RESEARCH LETTER

COVID-19 and Incidence of Acute and Chronic Hyponatremia: A Matched Cohort Study

To the Editor:

Hyponatremia has been reported at high frequency on admission among patients hospitalized with coronavirus disease (COVID)-19.[1-8] No studies have addressed the issue of persistence of chronic hyponatremia following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, a single case report describes an syndrome of inappropriate antidiuretic hormone secretion (SIADH)-like syndrome following infection with SARS-CoV-2.[9] Additionally, COVID-19-associated hyponatremia has been linked to acute inflammation.[5,10]

In this context, we performed a series of retrospective cohort studies to address the question of whether COVID-19 is associated with the development of hyponatremia in the subacute (30-90 days) and chronic periods (>90 days) and what relationship this may have to the inflammatory markers C-reactive protein (CRP) and serum ferritin levels.

This study used the TriNetX federated health research network, comprises electronic medical records of approximately 93 million patient records. The data include demographics, diagnoses, laboratory values, and procedures searchable via standardized terminologies through TriNetX's online platform. Cohorts of patients at high risk of hyponatremia were assembled, and results are presented in this report. We also performed a sensitivity analysis in a low-risk patient cohort. We investigated the sodium laboratory test results at the following time points: 0-1, 2-7, 8-14, 15-30, 31-90, 91-180, 181-365, and 366-545 days after the index event. Laboratory test results were analyzed as raw values as well as classes of hyponatremia: mild (130-134 mmol/L), moderate (125-129 mmol/L), and severe (<124 mmol/L).

Differences in outcomes between the respective cases and control cohorts were evaluated after propensity score matching with t test for continuous variables (ie, raw sodium result values) and χ^2 test for dichotomous variables (eg, mild, moderate, or severe hyponatremia). We report the risk difference and the difference in the mean sodium result values between the cases and control cohorts. A P value <0.05 was considered statistically significant. All analyses were performed on the TriNetX analytics platform. Detailed methods are provided in Item S1.

Table 1. Clinical Characteristics of the COVID-19 and No COVID-19 Cohorts after Propensity Score Matching

	COVID-19 $N_{before\ match}$ = 16,765 $N_{matched}$ = 16,764	No COVID-19 $N_{before\ match}$ = 698,530 $N_{matched}$ = 16,764	*P* Value
Age at index, (y)	Mean 66.6	Mean 66.7	0.56
	SD 16.8	SD 16.5	
Gender			
Female	8,221 (49.1%)	8,285 (49.4%)	0.48
Race			
Black or African American	2,901 (17.3%)	2,909 (17.3%)	0.93
White	11,194 (66.8%)	11,159 (66.6%)	
Other	2,669 (15.9%)	2,696 (16.1%)	
Ethnicity			
Hispanic	752 (4.5%)	775 (4.6%)	0.97
Non-Hispanic	11,622 (69.3%)	11,625 (69.3%)	
Diagnosis			
COPD	2126 (12.7%)	2104 (12.6%)	0.72
Other pulmonary heart diseases	603 (3.6%)	529 (3.2%)	0.03
Heart failure	2230 (13.3%)	2155 (12.9%)	0.22
Viral hepatitis	532 (3.2%)	493 (2.9%)	0.22
Fibrosis and cirrhosis of liver	302 (1.8%)	272 (1.6%)	0.21
CKD	2234 (13.3%)	2113 (12.6%)	0.05
Stage 1 CKD	38 (0.2%)	37 (0.2%)	0.91
Stage 2 CKD	227 (1.4%)	190 (1.1%)	0.07
Stage 3 CKD	1278 (7.6%)	1216 (7.3%)	0.20
Stage 4 CKD	189 (1.1%)	166 (1%)	0.22
Medications			
Diuretics	2,779 (16.6%)	2,648 (15.8%)	0.05
Antidepressants	2,457 (14.7%)	2,374 (14.2%)	0.20
Anticonvulsants	1,694 (10.1%)	1,584 (9.4%)	0.04

Note: The cohorts were used to assess sodium laboratory values 0-1 days after the index event.
Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

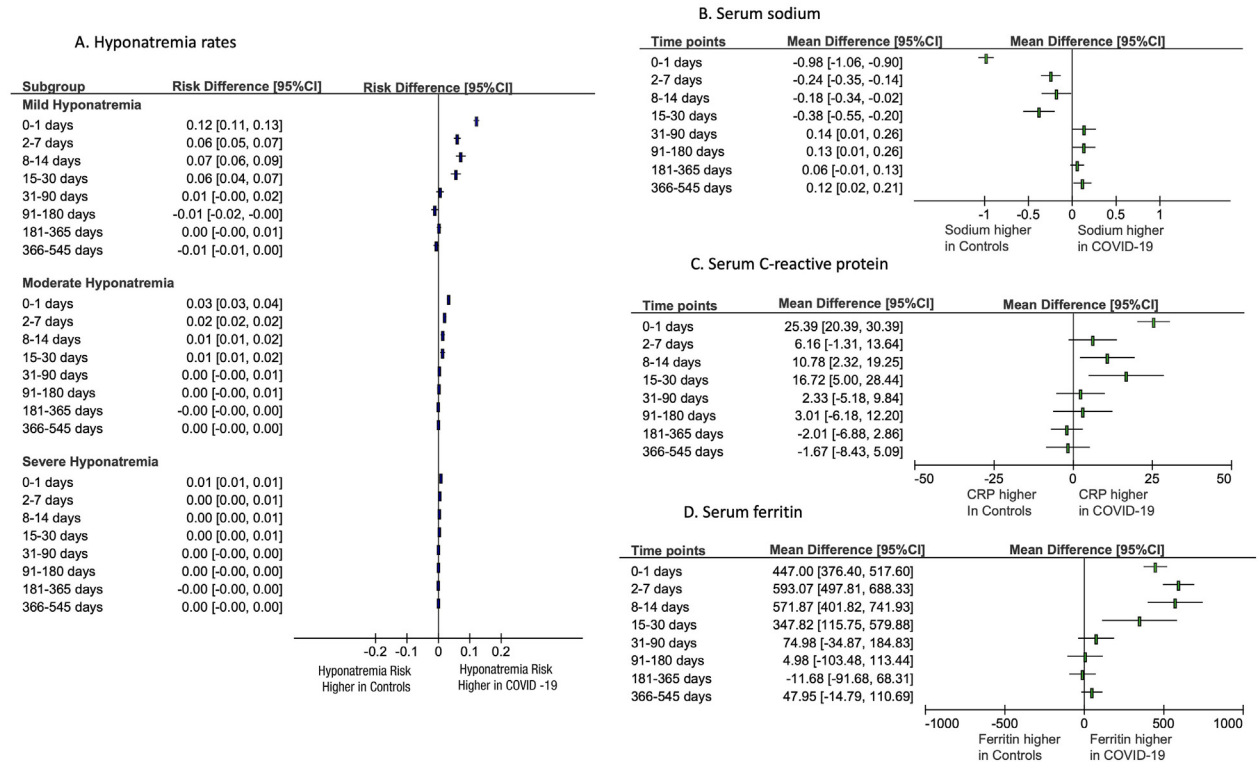

Figure 1. Mean differences and risk difference of listed outcome in cases (COVID-19 cohorts) and controls (no COVID-19 cohorts). Negative values indicate that the mean value of cases is lower than the mean value of controls. Zero values indicate no difference, and positive values indicate that the mean value of controls is lower than the mean value of cases.

Table 1 shows the demographic and diagnostic characteristics of the cases and controls cohorts after propensity score matching used to assess sodium laboratory values 0-1 days after the index event. The characteristics of the remaining matched cohorts assessing all other time points are included in Item S1. There were no statistically significant differences in the demographic or diagnostic characteristics of the cohorts.

Fig 1 summarizes the risk differences for development of hyponatremia (Fig 1A) and mean differences in sodium values (Fig 1B), CRP (Fig 1C) and ferritin values (Fig 1D) between cases and controls during follow-up. Cases had statistically significant higher risk of mild or moderate hyponatremia up to 30 days following COVID-19 than the controls and severe hyponatremia up to 90 days after COVID-19 (Fig 1A). Cases had statistically significant lower sodium values 0-1, 2-7, 8-14, and 15-30 days after COVID-19 than controls (Fig 1B). Cases had statistically significant higher CRP (Fig 1C) and ferritin (Fig 1D) values at 0-1, 2-7, 8-14 and 15-30 days after COVID-19 than controls. A sensitivity analysis was performed in a population at low risk of hyponatremia, and no significant difference in the results was found (Item S1).

Our findings demonstrate that COVID-19 is associated with hyponatremia that is acute to subacute in duration, but not with longer term (>90 days) durations of hyponatremia (Fig 1). The rates of hyponatremia were highest initially and then approached the control group at approximately 3 months. This time dependent variation very much mirrored elevations in the markers of inflammation, which also returned to baseline by approximately 3 months. These results are consistent with previous reports and support the concept that as inflammation resolves, rates of hyponatremia among COVID-19 survivors' returns to premorbid levels.[5,10]

The strengths of our study include the use of a large health network that allowed the creation of large cohorts of COVID-19-infected individuals and propensity score-matched cohorts of noninfected individuals representative of the national population. Limitations include the retrospective and observational nature of the study. Therefore, this study does not address whether hyponatremia is a marker of disease severity or whether disturbances in water balance play a pathogenic role in COVID-19. Additionally, because of limited access to individual patient data, the use of advanced modeling techniques, such as mixed models or transformations, was not feasible. This may have resulted in overestimation or underestimation of the estimates. Nevertheless, the results provide an opportunity to confirm or refute the findings in a prospective cohort study.

We have shown that COVID-19 is associated with hyponatremia that persists for up to 90 days following the onset of COVID-19. The duration of hyponatremia we

report closely mirrors the time course of elevation of serum ferritin and CRP levels, suggesting that inflammation plays a role in the persistence of hyponatremia following acute COVID-19. We find no association between COVID-19 and chronic hyponatremia.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Detailed methods and additional results.

ARTICLE INFORMATION

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