (0.90, 1.29)
Obesity (> 18.5 kg/m^2)	1.02 (0.92, 1.15)	1.05 (0.98, 1.13)	1.24 (1.03, 1.49)
Smoking status (reference = never smoker)			
Former smoker	1.15 (1.05, 1.25)	1.01 (0.96, 1.07)	1.11 (0.97, 1.28)
Current smoker	1.12 (0.99, 1.27)	1.11 (1.03, 1.19)	1.21 (1.00, 1.46)
Hypertension	0.87 (0.80, 0.94)	1.10 (1.04, 1.16)	0.81 (0.70, 0.92)
Diabetes	1.37 (1.26, 1.49)	1.23 (1.16, 1.29)	1.15 (1.00, 1.31)
Cancer	1.10 (0.99, 1.22)	1.36 (1.27, 1.47)	1.03 (0.88, 1.21)
Cardiovascular disease	1.17 (1.07, 1.27)	1.43 (1.35, 1.52)	1.15 (1.00, 1.31)
Cerebrovascular disease	1.09 (0.98, 1.20)	1.38 (1.29, 1.48)	1.04 (0.90, 1.21)
Dementia	1.81 (1.65, 2.00)	1.52 (1.41, 1.63)	1.37 (1.18, 1.59)
Chronic kidney disease	1.48 (1.36, 1.61)	1.27 (1.20, 1.35)	1.47 (1.28, 1.68)
Peripheral arterial disease	1.09 (0.92, 1.29)	1.31 (1.16, 1.48)	1.17 (0.92, 1.47)
HIV	1.05 (0.67, 1.58)	1.50 (1.22, 1.85)	1.23 (0.71, 2.03)
Pneumonia	1.44 (1.15, 1.80)	2.00 (1.71, 2.35)	1.22 (0.90, 1.62)
COPD	1.21 (1.10, 1.32)	1.40 (1.31, 1.49)	0.96 (0.83, 1.11)
Contextual factors			
ADI rank (reference = 1-33.2)			
33.3 to 66.6	0.99 (0.89, 1.10)	1.03 (0.96, 1.10)	0.94 (0.79, 1.11)
66.7 to 100	1.04 (0.93, 1.16)	1.16 (1.09, 1.25)	0.92 (0.77, 1.09)
COVID-19 testing capacity			
COVID-19 testing capacity (per 10,000 veterans)	0.92 (0.90, 0.94)	0.95 (0.94, 0.96)	0.90 (0.86, 0.93)
Hospital occupancy			
Hospital occupancy rate (an increase of 10%)	1.05 (1.01, 1.08)	Not included	1.08 (1.02, 1.15)
C-statistics	0.834	0.718	0.746

ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus.

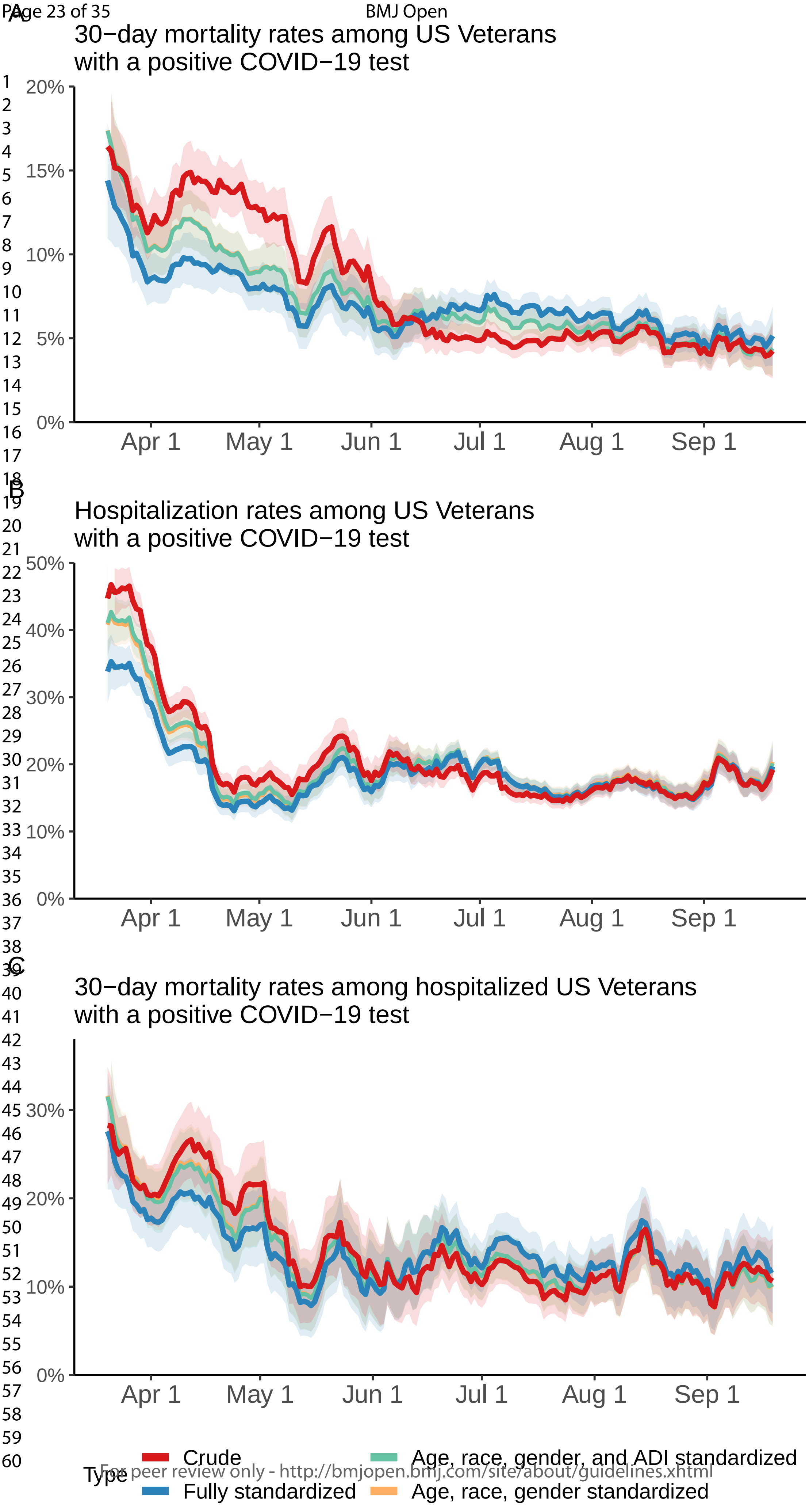
Figure Legends:

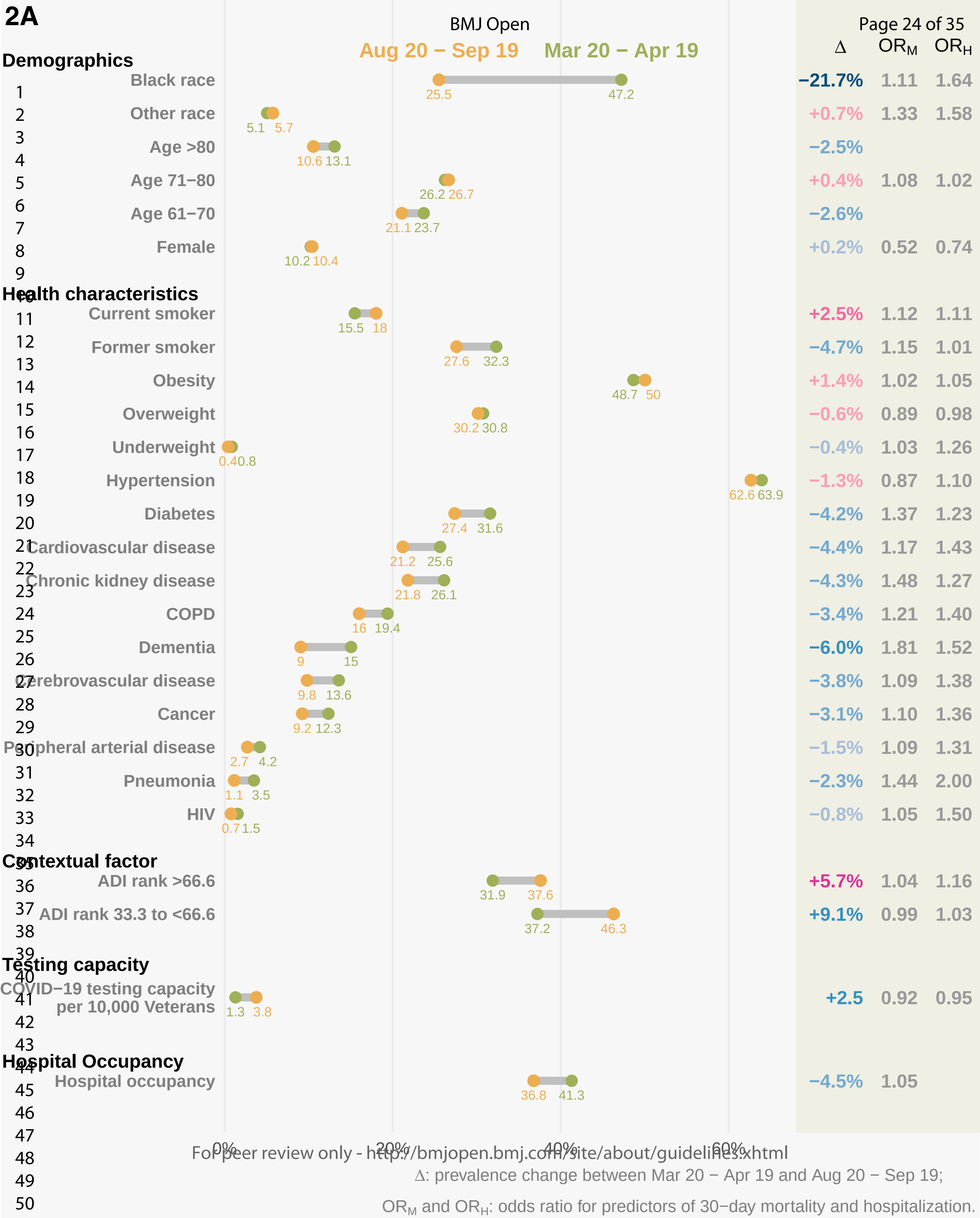
Figure 1. Temporal trends of COVID-19 30-day mortality and hospitalization among US Veterans. A and B: 30-day mortality and hospitalization rates in US Veterans who had a positive COVID-19 test (N=29,528). C: 30-day mortality rate in hospitalized US Veterans with a positive COVID-19 test (N=6,449). Fully standardized rates were adjusted for, demographics (age, race, gender), health characteristics (smoking status, body weight index, cancer, cardiovascular disease, chronic kidney disease, dementia, diabetes mellitus type 2, human immunodeficiency virus, hypertension, peripheral artery disease, pneumonia, and stroke), contextual factors (area deprivation index), COVID-19 testing capacity, and hospital occupancy.

Figure 2A The change in predictors of 30-day mortality and hospitalization among US Veterans with COVID-19 between 3/20–4/19, 2020 and 8/20–9/19, 2020. **The yellow dots** represent the prevalence of predictors in 3/20–4/19, 2020, while **the green dots** represent the prevalence of predictors in 8/20–9/19, 2020. In the delta column, **blue text** indicates that the change of predictor leads to decrease in mortality and hospitalization rates, while **red text** indicates the change of predictor leads to decrease in mortality and hospitalization rates. COPD: chronic obstrusive pulmonary disease.

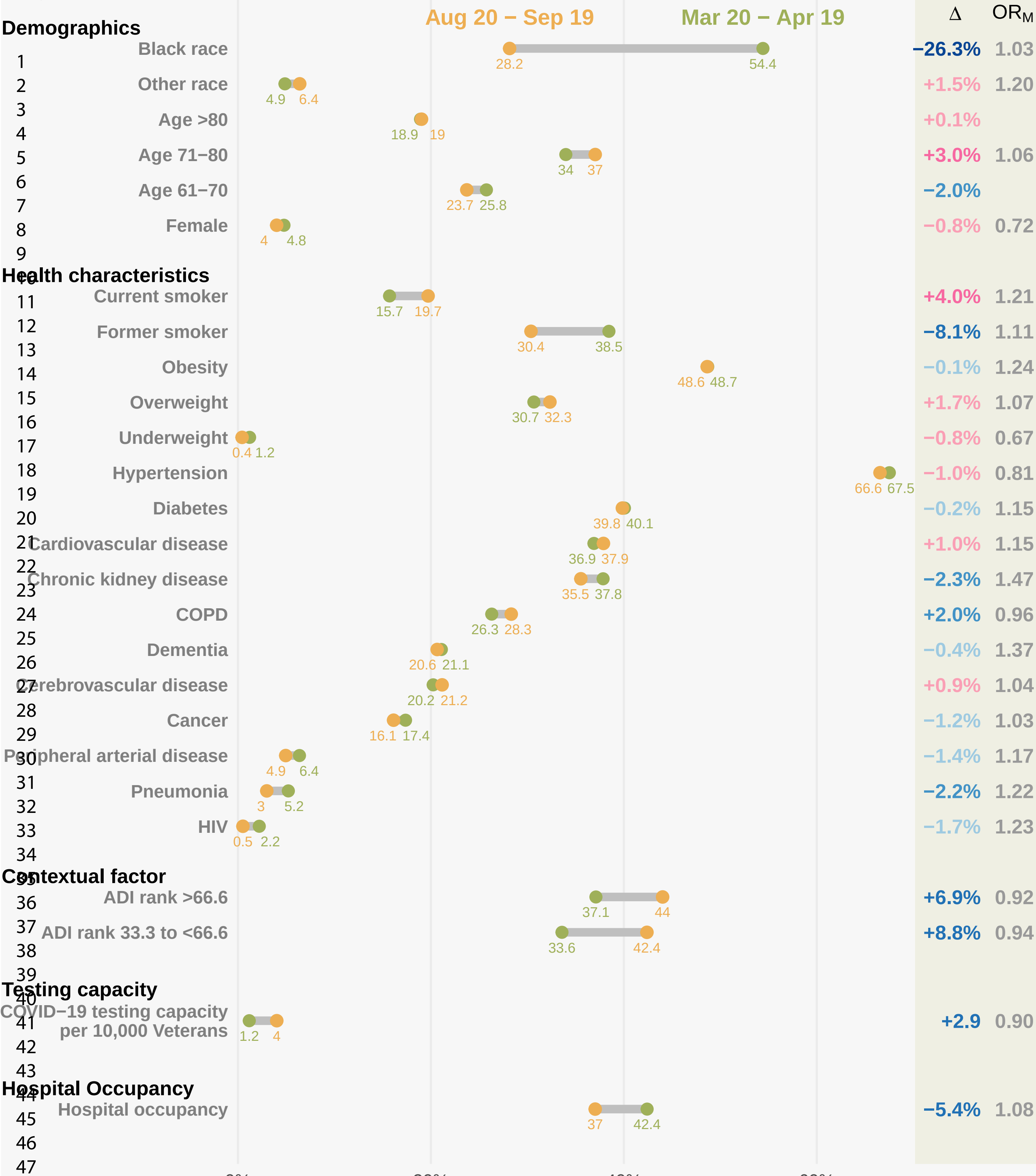
Figure 2B The change in predictors of 30-day mortality among hospitalized US Veterans with COVID-19 between 3/20–4/19, 2020 and 8/20–9/19, 2020. **The yellow dots** represent the prevalence of predictors in 3/20–4/19, 2020, while **the green dots** represent the prevalence of predictors in 8/20–9/19, 2020. In the Δ column, **blue text** indicates that the change of predictor leads to decrease in mortality rates, while **red text** indicates the change of predictor leads to decrease in mortality rates. COPD: chronic obstrusive pulmonary disease.

Figure 3 The contribution of changes in demographics, health characteristics, testing capacity, hospital occupancy, and contextual factors, and epidemiological changes to changes in 30-day mortality and hospitalization rates between 3/20–4/19, 2020 and 8/20–9/19, 2020. The red dot represents the observed change in rate of outcomes between the two periods, and the blue dot represents the change predicted based on demographics, health, contextual characteristics, COVID-19 testing capacity, and hospital occupancy. Hospital occupancy is not considered as predictor for the hospitalization outcome model. Epidemiological changes collectively represent the difference between predicted and observed rates and reflect the summative contribution of factors that are not accounted for in prediction models.


A
30−day mortality rates among US Veterans
with a positive COVID−19 test
20%
15%
10%
5%
0%
Apr 1
May 1
Jun 1
Jul 1
Aug 1
Sep 1
B
Hospitalization rates among US Veterans
with a positive COVID−19 test
50%
40%
30%
20%
10%
0%
Apr 1
May 1
Jun 1
Jul 1
Aug 1
Sep 1
C
30−day mortality rates among hospitalized US Veterans
with a positive COVID−19 test
30%
20%
10%
0%
Apr 1
May 1
Jun 1
Jul 1
Aug 1
Sep 1
Type
Crude
Fully standardized
Age, race, gender, and ADI standardized
Age, race, gender standardized

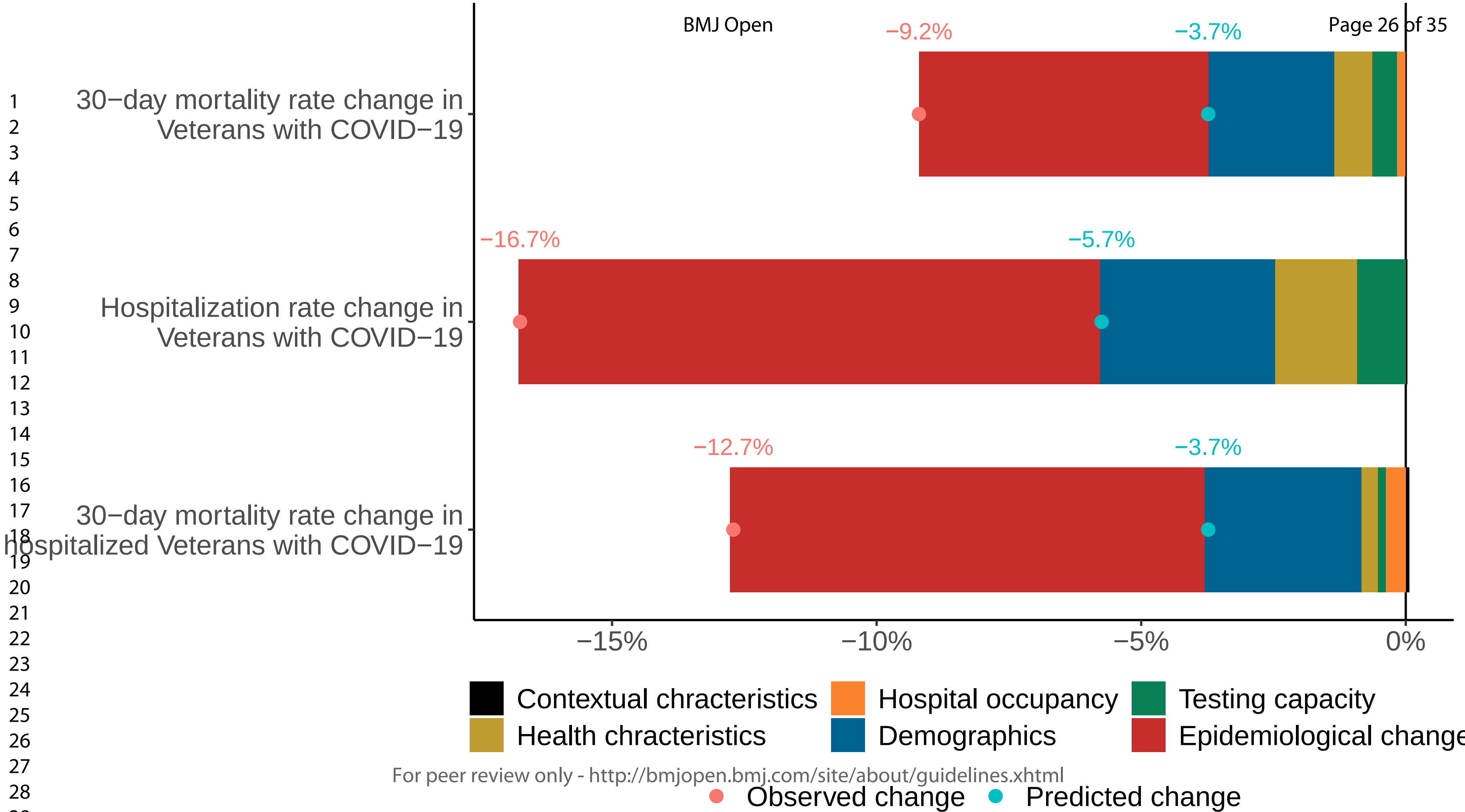

2A
Aug 20 − Sep 19
Mar 20 − Apr 19
Δ
OR_M
OR_H
Demographics
Black race 25.5 47.2 −21.7% 1.11 1.64
Other race 5.1 5.7 +0.7% 1.33 1.58
Age >80 10.6 13.1 −2.5%
Age 71−80 26.2 26.7 +0.4% 1.08 1.02
Age 61−70 21.1 23.7 −2.6%
Female 10.2 10.4 +0.2% 0.52 0.74
Health characteristics
Current smoker 15.5 18 +2.5% 1.12 1.11
Former smoker 27.6 32.3 −4.7% 1.15 1.01
Obesity 48.7 50 +1.4% 1.02 1.05
Overweight 30.2 30.8 −0.6% 0.89 0.98
Underweight 0.4 0.8 −0.4% 1.03 1.26
Hypertension 62.6 63.9 −1.3% 0.87 1.10
Diabetes 27.4 31.6 −4.2% 1.37 1.23
Cardiovascular disease 21.2 25.6 −4.4% 1.17 1.43
Chronic kidney disease 21.8 26.1 −4.3% 1.48 1.27
COPD 16 19.4 −3.4% 1.21 1.40
Dementia 9 15 −6.0% 1.81 1.52
Cerebrovascular disease 9.8 13.6 −3.8% 1.09 1.38
Cancer 9.2 12.3 −3.1% 1.10 1.36
Peripheral arterial disease 2.7 4.2 −1.5% 1.09 1.31
Pneumonia 1.1 3.5 −2.3% 1.44 2.00
HIV 0.7 1.5 −0.8% 1.05 1.50
Contextual factor
ADI rank >66.6 31.9 37.6 +5.7% 1.04 1.16
ADI rank 33.3 to <66.6 37.2 46.3 +9.1% 0.99 1.03
Testing capacity
COVID−19 testing capacity per 10,000 Veterans 1.3 3.8 +2.5 0.92 0.95
Hospital Occupancy
Hospital occupancy 36.8 41.3 −4.5% 1.05
0%
20%
40%
60%
Δ: prevalence change between Mar 20 − Apr 19 and Aug 20 − Sep 19;
OR_M and OR_H: odds ratio for predictors of 30−day mortality and hospitalization.

2B



Δ: prevalence change between Mar 20 − Apr 19 and Aug 20 − Sep 19;

OR_M: odds ratio for predictors of 30−day mortality.


−9.2%
−3.7%
30−day mortality rate change in Veterans with COVID−19
−16.7%
−5.7%
Hospitalization rate change in Veterans with COVID−19
−12.7%
−3.7%
30−day mortality rate change in hospitalized Veterans with COVID−19
−15%
−10%
−5%
0%
Contextual chracteristics
Hospital occupancy
Testing capacity
Health chracteristics
Demographics
Epidemiological change
Observed change
Predicted change

Supplemental material

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Supplemental Table 1 Health care resource utilization among hospitalized Veterans with COVID-19

Month	**ICU**	**Mechanical Ventilation**	**LOS**
March 20 - April 19	35.6%	20.6%	13.8
April 20 - May 19	31.0%	13.5%	16.2
May 20 - June 19	31.2%	11.4%	12.1
June 20 - July 19	29.7%	11.7%	11.4
July 20 - August 19	28.2%	11.2%	11
August 20 - September 19	31.6%	9.3%	9.6
Overall	31.2%	13.4%	12.3

ICU: intensive care units; LOS: length of stay.

Supplemental Table 2: C statistics (95% confidence intervals) for nested models using different combination of predictors

Cohort	**Veterans with COVID-19**		**Hospitalized Veterans with COVID-19**
Predictor variables	**30-day mortality**	**Hospitalization**	**30-day mortality**
Demographics	0.822 (0.816-0.828)	0.678 (0.673-0.684)	0.725 (0.712-0.738)
+ health characteristics	0.832 (0.826-0.838)	0.713 (0.707-0.719)	0.740 (0.726-0.753)
+ contextual factors	0.832 (0.826-0.838)	0.714 (0.708-0.720)	0.741 (0.726-0.754)
+ COVID-19 testing capacity	0.834 (0.828-0.840)	0.715 (0.709-0.721)	0.745 (0.730-0.758)
+ hospital occupancy	0.834 (0.828-0.841)	0.718 (0.712-0.723)	0.746 (0.732-0.759)

Each + indicates including all the variable above that row. For example, "+ contextual factors" indicates including demographics, health characteristics, and contextual factors as predictors.

Supplemental Table 3A: Characteristics of US Veterans with COVID-19 overall and by different month periods							
Characteristic	**Overall** N = 49238	**March 20 – April 19** N = 5896	**April 20 – May 19** N = 6685	**May 20 – June 19** N = 4824	**June 20 – July 19** N = 13084	**July 20 – August 19** N = 11874	**August 20 – September 19** N = 6875
Age, median (IQR), year	63.3 (49.8-73.1)	65.3 (53.7-73.8)	68.0 (56.6-76.1)	63.9 (50.0-73.4)	59.6 (44.7- 71.4)	62.9 (49.6-72.8)	64.3 (50.2-73.3)
Race, no. (%)							
White	29814 (60.6)	2814 (47.7)	3908 (58.5)	2877 (59.6)	7991 (61.1)	7496 (63.1)	4728 (68.8)
Black	16714 (33.9)	2784 (47.2)	2492 (37.3)	1693 (35.1)	4272 (32.7)	3720 (31.3)	1753 (25.5)
Other	2710 (5.5)	298 (5.1)	285 (4.3)	254 (5.3)	821 (6.3)	658 (5.5)	394 (5.7)
Sex, no. (%), women	5673 (11.5)	604 (10.2)	693 (10.4)	557 (11.5)	1671 (12.8)	1432 (12.1)	716 (10.4)
BMI category, no. (%)							
Underweight (<8.5 kg/m^2)	265 (0.5)	50 (0.8)	56 (0.8)	38 (0.8)	49 (0.4)	44 (0.4)	28 (0.4)
Normal weight (18.5 to <25 kg/m^2)	9939 (20.2)	1163 (19.7)	1645 (24.6)	1018 (21.1)	2508 (19.2)	2272 (19.1)	1333 (19.4)
Overweight (25 to <30 kg/m^2)	15032 (30.5)	1814 (30.8)	2030 (30.4)	1521 (31.5)	4025 (30.8)	3568 (30.0)	2074 (30.2)
Obesity (>18.5 kg/m^2)	24002 (48.7)	2869 (48.7)	2954 (44.2)	2247 (46.6)	6502 (49.7)	5990 (50.4)	3440 (50.0)
Smoke, no. (%)							
Never smoker	27492 (55.8)	3077 (52.2)	3411 (51.0)	2624 (54.4)	7799 (59.6)	6843 (57.6)	3738 (54.4)
Former smoker	13062 (26.5)	1906 (32.3)	2027 (30.3)	1292 (26.8)	2965 (22.7)	2974 (25.0)	1898 (27.6)
Current smoker	8684 (17.6)	913 (15.5)	1247 (18.7)	908 (18.8)	2320 (17.7)	2057 (17.3)	1239 (18.0)
Hypertension, no. (%)	30568 (62.1)	3769 (63.9)	4077 (61.0)	2993 (62.0)	8052 (61.5)	7370 (62.1)	4307 (62.6)
Diabetes, no. (%)	13717 (27.9)	1863 (31.6)	1996 (29.9)	1360 (28.2)	3301 (25.2)	3315 (27.9)	1882 (27.4)
Cancer, no. (%)	4558 (9.3)	728 (12.3)	695 (10.4)	443 (9.2)	1043 (8.0)	1014 (8.5)	635 (9.2)
Cardiovascular disease, no. (%)	10399 (21.1)	1512 (25.6)	1706 (25.5)	1048 (21.7)	2307 (17.6)	2368 (19.9)	1458 (21.2)
Cerebrovascular disease, no. (%)	5192 (10.5)	801 (13.6)	1011 (15.1)	503 (10.4)	1091 (8.3)	1112 (9.4)	674 (9.8)
Dementia, no. (%)	5350 (10.9)	887 (15.0)	1268 (19.0)	586 (12.1)	988 (7.6)	999 (8.4)	622 (9.0)
Chronic kidney disease, no. (%)	9573 (21.9)	1390 (26.1)	1477 (26.2)	963 (22.9)	2161 (18.4)	2237 (20.9)	1345 (21.8)
Peripheral artery disease, no. (%)	1411 (2.9)	247 (4.2)	261 (3.9)	140 (2.9)	301 (2.3)	277 (2.3)	185 (2.7)
HIV, no. (%)	504 (1.0)	91 (1.5)	75 (1.1)	58 (1.2)	130 (1.0)	99 (0.8)	51 (0.7)
Pneumonia, no. (%)	765 (1.6)	205 (3.5)	191 (2.9)	83 (1.7)	108 (0.8)	100 (0.8)	78 (1.1)
COPD, no. (%)	7666 (15.6)	1143 (19.4)	1285 (19.2)	765 (15.9)	1670 (12.8)	1702 (14.3)	1101 (16.0)
ADI rank category, no. (%)							
0 to 33.3	10248 (20.8)	1816 (30.8)	2003 (30.0)	1026 (21.3)	2356 (18.0)	1944 (16.4)	1103 (16.0)

33.4 to 66.6	20861 (42.4)	2203 (37.4)	2594 (38.8)	1967 (40.8)	5788 (44.2)	5113 (43.1)	3196 (46.5)
66.7 to 100	18129 (36.8)	1877 (31.8)	2088 (31.2)	1831 (38.0)	4940 (37.8)	4817 (40.6)	2576 (37.5)
COVID-19 testing capacity, mean (SD), per 10000 people	3.1 (1.9)	1.3 (0.9)	1.7 (1.0)	2.1 (1.2)	4.1 (2.1)	3.7 (1.6)	3.8 (1.7)
Hospital occupancy, mean (SD), %	37.0 (10.8)	41.3 (11.8)	35.4 (9.9)	35.8 (10.2)	36.5 (10.3)	37.0 (10.5)	36.8 (11.5)

ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus; IQR: interquartile range; IQR: interquartile range; SD: standard deviation.

Supplemental Table 3B: Characteristics of hospitalized US Veterans with COVID-19 overall and by different month periods

Characteristic	**Overall** N = 9428	**March 20 – April 19** N = 1992	**April 20 – May 19** N = 1152	**May 20 – June 19** N = 966	**June 20 – July 19** N = 2274	**July 20 – August 19** N = 1872	**August 20 – September 19** N = 1172
Age, median (IQR), year	70.6 (61.2-76.8)	70.7 (61.8, 76.7)	72.2 (63.7-79.3)	69.7 (59.7- 76.8)	69.1 (58.9-75.6)	70.8 (61.1-76.5)	71.5 (62.3-77.2)
Race, no. (%)							
White	5054 (53.6)	811 (40.7)	607 (52.7)	533 (55.2)	1255 (55.2)	1081 (57.7)	767 (65.4)
Black	3809 (40.4)	1084 (54.4)	496 (43.1)	389 (40.3)	861 (37.9)	649 (34.7)	330 (28.2)
Other	565 (6.0)	97 (4.9)	49 (4.3)	44 (4.6)	158 (6.9)	142 (7.6)	75 (6.4)
Sex, no. (%), women	527 (5.6)	95 (4.8)	53 (4.6)	73 (7.6)	147 (6.5)	112 (6.0)	47 (4.0)
BMI category, no. (%)							
Underweight (<8.5 kg/m^2)	83 (0.9)	24 (1.2)	14 (1.2)	10 (1.0)	18 (0.8)	12 (0.6)	5 (0.4)
Normal weight (18.5 to <25 kg/m^2)	1836 (19.5)	387 (19.4)	276 (24.0)	182 (18.8)	423 (18.6)	350 (18.7)	218 (18.6)
Overweight (25 to <30 kg/m^2)	2922 (31.0)	611 (30.7)	344 (29.9)	322 (33.3)	684 (30.1)	582 (31.1)	379 (32.3)
Obesity (>18.5 kg/m^2)	4587 (48.7)	970 (48.7)	518 (45.0)	452 (46.8)	1149 (50.5)	928 (49.6)	570 (48.6)
Smoke, no. (%)							
Never smoker	4713 (50.0)	913 (45.8)	511 (44.4)	474 (49.1)	1250 (55.0)	980 (52.4)	585 (49.9)
Former smoker	2956 (31.4)	766 (38.5)	409 (35.5)	283 (29.3)	607 (26.7)	535 (28.6)	356 (30.4)
Current smoker	1759 (18.7)	313 (15.7)	232 (20.1)	209 (21.6)	417 (18.3)	357 (19.1)	231 (19.7)
Hypertension, no. (%)	6347 (67.3)	1345 (67.5)	763 (66.2)	649 (67.2)	1546 (68.0)	1264 (67.5)	780 (66.6)
Diabetes, no. (%)	3695 (39.2)	798 (40.1)	473 (41.1)	386 (40.0)	856 (37.6)	715 (38.2)	467 (39.8)
Cancer, no. (%)	1443 (15.3)	346 (17.4)	169 (14.7)	150 (15.5)	328 (14.4)	261 (13.9)	189 (16.1)
Cardiovascular disease, no. (%)	3417 (36.2)	735 (36.9)	453 (39.3)	338 (35.0)	773 (34.0)	674 (36.0)	444 (37.9)
Cerebrovascular disease, no. (%)	1836 (19.5)	403 (20.2)	279 (24.2)	179 (18.5)	399 (17.5)	328 (17.5)	248 (21.2)
Dementia, no. (%)	1953 (20.7)	420 (21.1)	345 (29.9)	212 (21.9)	398 (17.5)	336 (17.9)	242 (20.6)
Chronic kidney disease, no. (%)	3042 (34.9)	704 (37.8)	368 (35.9)	293 (33.2)	716 (33.7)	575 (33.3)	386 (35.5)
Peripheral artery disease, no. (%)	543 (5.8)	127 (6.4)	87 (7.6)	59 (6.1)	120 (5.3)	92 (4.9)	58 (4.9)
HIV, no. (%)	141 (1.5)	44 (2.2)	16 (1.4)	12 (1.2)	40 (1.8)	23 (1.2)	6 (0.5)
Pneumonia, no. (%)	336 (3.6)	104 (5.2)	59 (5.1)	37 (3.8)	51 (2.2)	50 (2.7)	35 (3.0)
COPD, no. (%)	2429 (25.8)	524 (26.3)	311 (27.0)	251 (26.0)	549 (24.1)	462 (24.7)	332 (28.3)
ADI rank category, no. (%)							
0 to 33.3	1785 (18.9)	583 (29.3)	290 (25.2)	169 (17.5)	335 (14.7)	249 (13.3)	159 (13.6)
33.4 to 66.6	3643 (38.6)	671 (33.7)	454 (39.4)	383 (39.6)	904 (39.8)	733 (39.2)	498 (42.5)
66.7 to 100	4000 (42.4)	738 (37.0)	408 (35.4)	414 (42.9)	1035 (45.5)	890 (47.5)	515 (43.9)

COVID-19 testing capacity, mean (SD), per 10000 people	2.8 (1.8)	1.2 (0.9)	1.6 (0.8)	2.1 (1.1)	3.9 (1.5)	3.8 (1.4)	4.0 (1.7)
Hospital occupancy, mean (SD), %	38.1 (10.5)	42.4 (11.3)	35.0 (9.7)	36.1 (8.9)	38.1 (9.4)	37.1 (10.4)	37.0 (10.6)
ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus; IQR: interquartile range; SD: standard deviation.							

Supplemental Table 4 Contribution of changes in demographic, health, and contextual characteristics to temporal differences in outcomes between 3/20–4/19, 2020 and 6/20–7/20, 2020

Factors	Among Veterans with COVID-19				Among hospitalized Veterans with COVID-19	
	30-day mortality rate changes		Hospitalization rate changes		30-day mortality rate changes	
	Predicted rate of change	Percent contribution to total change (predicted/observed)	Predicted rate of change	Percent contribution to total change (predicted/observed)	Predicted rate of change	Percent contribution to total change (predicted/observed)
Demographics	-2.4%	26.1%	-3.3%	19.6%	-3.0%	23.6%
Health characteristics	-0.7%	7.6%	-1.5%	9.0%	-0.3%	2.4%
Contextual characteristics	0.1%	-1.1%	0.1%	-0.6%	0.1%	-0.8%
COVID-19 testing capacity	-0.5%	5.4%	-0.9%	5.4%	-0.2%	1.6%
Hospital occupancy	-0.2%	2.2%			-0.4%	3.1%
Net rate of change predicted by demographic, health, contextual characteristics, testing capacity, and hospital occupancy (A)	**-3.7%**	**40.2%**	**-5.6%**	**33.3%**	**-3.8%**	**29.9%**
Observed rate of change (B)	-9.2%		-16.8%		-12.7%	
Epidemiological change (difference between observed and net predicted rate of change) (B)-(A)	-5.5%	59.8%	-11.2%	66.7%	-8.9%	70.1%

Demographics include age, race, and gender; Health characteristics include BMI, diabetes, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, dementia, HIV, hypertension, peripheral artery disease, pneumonia, and smoking status; contextual factors include ADI; epidemiological change includes the 30-day periods of testing positive dates.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Page	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4	Explain the scientific background and rationale for the investigation being reported
Objectives	4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	6	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	5	Describe any efforts to address potential sources of bias
Study size	9	Explain how the study size was arrived at
Quantitative variables	6-7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7-8	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	9	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	9	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	9	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	10	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	12	Summarise key results with reference to study objectives
Limitations	14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	15	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Temporal Trends of COVID-19 Mortality and Hospitalization Rates: An observational cohort study from the US Department of Veterans Affairs

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Temporal Trends of COVID-19 Mortality and Hospitalization Rates: An observational cohort study from the US Department of Veterans Affairs

Miao Cai[a,b], PhD; Benjamin Bowe[a,b,c], MPH; Yan Xie[a,b,c], MPH; and Ziyad Al-Aly[a,b,d,e,f] MD

[a] Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[b] Veterans Research & Education Foundation of St. Louis, Saint Louis, Missouri

[c] Department of Epidemiology and Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri

[d] Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

[e] Nephrology Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[f] Institute for Public Health, Washington University in Saint Louis, Saint Louis, Missouri

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Corresponding Author:
Ziyad Al-Aly, M.D.
VA Saint Louis Health Care System
915 North Grand Boulevard, 151-JC
Saint Louis, MO 63106
Telephone: (314) 289-6333
Twitter @zalaly
Email: zalaly@gmail.com

Abstract

Objective: To investigate the temporal trends of 30-day mortality and hospitalization in United States Veterans with COVID-19 and 30-day mortality in hospitalized Veterans with COVID-19; and to decompose the contribution of changes in the underlying characteristics of affected populations to these temporal changes.

Design: Observational cohort study.

Setting: US Department of Veteran Affairs.

Participants: 49 238 United States Veterans with a positive COVID-19 test between March 20, 2020 and September 19, 2020; and 9 428 United States Veterans hospitalized with a positive COVID-19 test during the same period.

Outcome measures: 30-day mortality rate and hospitalization rate.

Results: Between March 20, 2020 and September 19, 2020 and in COVID-19 positive individuals, 30-day mortality rate dropped by 9.2% from 13.6% to 4.4%; hospitalization rate dropped by 16.8% from 33.8% to 17.0%. In hospitalized COVID-19 individuals, 30-day mortality rate dropped by 12.7% from 23.5% to 10.8%. Among COVID-19 positive individuals, decomposition analyses suggested that changes in demographic, health and contextual characteristics, COVID-19 testing capacity, and hospital occupancy accounted for 40.2% and 33.3% of the decline in 30-day mortality and hospitalization, respectively. Changes in the underlying characteristics of hospitalized COVID-19 individuals accounted for 29.9% of the decline in 30-day mortality.

Conclusion: Between March and September 2020, changes in demographic and health characteristics of people infected with COVID-19 contributed measurably to the substantial decline in 30-day mortality and hospitalization.

Strengths and limitations of the study

- National large-scale individual-level data from the US Department of Veterans Affairs which operated the largest integrated health care system in the United States.
- Advanced decomposition methods disentangle the influence of changes in demographics and health characteristics on temporal trends of 30-day mortality and hospital rates.
- The study accounted for important but less studied drivers of change in mortality and hospitalization including contextual variables, testing capacity, and hospital occupancy rates.
- The Veteran population includes mostly older White males, which may limit the generalizability.

Introduction

Reports from regional health systems and the Center of Disease Control suggest substantial temporal variations in COVID-19 mortality rates[1-3]; however, a national temporal analysis of mortality and hospitalization rates accounting for individual-level characteristics is lacking and the relative contribution of changes in demographic and health characteristics of people infected with COVID-19 to temporal differences in mortality rates is not clear.

A deeper understanding of the changes in hospitalization and mortality rates and the drivers of such changes in the first wave of the pandemic will aid effort to optimize management of future waves of this global pandemic.

In this work, we leveraged the breadth and depth of the United States Department of Veterans Affairs electronic health care databases to describe temporal changes in mortality rates and hospitalization among COVID-19 positive Veterans, and temporal changes in mortality rates of hospitalized veterans with COVID-19. We then decomposed the contribution of changes in demographic, health, contextual characteristics to these temporal changes.

Methods

Identification of COVID-19 test positive individuals

Using the comprehensive COVID-19 Shared Data Resource (CSDR) [4 5] developed by the Department of Veterans Affairs (VA), we identified unique US Veterans with their first laboratory confirmed COVID-19 positive test between March 20, 2020 and September 19, 2020. The CSDR captures COVID-19 cases based on laboratory results that comply with

Centers for Disease Control and Prevention standards, including 2019-nCOV RT-PCR (reverse transcription-polymerase chain reaction) Diagnostic Panel and the SARS-CoV-2 Multiplex Assay, or human-confirmed case review[5]. The VA had its first COVID-19 positive patient on March 02, 2020. In this study, March 20, 2020 was selected as the first day of observation where it was the first day that VA had more than 100 COVID-19 positive patients nationally, facilitating stabilization of rate calculations. September 19, 2020 was selected as the last day of observation to ensure 30 days of follow-up for observation of outcomes.

Data sources

Data were obtained from the VA CSDR[4] and Corporate Data Warehouse (CDW)[6-18], which provides electronic health record information during routine healthcare. Demographic information and dates of death were collected from the CDW SPatient domain. Patient clinical diagnoses, procedures, and hospitalization characteristics were obtained from the CDW Outpatient Encounter and Inpatient Encounter domains. Smoking status was obtained from the CDA Health Factors domain. Laboratory results, including serum creatinine, were obtained from the CDW Patient Laboratory Chemistry domain. Data on height, weight, and blood pressure were procured from the CDW Vital Signs domain. The CDW Outpatient Pharmacy domain was used to obtain diabetes medication data. The Planning System Support Group Enrollee provided the Federal Information Processing Standard (FIPS) code of residence. The 2015 Area Deprivation Index (ADI) were obtained from the University of Wisconsin. The ADI is a composite measure of a census block group's socio-economic disadvantage, and is constructed from data elements including education, employment, housing quality, and poverty measures[19].

Outcomes

We examined the temporal trends in a) rates of 30-day mortality and hospitalization among those with a positive COVID-19 test, and b) rates of 30-day mortality among those hospitalized with COVID-19. 30-day mortality was defined as all-cause mortality occurring within the 30 days after the participant's first COVID-19 positive test. Hospitalization is defined by a hospital admission between 5 days before and 30 days after the first COVID-19 positive test.

Participant characteristics

Race was categorized as White, Black, and other. Health features included body weight index (BMI) and smoking status. BMI was computed from the last measurements of the participant's height and weight prior and closest to the first COVID-19 positive test date. Smoking status was categorized as never smoker, former smoker, and current smoker, based on the most recent record prior to the first COVID-19 positive test. Comorbidities included cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), dementia, diabetes mellitus, human immunodeficiency virus (HIV), hypertension, peripheral artery disease, and pneumonia. Cancer, cardiovascular disease, cerebrovascular disease, dementia, HIV, peripheral artery disease, pneumonia, and COPD were identified in the two years prior to testing positive for COVID-19 through International Classification of Diseases Tenth Version Clinical Modification diagnosis codes[18-20]. Chronic kidney disease was defined as baseline estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73m^2. Baseline eGFR was calculated using the CKD-EPI equation[21] and was assessed as the Veteran's last outpatient value prior to the date of first COVID-19 test positive. Participants who had no measurement of baseline eGFR (N=5 447, 11.1% for Veterans with COVID-19; N=717, 7.6% for hospitalized Veterans with COVID-19) were assumed to have no chronic kidney disease. Diabetes was defined as any use of antihyperglycemic medications[22 23] or incidence of hemoglobin A1C greater or equal to 6.5%[24]. Hypertension was defined as median systolic blood pressure greater than or equal to 130 mmHg or median diastolic blood pressure greater than or equal to 80 mmHg in one year[25]. Participants who had no measurement of blood pressure (N=2 699, 5.5% for Veterans with COVID-19; N=235, 2.5% for hospitalized Veterans with COVID-19) were assumed to have no chronic kidney disease. ADI is a composite measure of a geographic location's socio-economic disadvantage, and ranges from 0 (low disadvantage) to 100 (high disadvantage). County level ADI of the participants was assigned based on the participant's FIPS code of residence location at the first COVID-19 positive test date. Mean imputation was applied to missing values of covariates including BMI (missing = 111, 0.2% of Veterans with COVID-19; missing = 11, 0.1% of hospitalized Veterans with COVID-19) and ADI (missing = 1303, 2.6% of Veterans with COVID-19; missing = 88, 1.0% of hospitalized Veterans with COVID-19). COVID-19 testing capacity was calculated as 7-day averages of the number of COVID-19 tests conducted in a hospital system divided by the total number of veterans served in that hospital system in the last calendar year. Hospital occupancy was defined as the percentage of beds occupied by hospitalized patients in a hospital system within a calendar week. COVID-19 testing capacity and hospital occupancy were linked to the Veterans by the hospital system in which the individuals had their first positive COVID-19 test.

Statistical analyses

We calculated and plotted 7-day moving averages of crude and standardized 30-day mortality and hospitalization rates in COVID-19 positive participants, as well as 30-day mortality rates in hospitalized COVID-19 positive participants. The 7-day range included the current day, and the three days before and after. Standardized rates were adjusted for age, race, gender, health behaviors (smoking status and BMI), comorbidities, and ADI through indirect standardization[26]. The standardization was based on the ratio difference between expected and observed number of outcomes, where expected number of outcomes were estimated from individual-level logistic regressions.

To understand driving factors of the temporal tends in the outcomes, we decomposed the contribution of the changes in key participant characteristics to changes in the observed rates of outcomes over time. We first constructed individual-level logistic regression models for the different outcomes using four sets of factor domains: demographics (age, race, gender), health characteristics (BMI, diabetes, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, dementia, HIV, hypertension, peripheral artery disease, pneumonia, and smoking status), contextual factors (ADI), COVID-19 testing capacity, and hospital occupancy. Hospital occupancy rate was not included as a predictor of hospitalization since they are measuring the same variable. For each individual, we then computed the expected probabilities of the outcome based on a participants observed characteristics and under a reference characteristics set, where probability of the outcome was minimized (age was set as zero, and other categorical variables were set to be the reference group). We estimated the additive contribution of the six set of factor domains to the estimated rates of the outcome using decomposition analysis[27]. Then the change in outcome rates between the first (March 20 to April 19) and the last (August 20 to September 19) 30 day periods associated with each domain were calculated by taking the difference of the contributions between the two periods.

All statistical tests were two sided, and a p-value less than 0.05 or a 95% confidence interval that did not contain unity was considered statistically significant. Statistical analyses and data visualization were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC) and R 4.0.2[28]. The participants were not involved in the design, or conduct, or reporting, or dissemination plans of the study.

Ethics approval statement

The study was approved by the Institutional Review Board of the Department of Veterans Affairs St Louis Health Care System, St Louis, MO (approval number: 1163689). The requirement for informed consent was waived as the risk to participants was intangible.

Patient and public involvement

No patients were involved in developing the hypothesis, the specific aims, or the research questions, nor were they involved in developing plans for design or implementation of the study. No patients were involved in the interpretation or writing up of results.

Results

Between March 20, 2020 and September 19, 2020, we identified 49 238 US Veterans who tested positive for COVID-19 and 9 428 US Veterans hospitalized with COVID-19. Characteristics of the two cohorts are reported in Table 1. Among individuals with COVID-19, the median age was 63.3 years (interquartile range [IQR], 49.8 to 73.1 years); 60.6% were White, 33.9% were Black, and 11.5% were women. Among hospitalized individuals, the median age was 70.6 years (IQR 61.2 to 76.8 years), 53.6% were White, 40.4% were Black, and 6.0% were women.

Temporal trends in 30-day mortality and hospitalization rates

Between March 20, 2020 and September 19, 2020 and among individuals with a COVID-19 positive test the 30-day mortality rate dropped by 9.2% from 13.6% to 4.4%; the hospitalization rate dropped by 16.8% from 33.8% to 17.0% (Table 2 and Figure 1). Among hospitalized individuals with COVID-19, the 30-day mortality rate dropped by 12.7% from 23.5% to 10.8% (Table 2 and Figure 1). After accounting for demographics, contextual factors, health characteristics, COVID-19 testing capacity, and hospital occupancy, standardized rates showed consistent decline during the period (Figure 1).

Between March 20, 2020 and September 19, 2020 and among hospitalized individuals with COVID-19, we observed consistent decline in healthcare resource utilization including decline in rates of intensive care unit (ICU) admission, mechanical ventilator use, and length of hospital stay (Supplemental Table 1). The rate of ICU stay dropped by 4% from 35.6% to 31.6%; the rate of mechanical ventilator use dropped by 11.3% from 20.6% to 9.3%; the mean length of stay dropped by 4.2 days from 13.8 to 9.6 days.

Predictors of 30-day mortality and hospitalization

Adjusted odds ratios for the association between potential predictors and risk of 30-day mortality and hospitalization among Veterans with COVID-19, as well as risk of 30-day mortality among hospitalized Veterans with COVID-19 are presented in Table 3. Among Veterans with COVID-19, older age, Black and other race, male gender, current smoker, diabetes, cancer, cardiovascular disease, dementia, chronic kidney disease, pneumonia, COPD, and higher hospital occupancy rate were associated with higher risk of 30-day mortality and hospitalization; higher COVID-19 testing capacity was associated with lower risk of 30-day mortality and hospitalization. Among hospitalized Veterans with COVID-19, older age, male gender, obesity, current smoker, diabetes, cardiovascular disease, chronic kidney disease, dementia, and higher hospital occupancy rate were associated with higher risk of 30-day mortality; higher COVID-19 testing capacity was associated with lower risk of 30-day mortality. The models for 30-day mortality and hospitalization among those who tested positive, and the model for 30-day mortality among hospitalized achieved reasonably good predictive performance, with the c-statistics of 0.834, 0.718, and 0.746, respectively. The c-statistics for nested models, showing the predictive performance improvement when adding different variable sets, are included in Supplemental Table 2.

Temporal change of predictors of 30-day mortality and hospitalization

The demographic, health, and contextual characteristics as well as hospital occupancy and testing capacity in each one-month interval after March 20, 2020 and before September 19, 2020 are described in Figure 2 and 3 and Supplemental Table 3A and 3B. We observed substantial decline in percent of Black patients over time in both individuals with COVID-19 (from 47.2% to 25.5%, dropping by 21.7%) and hospitalized individuals with COVID-19 (from 54.4% to 28.2%, dropping by 26.3%). The prevalence of comorbidities was consistently dropping between the two period in individuals with COVID-19; the overall trend of comorbidity prevalence was still declining while less consistent in hospitalized individuals with COVID-19. In both of two cohorts, the percent of individuals living in disadvantaged neighborhood (higher ADI) and COVID-19 testing capacity were increasing over time, while hospital occupancy was decreasing.

The contribution of changes in predictors to temporal changes in 30-day mortality and hospitalization rates

Decomposition analyses showed that from March 20, 2020 to September 19, 2020 and among COVID-19 positive individuals, changes in demographics, health characteristics, and contextual characteristics, expansion of testing capacity, and decreasing hospital occupancy contributed to 26.1%, 7.6%, 5.4%, -1.1%, and 2.2% of the decline in 30-day mortality rates respectively. Altogether, these predictors accounted for 40.2% of the decline in 30-day mortality in Veterans with COVID-19 (Figure 4 and Supplemental Table 4).

Changes in demographics, health characteristics, and contextual characteristics, and expansion of testing capacity, and decreasing hospital occupancy contributed to 19.6%, 9.0%, -0.6%, and 5.4% of the decline in hospitalization rates. Altogether, they accounted for 33.3% of the decline in hospitalization rates in Veterans with COVID-19 (Figure 4 and Supplemental Table 4).

Among those hospitalized with COVID-19, changes in demographic, health characteristics, and contextual characteristics, expansion of testing capacity, and decreasing hospital occupancy accounted for 23.6%, 2.4%, -0.8%, 1.6%, and 3.1% of the decline in 30-day mortality rate respectively. All predictors collectively accounted for, 29.9% of the decline in 30-day mortality (Figure 4 and Supplemental Table 4).

Discussion

This analysis of temporal trends of COVID-19 hospitalization and mortality suggests substantial decline between March 2020 and September 2020. We also observed substantial shifts in the demographic and health characteristics of those who tested positive for COVID-19 and in those who were hospitalized with a positive COVID-19 test including substantial decline in the percentage of Black people and comorbidity burden as well as increase in testing capacity and reduction in hospital occupancy rates. Around 40.2% of the decline in mortality rates and 33.3% of decline in hospitalization rates were explained by changes in the underlying characteristics of people who tested positive for COVID-19. Around 29.9% of the decline in mortality rates among hospitalized individuals was explained by changes in their underlying characteristics.

Our analysis highlights the influence of individual-level demographic and health characteristics on hospitalization and mortality rates in COVID-19. The contribution of changes in testing capacity to these outcomes (albeit small) was measurable. The contribution of hospital occupancy rates to decline in mortality rates also highlights the importance of this variable as policy makers and health systems continue to optimize the public health response to this pandemic and may also be useful in preparing for and mitigating impact of future pandemics.

Slightly more than half of decline in rates was not predicted by the explanatory variables in our models and likely reflects the influence of factors that are not accounted for in our approach including improvement in medical care (to the extent that it may have influenced the outcomes), a putative seasonality effect, and the potential influence of the broader public health policy measures on these outcomes. In particular, it has been postulated that severity of COVID-19 may be proportionate to the viral inoculum which initiates the infection in the human host, and it is plausible that public health policies (e.g. physical distancing, masking, etc.) may have reduced the viral inoculum in some infected individuals and might have consequently resulted in less severe COVID-19 (and reduced hospitalization and mortality) – a hypothesis referred to as the variolation of coronavirus[29].

Our findings provide insight not only into the dynamic changes of key indicators of the COVID-19 pandemic (mortality and hospitalization rates), but also estimates of the influence of individual and contextual parameters on these indicators. The synergistic influence of both individual and contextual factors cannot be overstated[30]. The COVID-19 pandemic has brought to prominence the complex interplay of several dynamic drivers including individual-level demographic and health characteristics, health system-level characteristics, the influence of socioeconomic factors, and the broader contextual reality in which people live (public health response, etc.) — all collectively shape the ultimate health outcomes of COVID-19. Continued effort to surveil temporal trends of key indicators of this global pandemic, and careful analysis of drivers of any temporal change is needed to inform ongoing effort to optimize the management of this so far unabated pandemic and to guide development of better mitigation plans for future pandemics.

While we investigated the temporal trends of COVID-19 mortality and hospitalization rates within the US Veteran population, some important differences between our cohort and the general US population are noteworthy to better contextualize the broader implications of our findings; in our cohort the median age was 63.6 years, the percentages of White and Black race were 60.6% and 33.9%, 11.5% were women, and 17.6% were current smokers; whereas the median age is 38.1 years, the percentages of White and Black race are 60.1% and 13.4%, 50.8% are women, and 13.7% are current smokers in the US general population[31 32].

A key strength of this analysis is the use of individual level data from the US Department of Veterans Affairs which operates the largest nationally integrated health care system in the US, and use of advanced methods to decompose the influence of changes in demographics and health characteristics on temporal trends. In addition to accounting for individual-level demographic and health characteristics, our analyses also account for contextual variables, testing capacity, and measures of hospital occupancy rates — as important determinants of outcomes in this pandemic.

This analysis has several limitations. While we used validated definitions to identify covariates, we cannot completely rule out misclassification bias. While we accounted for known predictors, our analyses do not account for predictors that are not measured in the datasets including improvement in medical care as the pandemic progressed, and other unmeasured or unknown variables.

In sum, between March 2020 and September 2020, substantial decline in 30-day mortality and hospitalization among COVID-19 positive individuals and substantial decline in 30- day mortality among hospitalized Veterans with COVID-19. The temporal decline in these outcomes was partially explained by changes in underlying demographic, health, and contextual characteristics, and well as expansion of testing capacity, and reduction in hospital capacity. The results may be helpful in informing effort to optimize the collective public health response to this ongoing pandemic.

Author Contribution:

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Cai, Bowe, Xie.

Drafting of the manuscript: Cai, Al-Aly.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Cai, Bowe, Xie.

Supervision and funding: Al-Aly.

Conflict of Interest Disclosures: None reported.

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Reproducible Research Statement: Study protocol and Statistical code: Available by request. Data set: Available to those who have access to the Department of Veteran Affairs data sets.

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Table 1: Characteristics of the individuals with COVID-19 and hospitalized individuals with COVID-19

Characteristic	**Veterans with COVID-19 (N = 49238)**	**Hospitalized Veterans with COVID-19 (N = 9428)**
Demographics		
Age, median (IQR), year	63.3 (49.8-73.1)	70.6 (61.2-76.8)
Race, no. (%)		
White	29814 (60.6)	5054 (53.6)
Black	16714 (33.9)	3809 (40.4)
Other	2710 (5.5)	565 (6.0)
Sex, no. (%), women	5673 (11.5)	527 (5.6)
Health characteristics		
BMI category, no. (%)		
Underweight (<8.5 kg/m^2)	265 (0.5)	83 (0.9)
Normal weight (18.5 to <25 kg/m^2)	9939 (20.2)	1836 (19.5)
Overweight (25 to <30 kg/m^2)	15032 (30.5)	2922 (31.0)
Obesity (>18.5 kg/m^2)	24002 (48.7)	4587 (48.7)
Smoke, no. (%)		
Never smoker	27492 (55.8)	4713 (50.0)
Former smoker	13062 (26.5)	2956 (31.4)
Current smoker	8684 (17.6)	1759 (18.7)
Hypertension, no. (%)	30568 (62.1)	6347 (67.3)
Diabetes, no. (%)	13717 (27.9)	3695 (39.2)
Cancer, no. (%)	4558 (9.3)	1443 (15.3)
Cardiovascular disease, no. (%)	10399 (21.1)	3417 (36.2)
Cerebrovascular disease, no. (%)	5192 (10.5)	1836 (19.5)
Dementia, no. (%)	5350 (10.9)	1953 (20.7)
Chronic kidney disease, no. (%)	9573 (21.9)	3042 (34.9)
Peripheral artery disease, no. (%)	1411 (2.9)	543 (5.8)
HIV, no. (%)	504 (1.0)	141 (1.5)
Pneumonia, no. (%)	765 (1.6)	336 (3.6)
COPD, no. (%)	7666 (15.6)	2429 (25.8)
Contextual factors		
ADI rank category, no. (%)		
0 to 33.3	10248 (20.8)	1785 (18.9)
33.4 to 66.6	20861 (42.4)	3643 (38.6)
66.7 to 100	18129 (36.8)	4000 (42.4)
Testing capacity		
COVID-19 testing capacity, mean (SD), per 10000 people	3.1 (1.9)	2.8 (1.8)
Hospital occupancy		
Hospital occupancy, mean (SD), %	37.0 (10.8)	38.1 (10.5)

ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus; IQR: interquartile range; IQR: interquartile range; SD: standard deviation.

Table 2 30-day mortality and hospitalization rates in US veterans by 30-day periods, March 20, 2020 to September 19, 2020

Periods	**Total number of COVID-19 patients**	**30-day mortality, n (%)**	**Hospitalization, n (%)**	**30-day mortality among hospitalized COVID-19 patients, n (%)**
March 20 - April 19	5896	13.6%	33.8%	23.5%
April 20 - May 19	6685	12.3%	17.2%	17.0%
May 20 - June 19	4824	7.1%	20.0%	12.6%
June 20 - July 19	13084	4.9%	17.4%	11.8%
July 20 - August 19	11874	5.2%	15.8%	11.1%
August 20 - September 19	6875	4.4%	17.0%	10.8%
Overall	49238	7.2%	19.1%	14.8%

Table 3 Odd ratios (95% confidence intervals) of predictors associated with 30-day mortality and hospitalization among Veterans and hospitalized Veterans with COVID-19

Characteristics	**Veterans with COVID-19**		**Hospitalized Veterans with COVID-19**
	30-day mortality	**Hospitalization**	**30-day mortality**
Demographics			
Age	1.08 (1.07, 1.08)	1.02 (1.02, 1.02)	1.06 (1.06, 1.07)
Race (reference = white)			
Black	1.11 (1.01, 1.22)	1.64 (1.56, 1.74)	1.03 (0.90, 1.18)
Other	1.33 (1.12, 1.58)	1.58 (1.42, 1.76)	1.20 (0.92, 1.57)
Sex, women (reference = men)	0.52 (0.40, 0.67)	0.74 (0.67, 0.82)	0.72 (0.47, 1.06)
Health characteristics			
BMI category (reference = normal weight)			
Underweight (< 18.5 kg/m^2)	1.03 (0.64, 1.59)	1.26 (0.92, 1.71)	0.67 (0.29, 1.38)
Overweight (25 to < 30 kg/m^2)	0.89 (0.80, 1.00)	0.98 (0.91, 1.06)	1.07 (0.90, 1.29)
Obesity (> 18.5 kg/m^2)	1.02 (0.92, 1.15)	1.05 (0.98, 1.13)	1.24 (1.03, 1.49)
Smoking status (reference = never smoker)			
Former smoker	1.15 (1.05, 1.25)	1.01 (0.96, 1.07)	1.11 (0.97, 1.28)
Current smoker	1.12 (0.99, 1.27)	1.11 (1.03, 1.19)	1.21 (1.00, 1.46)
Hypertension	0.87 (0.80, 0.94)	1.10 (1.04, 1.16)	0.81 (0.70, 0.92)
Diabetes	1.37 (1.26, 1.49)	1.23 (1.16, 1.29)	1.15 (1.00, 1.31)
Cancer	1.10 (0.99, 1.22)	1.36 (1.27, 1.47)	1.03 (0.88, 1.21)
Cardiovascular disease	1.17 (1.07, 1.27)	1.43 (1.35, 1.52)	1.15 (1.00, 1.31)
Cerebrovascular disease	1.09 (0.98, 1.20)	1.38 (1.29, 1.48)	1.04 (0.90, 1.21)
Dementia	1.81 (1.65, 2.00)	1.52 (1.41, 1.63)	1.37 (1.18, 1.59)
Chronic kidney disease	1.48 (1.36, 1.61)	1.27 (1.20, 1.35)	1.47 (1.28, 1.68)
Peripheral arterial disease	1.09 (0.92, 1.29)	1.31 (1.16, 1.48)	1.17 (0.92, 1.47)
HIV	1.05 (0.67, 1.58)	1.50 (1.22, 1.85)	1.23 (0.71, 2.03)
Pneumonia	1.44 (1.15, 1.80)	2.00 (1.71, 2.35)	1.22 (0.90, 1.62)
COPD	1.21 (1.10, 1.32)	1.40 (1.31, 1.49)	0.96 (0.83, 1.11)
Contextual factors			
ADI rank (reference = 1-33.2)			
33.3 to 66.6	0.99 (0.89, 1.10)	1.03 (0.96, 1.10)	0.94 (0.79, 1.11)
66.7 to 100	1.04 (0.93, 1.16)	1.16 (1.09, 1.25)	0.92 (0.77, 1.09)
COVID-19 testing capacity			
COVID-19 testing capacity (per 10,000 veterans)	0.92 (0.90, 0.94)	0.95 (0.94, 0.96)	0.90 (0.86, 0.93)
Hospital occupancy			
Hospital occupancy rate (an increase of 10%)	1.05 (1.01, 1.08)	Not included	1.08 (1.02, 1.15)
C-statistics	0.834	0.718	0.746

ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus.

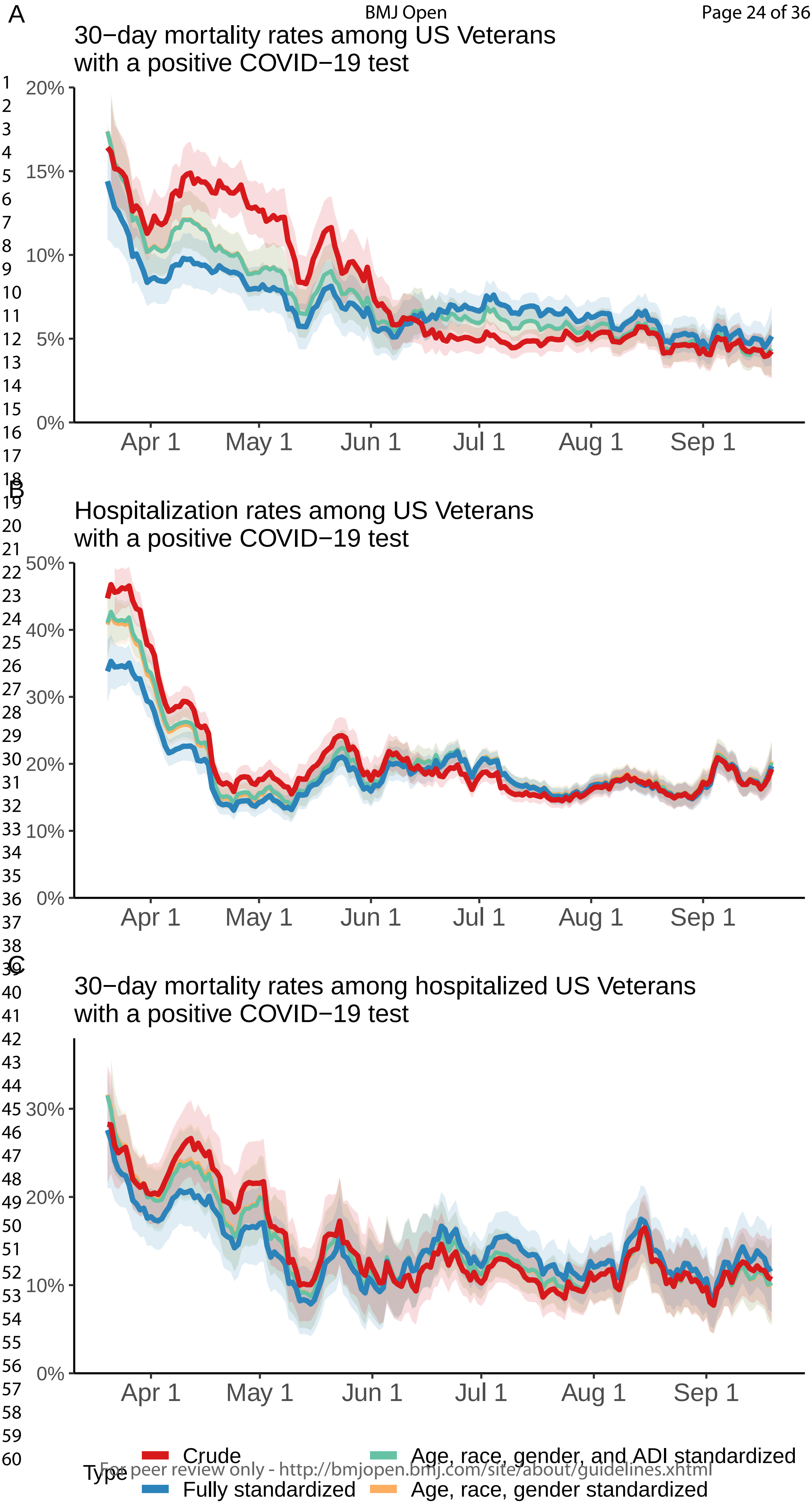
Figure Legends:

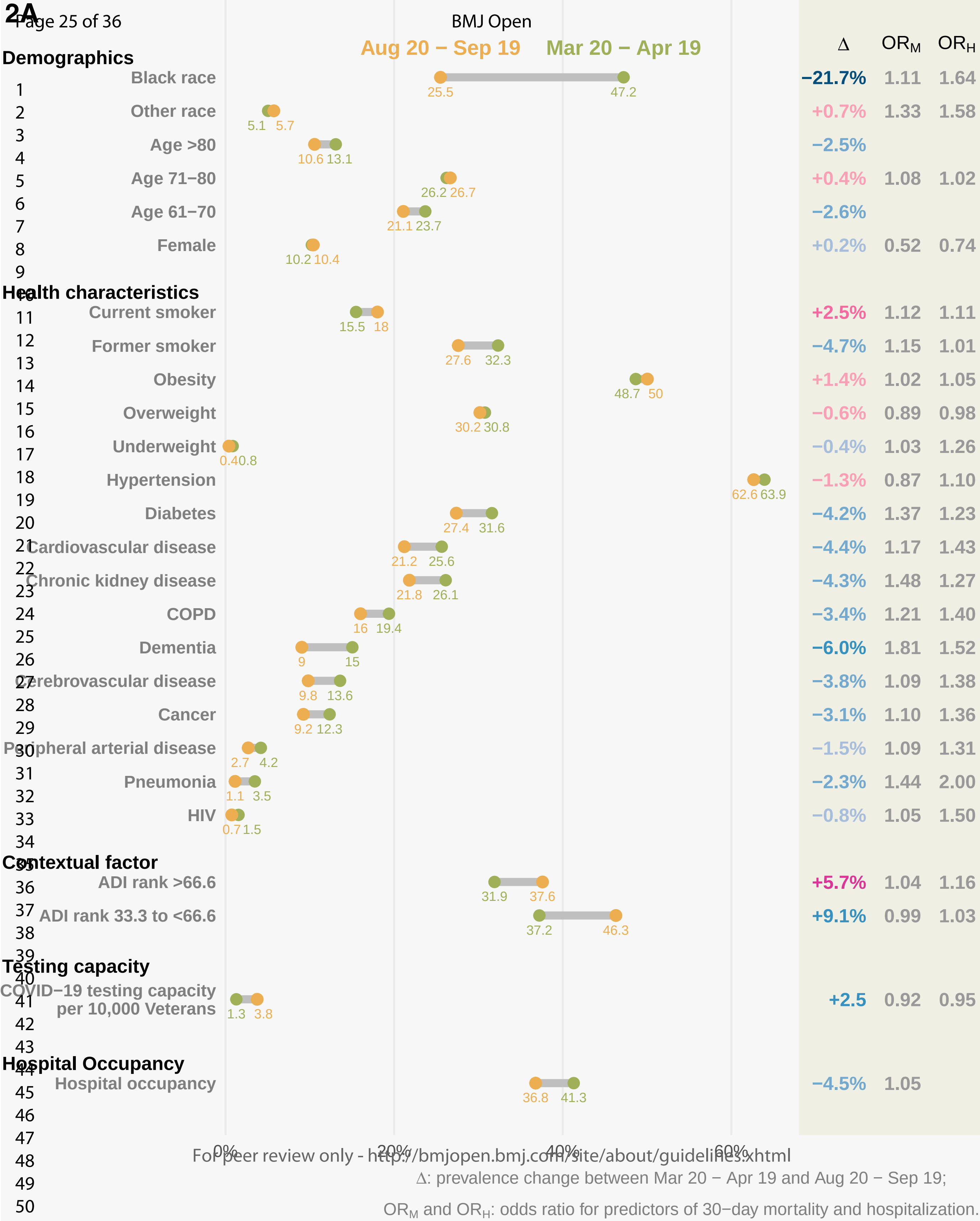
Figure 1. Temporal trends of COVID-19 30-day mortality and hospitalization among US Veterans. A and B: 30-day mortality and hospitalization rates in US Veterans who had a positive COVID-19 test (N=29,528). C: 30-day mortality rate in hospitalized US Veterans with a positive COVID-19 test (N=6,449). Fully standardized rates were adjusted for, demographics (age, race, gender), health characteristics (smoking status, body weight index, cancer, cardiovascular disease, chronic kidney disease, dementia, diabetes mellitus type 2, human immunodeficiency virus, hypertension, peripheral artery disease, pneumonia, and stroke), contextual factors (area deprivation index), COVID-19 testing capacity, and hospital occupancy.

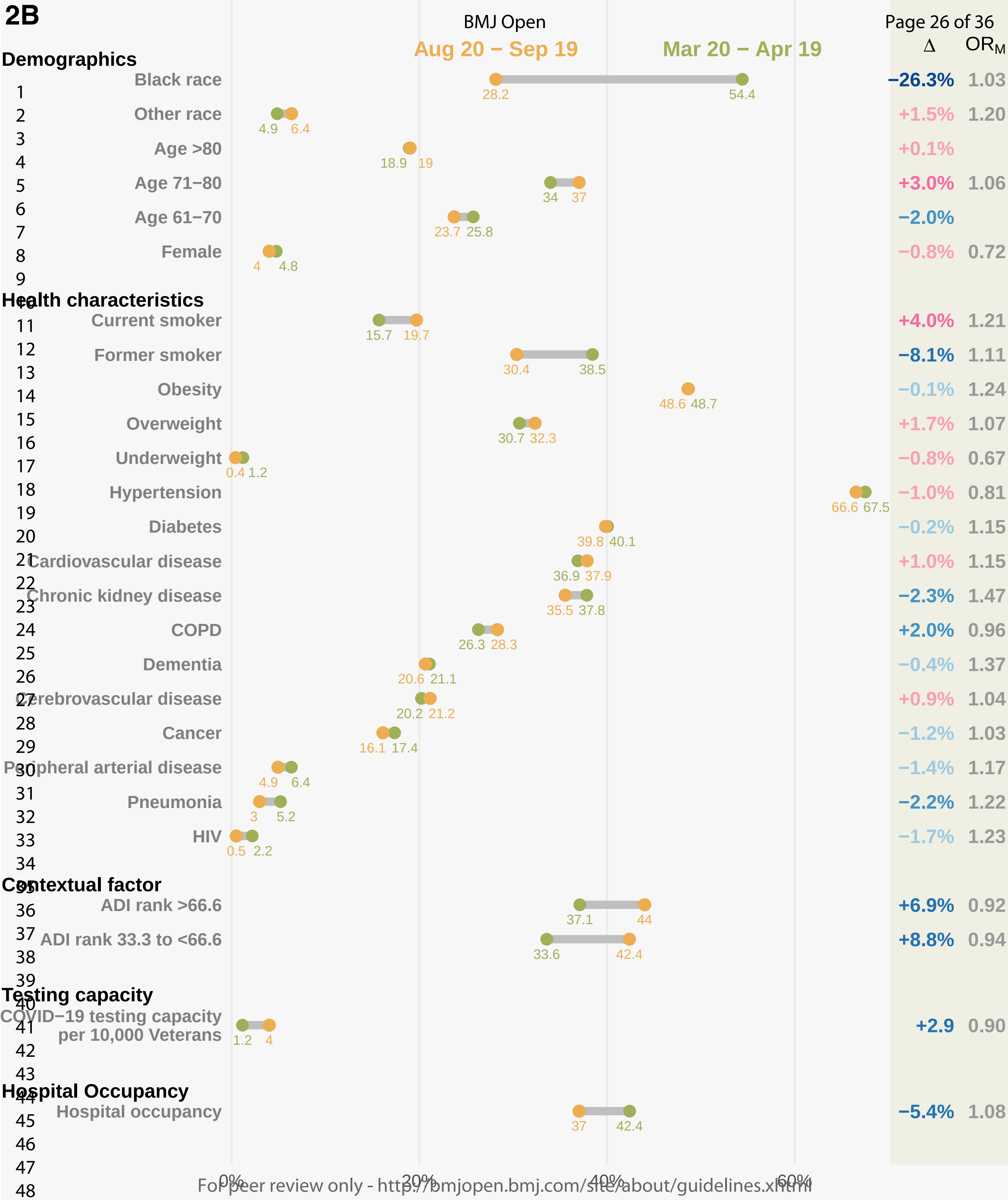
Figure 2 The change in predictors of 30-day mortality and hospitalization among US Veterans with COVID-19 between 3/20–4/19, 2020 and 8/20–9/19, 2020. **The yellow dots** represent the prevalence of predictors in 3/20–4/19, 2020, while **the green dots** represent the prevalence of predictors in 8/20–9/19, 2020. In the delta column, **blue text** indicates that the change of predictor leads to decrease in mortality and hospitalization rates, while **red text** indicates the change of predictor leads to decrease in mortality and hospitalization rates. COPD: chronic obstructive pulmonary disease.

Figure 3 The change in predictors of 30-day mortality among hospitalized US Veterans with COVID-19 between 3/20–4/19, 2020 and 8/20–9/19, 2020. **The yellow dots** represent the prevalence of predictors in 3/20–4/19, 2020, while **the green dots** represent the prevalence of predictors in 8/20–9/19, 2020. In the Δ column, the **blue text** indicates that the change of predictor leads to decrease in mortality rates, while the **red text** indicates the change of predictor leads to decrease in mortality rates. COPD: chronic obstructive pulmonary disease.

Figure 4 The contribution of changes in demographics, health characteristics, testing capacity, hospital occupancy, and contextual factors, and epidemiological changes to changes in 30-day mortality and hospitalization rates between 3/20–4/19, 2020 and 8/20–9/19, 2020. The red dot represents the observed change in rate of outcomes between the two periods, and the blue dot represents the change predicted based on demographics, health, contextual characteristics, COVID-19 testing capacity, and hospital occupancy. Hospital occupancy is not considered as predictor for the hospitalization outcome model. Epidemiological changes collectively represent the difference between predicted and observed rates and reflect the summative contribution of factors that are not accounted for in prediction models.

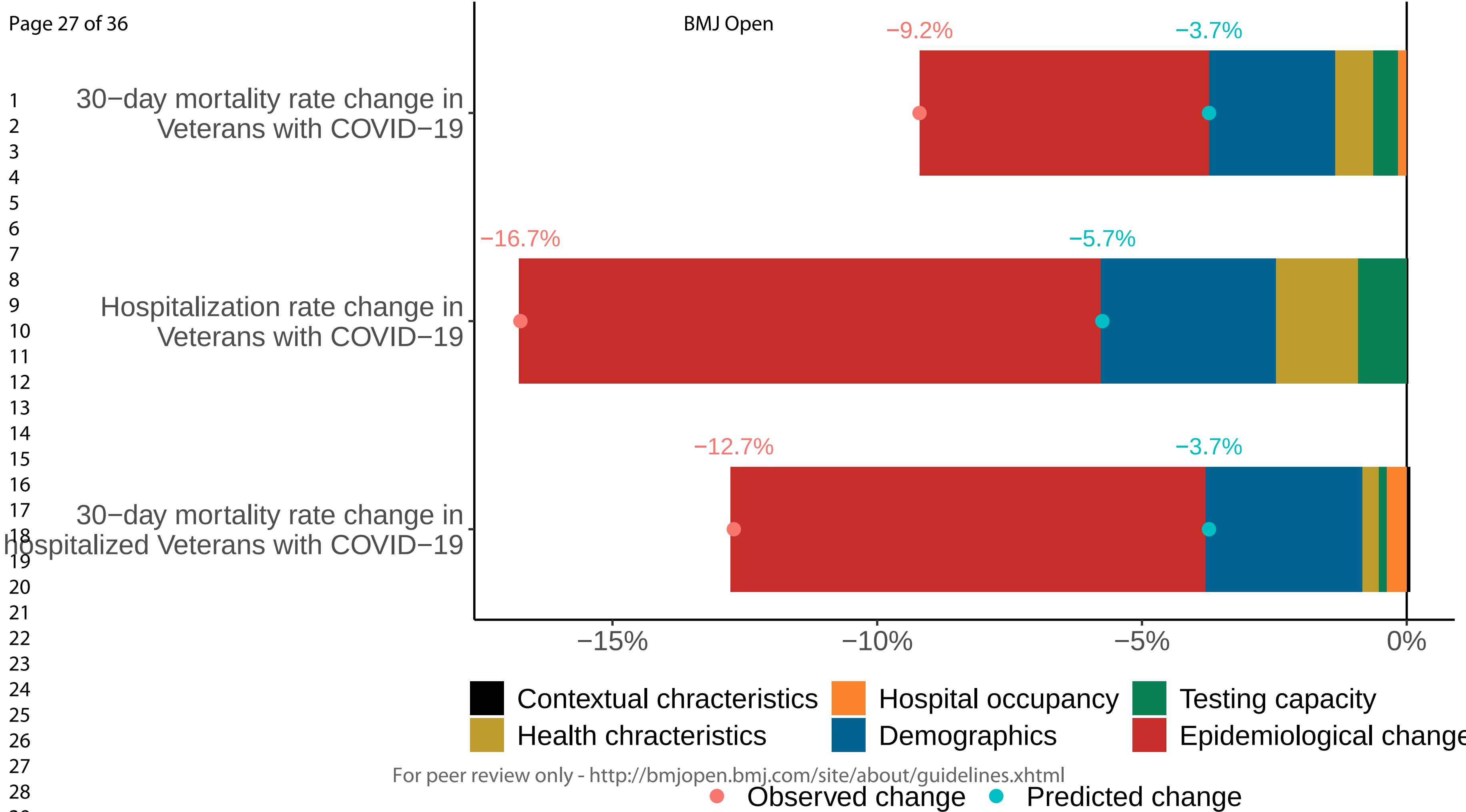

A
30−day mortality rates among US Veterans
with a positive COVID−19 test
20%
15%
10%
5%
0%
Apr 1
May 1
Jun 1
Jul 1
Aug 1
Sep 1
B
Hospitalization rates among US Veterans
with a positive COVID−19 test
50%
40%
30%
20%
10%
0%
Apr 1
May 1
Jun 1
Jul 1
Aug 1
Sep 1
C
30−day mortality rates among hospitalized US Veterans
with a positive COVID−19 test
30%
20%
10%
0%
Apr 1
May 1
Jun 1
Jul 1
Aug 1
Sep 1
Type
Crude
Fully standardized
Age, race, gender, and ADI standardized
Age, race, gender standardized


2A
Aug 20 − Sep 19
Mar 20 − Apr 19
Δ
OR_M
OR_H
Demographics
Black race 25.5 47.2 −21.7% 1.11 1.64
Other race 5.1 5.7 +0.7% 1.33 1.58
Age >80 10.6 13.1 −2.5%
Age 71−80 26.2 26.7 +0.4% 1.08 1.02
Age 61−70 21.1 23.7 −2.6%
Female 10.2 10.4 +0.2% 0.52 0.74
Health characteristics
Current smoker 15.5 18 +2.5% 1.12 1.11
Former smoker 27.6 32.3 −4.7% 1.15 1.01
Obesity 48.7 50 +1.4% 1.02 1.05
Overweight 30.2 30.8 −0.6% 0.89 0.98
Underweight 0.4 0.8 −0.4% 1.03 1.26
Hypertension 62.6 63.9 −1.3% 0.87 1.10
Diabetes 27.4 31.6 −4.2% 1.37 1.23
Cardiovascular disease 21.2 25.6 −4.4% 1.17 1.43
Chronic kidney disease 21.8 26.1 −4.3% 1.48 1.27
COPD 16 19.4 −3.4% 1.21 1.40
Dementia 9 15 −6.0% 1.81 1.52
Cerebrovascular disease 9.8 13.6 −3.8% 1.09 1.38
Cancer 9.2 12.3 −3.1% 1.10 1.36
Peripheral arterial disease 2.7 4.2 −1.5% 1.09 1.31
Pneumonia 1.1 3.5 −2.3% 1.44 2.00
HIV 0.7 1.5 −0.8% 1.05 1.50
Contextual factor
ADI rank >66.6 31.9 37.6 +5.7% 1.04 1.16
ADI rank 33.3 to <66.6 37.2 46.3 +9.1% 0.99 1.03
Testing capacity
COVID−19 testing capacity per 10,000 Veterans 1.3 3.8 +2.5 0.92 0.95
Hospital Occupancy
Hospital occupancy 36.8 41.3 −4.5% 1.05
0%
20%
40%
60%
Δ: prevalence change between Mar 20 − Apr 19 and Aug 20 − Sep 19;
OR_M and OR_H: odds ratio for predictors of 30−day mortality and hospitalization.



Δ: prevalence change between Mar 20 − Apr 19 and Aug 20 − Sep 19;

OR_M: odds ratio for predictors of 30−day mortality.



−9.2%
−3.7%
30−day mortality rate change in Veterans with COVID−19
−16.7%
−5.7%
Hospitalization rate change in Veterans with COVID−19
−12.7%
−3.7%
30−day mortality rate change in hospitalized Veterans with COVID−19
−15%
−10%
−5%
0%
Contextual chracteristics
Hospital occupancy
Testing capacity
Health chracteristics
Demographics
Epidemiological change
Observed change
Predicted change

Supplemental material

Table of Contents

Supplemental Table 1 Health care resource utilization among hospitalized Veterans with COVID-19

Month	**ICU**	**Mechanical Ventilation**	**LOS**
March 20 - April 19	35.6%	20.6%	13.8
April 20 - May 19	31.0%	13.5%	16.2
May 20 - June 19	31.2%	11.4%	12.1
June 20 - July 19	29.7%	11.7%	11.4
July 20 - August 19	28.2%	11.2%	11
August 20 - September 19	31.6%	9.3%	9.6
Overall	31.2%	13.4%	12.3

ICU: intensive care units; LOS: length of stay.

Supplemental Table 2: C statistics (95% confidence intervals) for nested models using different combination of predictors

Cohort	**Veterans with COVID-19**		**Hospitalized Veterans with COVID-19**
Predictor variables	**30-day mortality**	**Hospitalization**	**30-day mortality**
Demographics	0.822 (0.816-0.828)	0.678 (0.673-0.684)	0.725 (0.712-0.738)
+ health characteristics	0.832 (0.826-0.838)	0.713 (0.707-0.719)	0.740 (0.726-0.753)
+ contextual factors	0.832 (0.826-0.838)	0.714 (0.708-0.720)	0.741 (0.726-0.754)
+ COVID-19 testing capacity	0.834 (0.828-0.840)	0.715 (0.709-0.721)	0.745 (0.730-0.758)
+ hospital occupancy	0.834 (0.828-0.841)	0.718 (0.712-0.723)	0.746 (0.732-0.759)

Each + indicates including all the variable above that row. For example, "+ contextual factors" indicates including demographics, health characteristics, and contextual factors as predictors.

Supplemental Table 3A: Characteristics of US Veterans with COVID-19 overall and by different month periods

Characteristic	**Overall** N = 49238	**March 20 – April 19** N = 5896	**April 20 – May 19** N = 6685	**May 20 – June 19** N = 4824	**June 20 – July 19** N = 13084	**July 20 – August 19** N = 11874	**August 20 – September 19** N = 6875
Age, median (IQR), year	63.3 (49.8-73.1)	65.3 (53.7-73.8)	68.0 (56.6-76.1)	63.9 (50.0-73.4)	59.6 (44.7- 71.4)	62.9 (49.6-72.8)	64.3 (50.2-73.3)
Race, no. (%)							
White	29814 (60.6)	2814 (47.7)	3908 (58.5)	2877 (59.6)	7991 (61.1)	7496 (63.1)	4728 (68.8)
Black	16714 (33.9)	2784 (47.2)	2492 (37.3)	1693 (35.1)	4272 (32.7)	3720 (31.3)	1753 (25.5)
Other	2710 (5.5)	298 (5.1)	285 (4.3)	254 (5.3)	821 (6.3)	658 (5.5)	394 (5.7)
Sex, no. (%), women	5673 (11.5)	604 (10.2)	693 (10.4)	557 (11.5)	1671 (12.8)	1432 (12.1)	716 (10.4)
BMI category, no. (%)							
Underweight (<8.5 kg/m^2)	265 (0.5)	50 (0.8)	56 (0.8)	38 (0.8)	49 (0.4)	44 (0.4)	28 (0.4)
Normal weight (18.5 to <25 kg/m^2)	9939 (20.2)	1163 (19.7)	1645 (24.6)	1018 (21.1)	2508 (19.2)	2272 (19.1)	1333 (19.4)
Overweight (25 to <30 kg/m^2)	15032 (30.5)	1814 (30.8)	2030 (30.4)	1521 (31.5)	4025 (30.8)	3568 (30.0)	2074 (30.2)
Obesity (>18.5 kg/m^2)	24002 (48.7)	2869 (48.7)	2954 (44.2)	2247 (46.6)	6502 (49.7)	5990 (50.4)	3440 (50.0)
Smoke, no. (%)							
Never smoker	27492 (55.8)	3077 (52.2)	3411 (51.0)	2624 (54.4)	7799 (59.6)	6843 (57.6)	3738 (54.4)
Former smoker	13062 (26.5)	1906 (32.3)	2027 (30.3)	1292 (26.8)	2965 (22.7)	2974 (25.0)	1898 (27.6)
Current smoker	8684 (17.6)	913 (15.5)	1247 (18.7)	908 (18.8)	2320 (17.7)	2057 (17.3)	1239 (18.0)
Hypertension, no. (%)	30568 (62.1)	3769 (63.9)	4077 (61.0)	2993 (62.0)	8052 (61.5)	7370 (62.1)	4307 (62.6)
Diabetes, no. (%)	13717 (27.9)	1863 (31.6)	1996 (29.9)	1360 (28.2)	3301 (25.2)	3315 (27.9)	1882 (27.4)
Cancer, no. (%)	4558 (9.3)	728 (12.3)	695 (10.4)	443 (9.2)	1043 (8.0)	1014 (8.5)	635 (9.2)
Cardiovascular disease, no. (%)	10399 (21.1)	1512 (25.6)	1706 (25.5)	1048 (21.7)	2307 (17.6)	2368 (19.9)	1458 (21.2)
Cerebrovascular disease, no. (%)	5192 (10.5)	801 (13.6)	1011 (15.1)	503 (10.4)	1091 (8.3)	1112 (9.4)	674 (9.8)
Dementia, no. (%)	5350 (10.9)	887 (15.0)	1268 (19.0)	586 (12.1)	988 (7.6)	999 (8.4)	622 (9.0)
Chronic kidney disease, no. (%)	9573 (21.9)	1390 (26.1)	1477 (26.2)	963 (22.9)	2161 (18.4)	2237 (20.9)	1345 (21.8)
Peripheral artery disease, no. (%)	1411 (2.9)	247 (4.2)	261 (3.9)	140 (2.9)	301 (2.3)	277 (2.3)	185 (2.7)
HIV, no. (%)	504 (1.0)	91 (1.5)	75 (1.1)	58 (1.2)	130 (1.0)	99 (0.8)	51 (0.7)
Pneumonia, no. (%)	765 (1.6)	205 (3.5)	191 (2.9)	83 (1.7)	108 (0.8)	100 (0.8)	78 (1.1)
COPD, no. (%)	7666 (15.6)	1143 (19.4)	1285 (19.2)	765 (15.9)	1670 (12.8)	1702 (14.3)	1101 (16.0)
ADI rank category, no. (%)							
0 to 33.3	10248 (20.8)	1816 (30.8)	2003 (30.0)	1026 (21.3)	2356 (18.0)	1944 (16.4)	1103 (16.0)

33.4 to 66.6	20861 (42.4)	2203 (37.4)	2594 (38.8)	1967 (40.8)	5788 (44.2)	5113 (43.1)	3196 (46.5)
66.7 to 100	18129 (36.8)	1877 (31.8)	2088 (31.2)	1831 (38.0)	4940 (37.8)	4817 (40.6)	2576 (37.5)
COVID-19 testing capacity, mean (SD), per 10000 people	3.1 (1.9)	1.3 (0.9)	1.7 (1.0)	2.1 (1.2)	4.1 (2.1)	3.7 (1.6)	3.8 (1.7)
Hospital occupancy, mean (SD), %	37.0 (10.8)	41.3 (11.8)	35.4 (9.9)	35.8 (10.2)	36.5 (10.3)	37.0 (10.5)	36.8 (11.5)

ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus; IQR: interquartile range; IQR: interquartile range; SD: standard deviation.

Supplemental Table 3B: Characteristics of hospitalized US Veterans with COVID-19 overall and by different month periods

Characteristic	**Overall** N = 9428	**March 20 – April 19** N = 1992	**April 20 – May 19** N = 1152	**May 20 – June 19** N = 966	**June 20 – July 19** N = 2274	**July 20 – August 19** N = 1872	**August 20 – September 19** N = 1172
Age, median (IQR), year	70.6 (61.2-76.8)	70.7 (61.8, 76.7)	72.2 (63.7-79.3)	69.7 (59.7- 76.8)	69.1 (58.9-75.6)	70.8 (61.1-76.5)	71.5 (62.3-77.2)
Race, no. (%)							
White	5054 (53.6)	811 (40.7)	607 (52.7)	533 (55.2)	1255 (55.2)	1081 (57.7)	767 (65.4)
Black	3809 (40.4)	1084 (54.4)	496 (43.1)	389 (40.3)	861 (37.9)	649 (34.7)	330 (28.2)
Other	565 (6.0)	97 (4.9)	49 (4.3)	44 (4.6)	158 (6.9)	142 (7.6)	75 (6.4)
Sex, no. (%), women	527 (5.6)	95 (4.8)	53 (4.6)	73 (7.6)	147 (6.5)	112 (6.0)	47 (4.0)
BMI category, no. (%)							
Underweight (<8.5 kg/m^2)	83 (0.9)	24 (1.2)	14 (1.2)	10 (1.0)	18 (0.8)	12 (0.6)	5 (0.4)
Normal weight (18.5 to <25 kg/m^2)	1836 (19.5)	387 (19.4)	276 (24.0)	182 (18.8)	423 (18.6)	350 (18.7)	218 (18.6)
Overweight (25 to <30 kg/m^2)	2922 (31.0)	611 (30.7)	344 (29.9)	322 (33.3)	684 (30.1)	582 (31.1)	379 (32.3)
Obesity (>18.5 kg/m^2)	4587 (48.7)	970 (48.7)	518 (45.0)	452 (46.8)	1149 (50.5)	928 (49.6)	570 (48.6)
Smoke, no. (%)							
Never smoker	4713 (50.0)	913 (45.8)	511 (44.4)	474 (49.1)	1250 (55.0)	980 (52.4)	585 (49.9)
Former smoker	2956 (31.4)	766 (38.5)	409 (35.5)	283 (29.3)	607 (26.7)	535 (28.6)	356 (30.4)
Current smoker	1759 (18.7)	313 (15.7)	232 (20.1)	209 (21.6)	417 (18.3)	357 (19.1)	231 (19.7)
Hypertension, no. (%)	6347 (67.3)	1345 (67.5)	763 (66.2)	649 (67.2)	1546 (68.0)	1264 (67.5)	780 (66.6)
Diabetes, no. (%)	3695 (39.2)	798 (40.1)	473 (41.1)	386 (40.0)	856 (37.6)	715 (38.2)	467 (39.8)
Cancer, no. (%)	1443 (15.3)	346 (17.4)	169 (14.7)	150 (15.5)	328 (14.4)	261 (13.9)	189 (16.1)
Cardiovascular disease, no. (%)	3417 (36.2)	735 (36.9)	453 (39.3)	338 (35.0)	773 (34.0)	674 (36.0)	444 (37.9)
Cerebrovascular disease, no. (%)	1836 (19.5)	403 (20.2)	279 (24.2)	179 (18.5)	399 (17.5)	328 (17.5)	248 (21.2)
Dementia, no. (%)	1953 (20.7)	420 (21.1)	345 (29.9)	212 (21.9)	398 (17.5)	336 (17.9)	242 (20.6)
Chronic kidney disease, no. (%)	3042 (34.9)	704 (37.8)	368 (35.9)	293 (33.2)	716 (33.7)	575 (33.3)	386 (35.5)
Peripheral artery disease, no. (%)	543 (5.8)	127 (6.4)	87 (7.6)	59 (6.1)	120 (5.3)	92 (4.9)	58 (4.9)
HIV, no. (%)	141 (1.5)	44 (2.2)	16 (1.4)	12 (1.2)	40 (1.8)	23 (1.2)	6 (0.5)
Pneumonia, no. (%)	336 (3.6)	104 (5.2)	59 (5.1)	37 (3.8)	51 (2.2)	50 (2.7)	35 (3.0)
COPD, no. (%)	2429 (25.8)	524 (26.3)	311 (27.0)	251 (26.0)	549 (24.1)	462 (24.7)	332 (28.3)
ADI rank category, no. (%)							
0 to 33.3	1785 (18.9)	583 (29.3)	290 (25.2)	169 (17.5)	335 (14.7)	249 (13.3)	159 (13.6)
33.4 to 66.6	3643 (38.6)	671 (33.7)	454 (39.4)	383 (39.6)	904 (39.8)	733 (39.2)	498 (42.5)
66.7 to 100	4000 (42.4)	738 (37.0)	408 (35.4)	414 (42.9)	1035 (45.5)	890 (47.5)	515 (43.9)

COVID-19 testing capacity, mean (SD), per 10000 people	2.8 (1.8)	1.2 (0.9)	1.6 (0.8)	2.1 (1.1)	3.9 (1.5)	3.8 (1.4)	4.0 (1.7)
Hospital occupancy, mean (SD), %	38.1 (10.5)	42.4 (11.3)	35.0 (9.7)	36.1 (8.9)	38.1 (9.4)	37.1 (10.4)	37.0 (10.6)
ADI: area deprivation index; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated Glomerular Filtration Rate; HIV: Human immunodeficiency virus; IQR: interquartile range; SD: standard deviation.							

Supplemental Table 4 Contribution of changes in demographic, health, and contextual characteristics to temporal differences in outcomes between 3/20–4/19, 2020 and 6/20–7/20, 2020

Factors	Among Veterans with COVID-19				Among hospitalized Veterans with COVID-19	
	30-day mortality rate changes		Hospitalization rate changes		30-day mortality rate changes	
	Predicted rate of change	Percent contribution to total change (predicted/observed)	Predicted rate of change	Percent contribution to total change (predicted/observed)	Predicted rate of change	Percent contribution to total change (predicted/observed)
Demographics	-2.4%	26.1%	-3.3%	19.6%	-3.0%	23.6%
Health characteristics	-0.7%	7.6%	-1.5%	9.0%	-0.3%	2.4%
Contextual characteristics	0.1%	-1.1%	0.1%	-0.6%	0.1%	-0.8%
COVID-19 testing capacity	-0.5%	5.4%	-0.9%	5.4%	-0.2%	1.6%
Hospital occupancy	-0.2%	2.2%			-0.4%	3.1%
Net rate of change predicted by demographic, health, contextual characteristics, testing capacity, and hospital occupancy (A)	**-3.7%**	**40.2%**	**-5.6%**	**33.3%**	**-3.8%**	**29.9%**
Observed rate of change (B)	-9.2%		-16.8%		-12.7%	
Epidemiological change (difference between observed and net predicted rate of change) (B)-(A)	-5.5%	59.8%	-11.2%	66.7%	-8.9%	70.1%

Demographics include age, race, and gender; Health characteristics include BMI, diabetes, cancer, cardiovascular disease, cerebrovascular disease, chronic kidney disease, dementia, HIV, hypertension, peripheral artery disease, pneumonia, and smoking status; contextual factors include ADI; epidemiological change includes the 30-day periods of testing positive dates.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Page	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4	Explain the scientific background and rationale for the investigation being reported
Objectives	4	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	6	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	5	Describe any efforts to address potential sources of bias
Study size	9	Explain how the study size was arrived at
Quantitative variables	6-7	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	7-8	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	9	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	9	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	9	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	10	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	12	Summarise key results with reference to study objectives
Limitations	14	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	14	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	14	Discuss the generalisability (external validity) of the study results
Other information		
Funding	15	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.