


BRIEF REPORT

Clinical and virologic factors associated with outcomes of COVID-19 before and after vaccination among Veterans: Retrospective analysis from six New England states

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Abstract

We aimed to characterize clinical and demographic factors affecting clinical outcomes of COVID-19 and describe viral epidemiology among unvaccinated Veterans in New England. Veterans infected with COVID-19 in Veterans Administration healthcare systems in six New England states from April 8, 2020, to September 2, 2021, were correlated with outcomes of 30-day mortality, nonpsychiatric hospitalization, and intensive care unit admission (ICU-care). We sequenced 827 viral genomes. Of 3950 Veterans with COVID-19 before full vaccination, 81% were White, 8% were women, and the mean age was 60 years. Overall, 19% of Veterans required hospitalization, 2.8% required ICU care, and 4.9% died. In this largely male and older cohort, poor outcomes correlated with increasing age. Most New England Veterans (>97%) were infected with B.1 sublineages with the D614G mutation in 2020 and early 2021. B.1.617.2 lineage (68%) predominated after July 2021.

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has infected >80 million people in the United States and caused over 980,000 deaths as of early April, 2022.¹ While some host and viral factors have been found to be associated with transmission rates, disease severity, and mortality, there are significant variations in these outcomes among specific

populations.^{2,3} Some host factors that have been shown to have a significant association with clinical outcomes include age, Charlson comorbidity index score, and body mass index (BMI).^{4,5} Viral factors have similarly been investigated for affecting outcomes. The US Centers for Disease Control and Prevention and World Health Organization have been diligently maintaining active surveillance of the evolving SARS-CoV-2 virus across the globe and several mutations have been known to result in the generation of variants of concern and variants of interest.⁶

Early during the pandemic course in the United States, viral isolates on the East Coast of the United States were predominantly of the B.1 lineage that contained the Spike protein D614G substitution.⁷ This substitution has been suggested to have enhanced transmissibility.⁸ With the increasing focus on emerging SARS-CoV-2 genetic variants, both regional epidemiology of the virus as well as unique clinical characteristics of certain populations can play a role in determining outcomes of the infection.

US Veterans make a reasonably vulnerable population because of their average age of 58 years, which is higher than the average age of a US resident (38.5 years), and because Veterans are largely male (89%).⁹ At the beginning of the COVID-19 era, we conducted a small pilot study on Veterans with COVID-19 between April 2020 and September 2020 from the same region of New England and found age, dementia, and low BMI to be associated with mortality.¹⁰ Here, we present the analysis of outcomes throughout the COVID-19 era in these Veterans from the New England states.

In a region-wide analysis of Veterans who contracted COVID-19 before vaccination in New England, we aimed to (1) characterize clinical, demographic, and viral factors and (2) conduct genomic evaluations of lineages and spike mutations throughout the COVID-19 era to determine the evolution of SARS-CoV-2.

METHODS

We conducted a retrospective analysis of demographic and clinical variables to identify their relationship with outcomes of COVID-19 among Veterans in New England. The Veterans Affairs Connecticut Healthcare System (VACHS) in West Haven, Connecticut, has carried out testing for SARS-CoV-2 on nasopharyngeal specimens from VA healthcare centers in all six New England states. The VACHS Institutional Review Board approved the creation and maintenance of a data repository of all Veterans in New England diagnosed with COVID-19 and a viral repository of the SARS-CoV-2 RNA received from all six New England facilities.

Cohort

Our cohort included all Veterans receiving care at VA healthcare centers in six New England states from April 8, 2020, to September 2, 2021, who had a diagnosis of COVID-19 before full vaccination and accessible chart records. Vaccination status was defined as “fully vaccinated” 2 weeks after two doses of the Pfizer-BioNTech (BNT162b2, Comirnaty) or Moderna (mRNA-1273, SpikeVAX) vaccines, or 1 week after one dose of the Janssen COVID-19 (Ad.26.COV2.S) vaccine.

Data collection

Data collection methods included utilizing structured query language (SQL) to query the VA Corporate Data Warehouse (CDW) to identify

a Veteran cohort of confirmed SARS-CoV-2 cases. Tests performed at VA facilities outside of this area or non-VA institutions were not included in the cohort. The data set included demographic variables (age, sex, race, BMI, and state of residence when diagnosed with COVID-19) as recorded in Veteran medical records. ICD-9 and ICD-10 diagnostic codes were used to document comorbidities.

The recorded primary outcomes were hospitalization, intensive care unit (ICU) admission, and 30-day all-cause mortality. Hospitalization was defined as within 2 days of a positive COVID test, as most patients admitted for COVID-19 were retested if the last test was over 48 h before admission. Hospitalization for rehabilitation or psychiatry was excluded. Deaths were identified as occurring within the VA facility or if the VA was provided a death certificate, which was archived in the electronic Veteran registration package of VISTA.

Genomic analysis

We evaluated viral genomes from 827 Veterans (details in Supporting Information Methods). Of these, we had complete clinical data for 778 individuals. Genotyping was done on as many samples as the lab could obtain. We identified variants, spike mutations, and lineages in three time periods: early (March–September 2020), middle (October 2020–March 2021), and late (April 2021–July 2021).

Statistical analysis

Logistic correlation analysis was used to find correlates of hospitalization, mortality, and ICU admission. We first conducted a univariate analysis, then used variables from the univariate analysis with $p < .10$ to use in a stepwise multivariate model with a forward selection level of .1 and backward selection level of .15. All analyses were performed using STATA v16.

RESULTS

Veteran characteristics

Of 3950 Veterans in six New England states with confirmed SARS-CoV-2+ test before full vaccination during the study period, the average age was 60 ± 18 years, with 8% female and 81% White. An early cohort of 274 Veterans from our pilot study was included in this analysis to ensure the completeness of our analysis.¹⁰

Associations with outcomes before vaccination

Of the 3950 Veterans with COVID-19, 759 Veterans were hospitalized (19%), with 112 needing ICU care (2.8%), and 194 died (4.9%) (Table 1). On multivariate regression, significant correlates of hospitalization were age, male gender, Black race, BMI of 30–34.9, chronic heart disease,

TABLE 1 Patient characteristics (n = 3950)

	Not hospitalized (n = 3191)	Hospitalized (n = 759)	Hospitalization (multivariate regression)
Demographics			
Age (years), mean (SD)	56.8 (17.2)	71.9 (14.2)	1.05 (1.04, 1.06)*
Sex			
Male	2895 (91)	734 (97)	1.66 (1.04, 2.65)*
Female	296 (9.3)	25 (3.3)	Ref.
Race			
White	2495 (81)	599 (80)	
Black	386 (13)	114 (15)	1.60 (1.22, 2.08)*
Other/unknown	205 (6.6)	33 (4.4)	1.37 (0.88, 2.16)
BMI category			
<25	546 (24)	145 (21)	1.13 (0.83, 1.53)
25-30	729 (32)	175 (25)	0.93 (0.72, 1.23)
30-35	739 (32)	234 (34)	0.75 (0.57, 0.97)*
>35	298 (13)	135 (20)	Ref.
Comorbidities			
Dementia	48 (1.5)	30 (4.0)	1.65 (0.91, 2.98)
Alcohol use	194 (6.1)	69 (9.1)	1.38 (0.98, 1.96)
Tobacco use	542 (17)	160 (21)	
Drug use	116 (3.6)	44 (5.8)	1.68 (1.10, 2.57)*
Chronic heart disease	765 (24)	428 (56)	1.67 (1.36, 2.05)*
COPD	425 (13)	228 (30)	1.44 (1.16, 1.80)*
Asthma	281 (8.8)	67 (8.8)	
Chronic liver disease	248 (7.8)	80 (11)	1.47 (1.08, 2.00)*
CKD	134 (4.2)	111 (15)	1.75 (1.28, 2.57)*
Malignancy	63 (2.0)	27 (4.9)	
Diabetes	746 (23)	311 (41)	1.11 (0.91, 1.41)

Note: Results presented as n (%).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

*Denotes statistically significant association.

chronic obstructive pulmonary disease, chronic liver disease, and chronic kidney disease. Significant correlates of ICU admission were age, BMI 30-34.9, BMI 24-24.9, and tobacco use (Supporting Information: Table 1). The only significant correlate of mortality was age.

Viral sequencing

New England Veterans were primarily infected with B.1 and its sublineages with the D614G mutation in the early (n = 282) and middle period (n = 347) of the study.¹⁰ In the late period (n = 198), the delta (B.1.617.2, 68%) lineage predominated (Supporting Information: Table 2).

The most common lineages and subsequent hospitalizations are shown in Figure 1. The most common spike mutations are shown in Supporting Information: Table 3.

DISCUSSION

Our study found that in an older cohort of Veterans with a high comorbidity burden, age significantly correlated with hospitalization, ICU admission, and mortality in unvaccinated populations. The most common lineages in 2020 were B.1 and B.1.2, while B.1.617.2 dominated infections during the summer and fall of 2021.

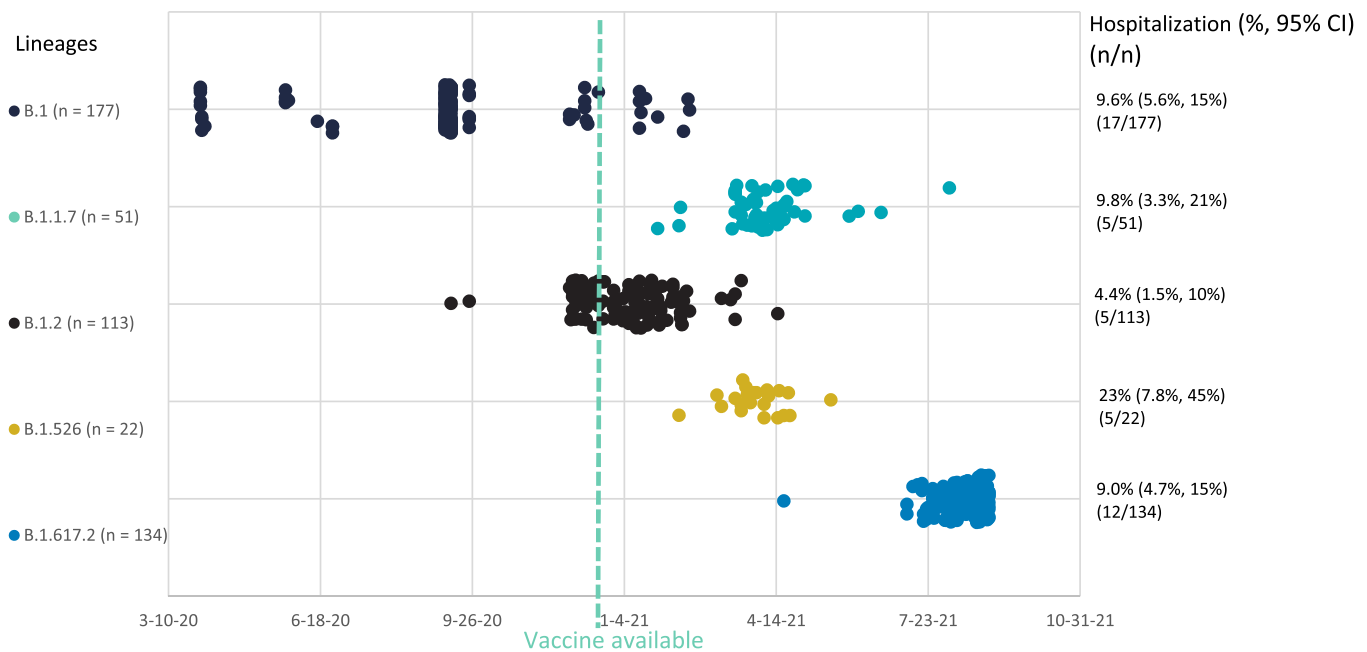


FIGURE 1 Frequency of SARS-CoV-2 lineages and associated hospitalization rates among 497 patients diagnosed with COVID-19. CI, confidence interval; COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2.

Understanding clinical factors that impact outcomes in this population can help clinicians determine risks for Veterans with similar demographics, and understanding the regional genomic variants can help scientists track the evolution of the virus.

The comorbidities correlating with worse outcomes in our study were similar to analyses in some other populations of patients with COVID-19. Like other studies, we found that age was a significant correlate of worse outcomes.^{4,5,11-14} Male sex, which was associated with hospitalization in our study, is another widely cited predictor of worse prognosis,¹⁵ with one meta-analysis citing a global odds ratio of 2.84 for ICU admission, and 1.39 for death.¹⁵ Our data also showed an increased rate of hospitalization among black participants, but no difference in mortality, as has been shown in some previous studies.

Limitations of this work include that it is specific to Veterans, a largely older male cohort, and results may not be generalizable to other populations. Evaluation of the Veteran population is critical, however, because these sex and age limitations are known associations for COVID-19 infection. We were only able to record hospitalizations within the VA system and did not have results if Veterans were seen at outside hospitals. Furthermore, we are limited by the retrospective nature of our review, and analysis via ICD codes may have missed diagnoses due to incorrect or inaccurate coding. Although we genotyped every sequence we could obtain, we did not have genotypes for all Veterans in our population, which may affect the generalizability of our results.

Future studies should assess how time-based factors (including waves of the virus and temporal effect of vaccination) affect outcomes, as well as COVID incidence and disease outcomes in similar demographic groups of vaccinated versus unvaccinated

populations. Our analysis was conducted before Omicron became a prominent lineage within the United States and future studies should continue to sequence and report the ever-changing landscape of the SARS-CoV-2 virus and conduct clinical correlation to outcomes. Our study's strengths include its comprehensive inclusion of Veterans in New England, large study size, and presentation of viral variants.

CONCLUSION

We found that in this regional cohort of Veterans with an average age of 60 years and multiple comorbidities, age significantly correlated with hospitalization, ICU admission, and mortality. While the most common lineages in 2020 were B.1 and B.1.2, the delta variant of SARS-CoV-2 (B.1.617.2) dominated infections during the summer and early fall of 2021.

AUTHOR CONTRIBUTIONS

All authors participated in manuscript preparation. Megan Lee and Shaili Gupta participated in the conception, design, data collection, analysis, and interpretation of results. Danielle Cosentino participated in the data collection, analysis, and interpretation of results. Tassos C. Kyriakides participated in the analysis and interpretation of the results. Tricia Cavallaro and Gary Stack participated in the conduction, analysis, and interpretation of whole-genome sequencing (WGS).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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