אוניברסיטת בן-גוריון בנגב

הפקולטה למדעי הבריאות

ביה"ס לרפואה ע"ש גולדמן

בקשה לביצוע עבודה בהתנסות מחקרית- קלינית

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המשמעות של היפונתרמיה בחולי קורונה – הניסיון המצטבר של מרכז רפואי בודד בישראל

**The significance of hyponatremia in SARS-CoV-2 infections.
A single-center experience in Israel**

**מילות מפתח באנגלית(Key words) : )**

Hyponatremia, SARS -Covid -19 infection, Mechanical ventilation, ECMO,

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**Background**

Hyponatremia is one of the most common water–electrolyte imbalances experienced by humans. Its prevalence is 15%–30% among hospitalized patients but is even higher in the intensive care unit (ICU), reaching 40% (1-2).

Hyponatremia has been described in many infectious diseases. In terms of bacterial diseases, it has mostly been associated with community-acquired bacterial pneumonia such as *Legionella*, spontaneous bacterial peritonitis, tuberculosis, and sepsis. Moreover, hyponatremia commonly develops with many other viral infections, such as CNS infections, HIV, and influenza B (3).

The main pathogenesis is normovolemic hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (3-4). Hyponatremia prevalence is positively associated with comorbidity, scored using the Charleston Comorbidity Index, and is more common in most moribund patients (4-5). Xu et al. (6) showed that hyponatremia was significantly more prevalent in patients who died from infectious disease and presented with fever and thrombocytopenia than in those who survived. Winzler et al. (7) also reported a 20% one-year mortality rate among patients admitted to the hospital due to severe hyponatremia (<125 mmol/L), which emphasizes the gravity of this pathology and the need for adequate causal treatment. A recent meta-analysis confirmed that amelioration of hyponatremia is independently associated with a reduction in all-cause-mortality risk (8).

Hyponatremia may be a common laboratory finding in patients with COVID-19 (9). However, various reports have shown that hyponatremia in this patient cohort may not only be associated with SIADH due to COVID-19-related pneumonia, but also be attributed to patients’ inadequate dietary intake or the gastrointestinal loss presenting in 14% of patients with hyponatremia, irrespective of the hyponatremia etiology (9-11). The condition develops more frequently in patients with a hospital stay longer than 14 days. Nonetheless, in a multivariate analysis (8), hyponatremia was not recognized as an independent risk factor associated with long-term hospitalization in patients with COVID-19. Berni et al. (5) reported that among non-ICU COVID-19 patients hyponatremia was positively correlated with the oxygenation index (PaO2/FiO2 ratio) and inversely with IL-6 levels. The patient cohort investigated in that study partially qualified for treatment with tocilizumab (an anti-IL-6 antibody), based on the IL-6 levels. Interestingly, the initiation of such treatment was associated with a significant improvement in hyponatremia at 48 h compared with the control group. The authors of that work also emphasized that hyponatremic patients had worse outcomes (more ICU transfers and more noninvasive ventilation initiations) than their normonatremic counterparts.

The largest multicenter study of COVID-19, the HOPE registry (12), from Spain and Italy, included 4664 patients and found a hyponatremia prevalence of 20.5%. Mild hyponatremia was found in 16.7% and severe hyponatremia in 1.3%. The mortality rates were 17.4% among normonatremic COVID-19 patients with pneumonia and 29.4% among hyponatremic patients, with the mortality rate higher for mild and severe hyponatremia, presenting a U-shaped curve.

Only a few papers based on case series have investigated the significance of hyponatremia at admission in COVID-19 patients in terms of mortality and disease severity and as a risk factor for ICU admission, mechanical ventilation, prolonged length of stay, and extracorporeal mechanical oxygenation (ECMO) usage.

Soroka University Medical Center (SUMC) is the main hospital in the south of Israel, serving a population of approximately one million people. The first SARS-CoV-2-infected patients were hospitalized in SUMC in March 2020. The goal of our study is to extend our understanding of the prevalence and correlations of hyponatremia at admission and the influence of the severity grade on the outcomes of hospitalized patients with COVID-19. Moreover, the definition of the relationship between hyponatremia and the severity of the lung injury in COVID-19 patients could be another independent indicator for the treatment of COVID-19 patients with tocilizumab and remdesivir, the main medications indicated for the treatment of severe COVID-19. The commonly accepted score used for assessing disease severity in COVID-19-hospitalized patients is the NEWS (National Early Warning Score) (Table 1). We believe that the identification of a relationship between hyponatremia and disease severity would extend the NEWS criteria.

**Research hypothesis**

Hyponatremia will be associated with increases in mortality, rate of mechanical ventilation, and length of hospital stay in COVID-19-hospitalized patients.

**Research goal**

To estimate the prevalence of hyponatremia among COVID-19 patients hospitalized in SUMC and study the association between hyponatremia and major clinical outcomes, including 28-day mortality and length of hospital stay.

**Secondary goals**

To investigate the relationship of hyponatremia with disease severity by examining various aspects of severe disease in COVID-19 patients, such as deterioration leading to the need for mechanical ventilation or ECMO support and development of pneumonia on chest X-ray, as well as demographic characteristics such as age, sex, and ethnicity.

**Research methods**

Research type:

A retrospective cohort study.

Research population:

Between March 2020 and May 2021, nearly 1300 patients were admitted to the COVID-19 wards at SUMC. For the first two months (March to May 2020), all positive patients were hospitalized regardless of their medical condition. Beginning in June 2020, there were two types of hospitalized patients, those who were admitted due to COVID-19 and those who were admitted for other reasons (e.g., trauma, labor) and were found to be SARS-CoV-2 positive and required quarantine during their hospital stay.

To determine patients’ condition and assess their severity, a global score known as the NEWS has been used since March 2020 (13) (Table 1, Appendix).

In this study, we plan to use the entire cohort admitted between March 2020 and May 2021 to determine the prevalence of hyponatremia and describe the characteristics of patients with hyponatremia.

After the exclusion of patients with a low NEWS (<5) and those who were found to be SARS-CoV-2 positive but were hospitalized for other medical reasons, the remaining patients will be divided into two groups:

Group A, which is the hyponatremic group and includes all patients with moderate-to-severe SARS-CoV-2 infection with hyponatremia at admission.

Group B, which includes all other patients with moderate-to-severe SARS-CoV-2 infection without hyponatremia at admission.

Inclusion and exclusion criteria:

All patients aged 18 years and older with a positive PCR swab for SARS-CoV-2 who were hospitalized in the COVID-19 department will be included in the study population.

We will exclude patients with chronic hyponatremia, chronic loop diuretic treatment, chronic parenchymal lung diseases, lung cancer, and lung metastasis, a NEWS < 5, and age younger than 18 years.

**Statistical analysis**

Dependent variables

Death within 28 days (0 – alive, 1 – dead)

Mechanical ventilation (0 – no use of ventilation, 1 – use of ventilation)

ECMO placement requirement (0 – no need, 1 – needed)

Length of hospital stay (days, quantitative variable)

Transfer to ICU (0 – not transferred, 1 – transferred)

Independent variables

Na+ level (0 – 135–145 mg%, 1 – 130–134 mg%, 2 – 121–129 mg%, 3 – less than 121 mg%); Table 1 describes the values for determining hyponatremia severity

Chest X-ray result (0 – no pneumonia, 1 – less than mid-lung bilateral pneumonia, 2 – mid-lung bilateral pneumonia, 3 – whole-lung bilateral pneumonia)

Severity score at admission (NEWS is a quantitative variable that ranges from 5 to 29 points)

Age (quantitative variable)

Sex (0 – female, 1 – male)

Ethnicity (0 – Jewish, 1 – Arabic, 2 – Asian, 3 – Caucasian, 4 – American)

**Medical history**

Diabetes mellitus (0 – no, 1 – yes)

Chronic heart failure (0 – no, 1 – yes)

Chronic ischemic heart disease (0 – no, 1 – yes)

Hypertension (0 – no, 1 – yes)

Lung disease such as chronic obstructive pulmonary disease or asthma (0 – no, 1 – yes)

Obesity: as defined in the patient's medical history (0 – no, 1 – yes)

Liver cirrhosis (0 – no, 1 – yes)

Organ transplantation (0 – no, 1 – yes)

Smoker (0 – no, 1 – yes)

**Chronic medication usage**

ACE inhibitors (0 – no, 1 – yes)

Steroid treatment (0 – no, 1 – yes)

Biological and/or immunological treatment (0 – no, 1 – yes)

Sample size calculation

Because we will use the nonhyponatremic patients as the control group, the minimum sample size in a study of independent cohort cases should be calculated using the calculation required for a matched case control study. Prior data from the HOPE study indicated a failure rate of 0.174 among controls (12). If the true failure rate for experimental subjects is 0.294, we will need to study 194 experimental subjects and 194 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with 0.8 probability (power). The type 1 error probability associated with this test of the null hypothesis is 0.05. We will use an uncorrected chi-square statistic to evaluate this null hypothesis (Table 3, Appendix).

We would like to prove a clinical effect of 15%.

Data collection methods

Data will be collected from the Camillion database and MetaVision database, which are used for the medical records of all hospitalized patients in SUMC. These databases include medical diagnoses and demographic characteristics according to ICD-9 codes.

**Statistical methods**

The statistical analysis will be performed in three steps. The first step will be the descriptive analysis concerning all quantitative variables. Normally distributed variables (e.g., age) will be described by mean and standard deviation. Non-normally distributed variables (length of hospitalization and NEWS) will be described by median, range, and interquartile range, whereas qualitative variables (e.g., sex and overweight) will be described by their distribution by percent. The second step will be univariate analysis. In this stage, we will compare each dependant variable. For the comparison of qualitative dependant variables (e.g., death) with qualitative independent variables (e.g., obesity), we will use the chi-square test or Fisher exact test, as appropriate. For the comparison of qualitative dependant variables (e.g., death) with age, we will use a *t*-test for independent samples and will use the Mann-Whitney *U* test for the comparison of such variables with the NEWS. For the comparison of dependant variables (e.g., length of hospitalization) with qualitative independent variables (e.g., obesity), we will use the Mann-Whitney *U* test, as well as the Kruskal-Wallis test for comparison with non-dichotomous variables (e.g., ethnicity). The third stage is multivariate analysis. In this stage, we will conduct multivariate logistic regression for dichotomous dependant variables (e.g., death). For quantitative dependant variables (e.g., length of hospitalization), we will construct a Poisson or negative binomial multivariate regression model. The regression will include independent variables found to be significant in the second stage and/or clinically significant. In this stage, we will check for possible interactions.

P < 0.05 will be considered statistically significant. SPSS software version 26 will be used for the statistical analyses.

**Limitations of study**

1. Small patient cohort: we will require a cohort with a minimum of 194 patients to find a clinically significant effect of 15% with a null hypothesis of 0.05.
2. Single-center design.
3. A new parameter was introduced in February 2021, namely immunization with the Pfizer BNT162b2 vaccine.
4. A short observation period of 28 days: we decided to focus on that period because after that timeframe patients would be considered to have “long COVID” and we will not address that condition in this study.
5. Vague definitions of variables, such as obesity (can be defined by BMI or by weight threshold): obesity will be defined according to the patient's medical history, and the same approach will be used for other background medical variables and drug use.

**Student’s responsibilities and schedule**

1. Conduct a review of recent publications and plan the study – May 2022
2. Data collection and statistical analysis, under the guidance of Prof. Friger – June to July 2022
3. Initial inference and analysis of statistical results – August 2022
4. Play a major role in writing a scientific paper under the guidance of the accompanying facilitators – September 2022

**Approval of the institutional ethics committee**

The study was approved by the Helsinki committee on May 7, 2021 (approval no. SOR-089-21).

**References**

1. Mohan, S.; Gu, S.; Parikh, A.; Radhakrishnan, J. Prevalence of Hyponatremia and Association with Mortality: Results from NHANES. Am. J. Med. **2013**, 126, 1127–1137.
2. Corona, G.; Giuliani, C.; Parenti, G.; Norello, D.; Verbalis, J.G.; Forti, G.; Maggi, M.; Peri, A. Moderate Hyponatremia Is Associated with Increased Risk of Mortality: Evidence from a Meta-Analysis. PLoS ONE **2013**, 8, e80451.

3.Krolicka AL, Kruczkowska A,Krajewska M,Kusztal MA. Hyponatremia in infectious diseases-a literature review.Int J Environ Res Public Health 2020;17(15):5320–5336.

4.Liamis G,Milionis HJ,Elisaf M.Hyponatremia in patients with infectious diseases.
J Infec 2011;63(5):327–335.

5. Berni, A.; Malandrino, D.; Parenti, G.; Maggi, M.; Poggesi, L.; Peri, A. Hyponatremia, IL-6, and SARS-CoV-2 (COVID-19) infection: May all ft together? J. Endocrinol. Investig. **2020**.

6. Xu, X.; Sun, Z.; Liu, J.; Zhang, J.; Liu, T.; Mu, X.; Jiang, M. Analysis of clinical features and early warning indicators of death from severe fever with thrombocytopenia syndrome.
Int. J. Infect. Dis. **2018**, 73, 43–48.

7. Winzeler, B.; Jeanloz, N.; Nigro, N.; Suter-Widmer, I.; Schuetz, P.; Arici, B.; Bally, M.; Blum, C.; Bock, A.;Huber, A.; et al. Long-term outcome of profound hyponatremia: A prospective 12 months follow-up study. Eur. J. Endocrinol. **2016**, 175, 499–507.

8. Wu, Y.; Hou, B.; Liu, J.; Chen, Y.; Zhong, P. Risk Factors Associated With Long-Term Hospitalization in Patients With COVID-19: A Single-Centered, Retrospective Study. Front. Med. **2020**, 7, 315.
9. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM: Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis 7(2):91, 2020.

10. Ata F, Almasri H, Sajid J, Yousaf Z: COVID-19 presenting with diarrhoea and hyponatraemia. BMJ Case Rep 13(6), 2020.

11. Hong X-w, Chi Z-p, Liu G-y, et al.: Analysis of early renal injury in COVID-19 and diagnostic value of multi-index combined detection. medRxiv 2020. 03.07.20032599, 2020.
12.Sanchez JGR, Nunez-Gil IJ, Cuesta M, Rubrio MA, Maroun-Eid CM et al. /Prognostic impact of hyponatremia and hypernatremia in COVID 19 pneumonia.A HOPE-COVID-19 (Health Outcome Predictive Evaluation for Covid-19) Registry analysis Front Endocrinol 30 Nov 2020:http://doi.org/10.3389/fendo.2020.599255.
13. Pimental MA, Redfern OC, Gerry S, Collins GS, Malycha J, Prytherch D, Scmidt P, Smith GB, Watkinson PJ. A comparison of the ability of the National Early Warning Score and the National Early Warning Score 2 to identify patients at risk of in-hospital mortality: A multi-centre database study. Resuscitation 2019; 134:147–156.