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Risk factors for delirium among SARS-CoV-2 positive veterans

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ABSTRACT

There have been increasing reports of atypical neuropsychological symptoms among patients hospitalized with Coronavirus Disease 2019 (COVID-19). Although numerous pathophysiological mechanisms have been proposed to account for the association between COVID-19 and delirium, few studies have examined factors associated with its development and none have done so in the context of a veteran sample. The current study exploratorily examined demographic and medical variables that might be associated with delirium among a cohort of SARS-CoV-2 positive veterans. Demographic and medical data were extracted from the computerized patient records of 162 veterans who were admitted to a large southeastern Veterans Affairs hospital for COVID-19 complications between March 1, 2020 and April 20, 2020. At the zero-order level, age, a history of cardiovascular illness, length of stay, intensive care unit admission, initiation of new dialysis, and the development of new thromboembolic or cardiac findings were associated with delirium. However, when simultaneously examining the impact of these predictor variables in a logistic regression, only length of stay and new cardiac findings increased the odds of delirium. Findings highlight the importance of continued investigation into factors that may account for neuropsychiatric dysfunction among COVID-19 patients.

1. Introduction

First reported in Wuhan, Hubei Province, China in December of 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes the Coronavirus Disease 2019 (COVID-19), has been declared a pandemic (Platto et al., 2020). As of December 23, 2021, there have been 276, 436, 619 confirmed cases including 5, 374, 744 deaths worldwide (World Health Organization, 2021). Although predominately a respiratory disease characterized by a high fever, fatigue, dry cough, and shortness of breath (Koh et al., 2020), there have been increasing reports, both anecdotal and empirical, of psychological problems (Gallagher et al., 2020) and in particular, atypical neuropsychological symptoms including delirium (Beach et al., 2020; Garcez et al., 2020; Kennedy et al., 2020). Delirium is a poorly understood syndrome of neuropsychiatric dysfunction characterized by fluctuating changes in cognition and attention (American Psychiatric Association, 2013). Although a relatively common complication of critical illness (Ely et al., 2004), delirium appears to be more frequent and pronounced among patients with COVID-19 than their non-COVID-19 hospitalized counterparts (55% vs 25%, respectively; Pieralli et al., 2014; Pun et al., 2021). Recently, numerous pathophysiological mechanisms have been proposed to account for the association between COVID-19 and delirium (Ferrando et al., 2020; Sher et al., 2020), with some studies having implicated mechanical ventilation, medication use, and lack of family visitation as contributory factors (Pun et al., 2021). Few studies, however, have systematically examined factors that may be associated with the development of delirium in COVID-19 patients (Ticinesi et al., 2020), and none have done so in the context of a veteran population. This is particularly important as veterans are known to have overall poorer health and more medical conditions than the general population (Agha et al., 2000; Hoerster et al., 2012). To bridge this gap, we exploratorily examined factors, both demographic and medical, that may be associated with delirium among a cohort of SARS-CoV-2 positive patients who were admitted to a large southeastern Veterans Affairs (VA) healthcare facility.

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2. Methods

Demographic and medical data were extracted from the computerized patient records of all veterans ($N = 162$) who were hospitalized for SARS-CoV-2 (based on a polymerase chain reaction [PCR] test) at a large southeastern VA hospital between March 1, 2020 and April 20, 2020. All data, which were culled by a group of physicians and nurse practitioners during a systematic chart review, were entered into a de-identified database. Basic demographic variables collected included veteran age, sex, race, and marital status. Medical variables, which were selected at the time of data collection based on risk factors identified by the Centers for Disease Control and Prevention (CDC), included the following pre-existing medical conditions: hypertension, diabetes mellitus, kidney disease, lung disease, underlying cardiovascular disease (i.e., heart, stroke, peripheral), cancer (active or history of excluding skin cancers), and severe obesity (as evidenced by a BMI $\geq$ 40). Further, several variables representative of the severity of the illness were also collected including: length of stay, intensive care unit (ICU) admission status, elevated liver function test, respiratory problems (i.e., requiring oxygen or high flow via nasal cannula, bilevel positive airway pressure, or mechanical ventilation), new dialysis, new thromboembolic diagnoses (i.e., deep vein, pulmonary embolism, or clots), new cardiac findings (i.e., heart attack, arrhythmia, or elevation in serum troponin), and delirium (as diagnosed by the medical team). All medical data including the dependent variable were coded as "1″ for the presence or "0″ for the absence of each condition. Given the retrospective nature of data collection, informed consent was not obtained. Nevertheless, the local VA Institutional Review Board approved the use of these data for research purposes.

2.1. Data analytic plan

Prior to conducting analyses, data screening was performed. This included running descriptive statistics to check for data entry errors, missing data, and outliers. Next, descriptive statistics were examined for the complete sample by variable and delirium status. Following this, bivariate associations among all predictor variables and the outcome of interest were examined in order to assess for multicollinearity (as evidenced by high correlations among the predictor variables) and to identify relevant predictors to be included in the model. Given that a small number of cases and large number predictor variables can cause problems with model convergence (Ranganathan et al., 2017), only those variables significant at the bivariate level were included in the main analysis. Finally, a hierarchical binary logistic regression analysis was performed to examine the impact of relevant demographic and medical variables on delirium status. Step one of the model included pertinent demographic variables, step two included preexisting medical conditions, and step three included illness severity variables.

3. Results

Veterans were primarily male (95%) with a mean age of 67.66 (SD = 12.59). The sample was predominately Black/African American (85%) and married or with a partner (51%). Fifteen percent of the sample were diagnosed with delirium. Descriptive statistics for the sample by outcome status (i.e., delirium) can be found in Table 1. In terms of zero-order correlations, there was a significant association between delirium status and veteran age ($r = 0.16$, $p = .046$) but not veteran sex, race, or marital status (p's > 0.218). There was also a significant relationship between the outcome of interest and underlying cardiovascular problems ($r = 0.19$, $p = .018$) but not hypertension, diabetes mellitus, kidney disease, lung disease, cancer, or severe obesity (p's > 0.207). Further, there was a significant association between delirium and the following illness severity indicators: length of stay ($r = 0.57$, $p < .001$), ICU admission ($r = 0.18$, $p = .023$), new dialysis ($r = 0.22$, $p = .006$), new thromboembolic ($r = 0.20$, $p = .009$), and new cardiac findings ($r = 0.27$, $p < .001$) but not respiratory failure or liver functioning (p's > 0.067). Variables not significant at the zero-order level were not included as predictors in the full model.

Table 1
Demographics and clinical characteristics by delirium status.

	Total $N = 162$	Outcome Status Delirium $n = 25$	No Delirium $n = 137$
Demographic Variables			
Age	$M = 67.66$, $SD = 12.59$	$M = 72.28$, $SD = 10.11$	$M = 66.82$, $SD = 12.84$
Male	$n = 154$ (95%)	$n = 25$ (100%)	$n = 129$ (94%)
Black/African American	$n = 137$ (85%)	$n = 23$ (92%)	$n = 114$ (83%)
Married/Partnered	$n = 82$ (51%)	$n = 11$ (44%)	$n = 71$ (52%)
Preexisting Medical Variables			
Hypertension	$n = 127$ (78%)	$n = 22$ (88%)	$n = 105$ (77%)
Diabetes Mellitus	$n = 68$ (42%)	$n = 12$ (48%)	$n = 56$ (41%)
Underlying Kidney Disease	$n = 47$ (29%)	$n = 8$ (32%)	$n = 39$ (29%)
Underlying Lung Disease	$n = 18$ (11%)	$n = 4$ (16%)	$n = 14$ (10%)
Underlying Vascular Disease	$n = 46$ (28%)	$n = 12$ (48%)	$n = 34$ (25%)
Cancer (or history of)	$n = 25$ (15%)	$n = 3$ (12%)	$n = 22$ (16%)
Severe Obesity	$n = 17$ (11%)	$n = 3$ (12%)	$n = 14$ (10%)
Illness Severity Variables			
Length of Stay	$M = 10.95$, $SD = 12.28$	$M = 27.28$, $SD = 20.65$	$M = 7.97$, $SD = 6.73$
ICU Status	$n = 64$ (40%)	$n = 15$ (60%)	$n = 49$ (36%)
Elevated Liver Function Test	$n = 58$ (36%)	$n = 13$ (52%)	$n = 45$ (33%)
Respiratory Problems	$n = 126$ (78%)	$n = 21$ (84%)	$n = 105$ (77%)
New Dialysis	$n = 19$ (12%)	$n = 7$ (28%)	$n = 12$ (9%)
New Thromboembolic Disease	$n = 20$ (12%)	$n = 7$ (28%)	$n = 13$ (10%)
New Cardiac Disease	$n = 40$ (25%)	$n = 13$ (52%)	$n = 27$ (20%)

To examine the impact of various demographic and medical variables on delirium, a hierarchical binary logistic regression analysis was performed. Step one of the model, which included veteran age, explained between 3% (Cox and Snell R Square) and 5% (Nagelkerke R Square) of the variance in delirium with 84% of cases correctly identified. Step two of the model, which included underlying cardiovascular problems, explained between 5% (Cox and Snell R Square) and 8% (Nagelkerke R Square) of the variance with 85% of cases correctly identified. The third and final step of the model, which included length of stay, ICU admission status, and new dialysis, thromboembolic, and cardiac findings, explained between 26% and 46% of the variance in delirium with 92% of cases correctly identified. The full model containing all predictors was statistically significant χ^2 (7, $N = 162$) = 49.33, $p < .001$). As shown in Table 2, only two of the independent variables made a statistically significant contribution to the final model with new cardiac problems evincing the strongest association (OR = 3.54).

4. Discussion

Despite a growing body of literature demonstrating an increased incidence of delirium in SARS-CoV-2 positive patients, few studies have been published examining risk factors or COVID-19 disease correlates associated with the development of this neuropsychiatric condition. To

Table 2
Summary of Hierarchical Binary Logistic Regression Analysis.

Variable	*B*	S. E.	Wald	df	*p*	Odds Ratio
Step 1: Demographic Variables						
Age	.02	.03	.47	1	.491	1.02
Step 2: Preexisting Medical Variables						
Vascular Disease	.47	.63	.57	1	.452	1.60
Step 3: Illness Severity Variables						
Length of Stay	.11	.03	15.58	1	<0.001	1.12
ICU Status	−0.75	.77	.96	1	.327	.47
New Dialysis	.58	.85	.47	1	.495	1.79
Thromboembolic Disease	.22	.86	.06	1	.800	1.24
Cardiac Problems	1.26	.62	4.11	1	.043	3.54

this end, the current study was designed to examine the impact of various demographic, pre-existing medical, and illness severity variables associated with delirium using a sample of SARS-CoV-2 positive veterans. At the zero-order level, we found that age, length of stay, ICU admission status, a history of cardiovascular illness, initiation of new dialysis, and the development of thromboembolic or cardiac findings were associated with delirium. However, when simultaneously examining the impact of these predictor variables on the odds that veterans would exhibit delirium, only length of stay and new cardiac findings made a statistically significant contribution.

Previous research has highlighted the role of a number of medical and environmental factors (i.e., hypoxia, inflammation, CVA, direct central nervous system (CNS) invasion, organ dysfunction, medications, and social isolation) in the development of delirium in COVID-19 patients (Pun et al., 2021; Sher et al., 2020). However, these studies have failed to identify cardiac dysfunction (defined herein as the development of a new finding such as acute coronary syndrome, new arrythmia, or elevation in serum troponin) as a neuropsychiatric marker. This is notable as cardiac dysfunction evinced the strongest association with delirium when accounting for all other variables in the current model. Some research has highlighted the bidirectional relationship between CNS and cardiac function (Buchmann et al., 2019; Suciu and Cristescu, 2017), potentially connecting findings from the present study to previous research. However, the specific pathway by which CNS and cardiac dysfunction might impact delirium it is unclear. Given the potential relevance of cardiac problems to development of delirium, particularly among veterans (Russell et al., 2020), future work should seek to elucidate mechanisms that might account for these relationships.

Unfortunately, due to limitations in data collection, information regarding medications was not collected. Given the potential deliriogenic nature of hydroxychloroquine and its widespread use during the early stages of the Coronavirus pandemic (Skipper et al., 2020), as well as its known complication of cardiac arrythmia (Uzelac et al., 2020), it is reasonable to assume that this may be one possible common cause for both phenomena. Another possibility is that cardiac dysfunction prompted the use of another anti-arrhythmic which may itself be deliriogenic. Further, cardiac dysfunction could be a marker for overall frailty in the patient, potentially causing alterations in mental status. Indeed, among older adults hospitalized with COVID-19, frail patients were more likely to present with delirium than non-frail patients of the same age (Zazzara et al., 2021).

Despite the well-established association between age and delirium in non COVID-19 related critically ill patients (Kubota et al., 2018), age was not a significant contributor to delirium in the overall model. Further, as previously noted, pre-existing medical conditions such as lung, kidney, and cardiovascular diseases were not associated with delirium when accounting for other medical variables. This is somewhat surprising given that these conditions are frequently associated with more severe illness in the context of COVID-19 (Raines et al., 2021); however, delirium is only one of many possible illness severity indicators. Lastly, marital status was not associated with delirium which might suggest that previously established protective factors, such as social support, were of little relevance during a pandemic where family were not allowed at bedside (Do et al., 2012).

To our knowledge, this is the first study to specifically examine risk factors associated with the development of delirium in SARS-CoV-2 positive veteran patients. Strengths of the present study include a racially diverse patient population (85% African American/Black) and a comprehensive description of patient medical status (i.e., medical variables). However, the current study was also limited by the retrospective study design, meaning inferences regarding causality cannot be made. Additionally, the use of dichotomous variables restricts the range of variability in outcomes, possibly limiting our ability to detect certain relationships. Authors of future research should use longitudinal designs to establish prospective associations between these variables and COVID-19 related delirium and should consider the use of continuous measures. Finally, this analysis relied on progress notes to delineate the presence or absence of delirium; validated screeners such as the Confusion Assessment Method (CAM) were not uniformly conducted on all patients. Future studies should assure the inclusion of such screeners to better elucidate associations among variables.

Despite these limitations, this study contributes to the growing body of evidence examining causes and consequences of this novel coronavirus. In a cohort of hospitalized veterans with COVID-19, results revealed that longer hospital length of stay and new cardiac findings increased the odds of delirium, while all other variables interestingly were not associated. Further research is needed to elucidate mechanisms that may account for the associations between COVID-19 and delirium and to help guide clinical care of patients testing positive for SARS-CoV-2.

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Declarations of interest

None.

CRediT authorship contribution statement

Charles J. Santos: Conceptualization, Investigation, Writing – original draft. **Nebil Nuradin:** Investigation, Writing – original draft. **Christopher Joplin:** Investigation, Writing – original draft. **Alexandra E. Leigh:** Investigation, Writing – review & editing. **Rebecca V. Burke:** Investigation, Writing – review & editing. **Robin Rome:** Investigation, Writing – review & editing. **Jonathan McCall:** Investigation, Writing – review & editing. **Amanda M. Raines:** Formal analysis, Supervision.

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