Correlation Between Hypertension and Hyponatremia in Hospitalized Coronavirus Disease 2019 Patients: A Single-Center Experience

Ayu Pramitha Wulandari, Dhani Tri Wahyu Nugroho

Department of Cardiology and Vascular Medicine, Dr. Wahidin Sudiro Husodo General Hospital, Mojokerto, Indonesia.

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ABSTRACT

Background: Hypertension has been presumed to be correlated with the coronavirus disease 2019 (COVID-19) severity. The most common electrolyte disturbance in COVID-19 patients is hyponatremia. It is correlated with increased mortality.

Objective: This research purposed to investigate the correlation between hypertension and hyponatremia in COVID-19 patients.

Methods: A cross-sectional study including hospitalized COVID-19 patients was conducted at Dr. Wahidin Sudiro Husodo General Hospital, Mojokerto, Indonesia, from December 2020 to January 2021. We analyzed data about the blood pressure and sodium level data of COVID-19 patients. The statistical analysis process was performed using IBM SPSS version 23.0.

Results: A total of 98 eligible patients were involved in the analysis. The prevalence of hypertension and hyponatremia among COVID-19 patients was 55.1% and 79.6%, respectively. Hyponatremia prevalence was higher in hypertensive patients than normotensive patients. Hypertension increased the risk of hyponatremia in COVID-19 patients (90.7% vs. 65.9%; OR = 5.06; 95% CI = 1.66 - 15.4; p = 0.002).

Conclusion: This single-center cross-sectional study revealed that, in COVID-19 patients, the presence of hypertension was correlated with a higher risk of hyponatremia.

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A novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was found at the end of 2019 and rapidly spread globally. This global pandemic is an emergency faced by all countries around the world. Research in SARS-CoV-2 revealed that some variables are correlated with the prognosis of COVID-19 patients. The comorbid condition, high d-dimer, older age, and multiple organ damage were risk factors for poor outcomes. Hypertension is one of the most frequent comorbidities in coronavirus disease 2019 (COVID-19) patients. The previous study revealed that hypertension is associated with the COVID-19 severity. That correlation has been presumed to be correlated to angiotensin-converting enzyme 2 (ACE2). The spike protein of SARS-CoV-2 attaches to ACE2 and leads downregulation or depletion of ACE2.

Prior studies demonstrated that patients with COVID-19 tend to suffer from electrolytes imbalance, particularly sodium balance disorder. It was correlated with greater mortality and severity of COVID-19 patients. The latest study demonstrated an association among COVID-19, ACE-2, and renin-angiotensin-aldosterone-system (RAS) pathway that contributes to electrolyte disturbance and disease severity of COVID-19. However, the evidence is limited and still need for further investigation with better study design. In developing countries such as Indonesia, the study related to this topic is still limited. Therefore, this research purposed to investigate the correlation between hypertension and hyponatremia in COVID-19 patients.

1. Method

1.1. Study Design

We completed a single-center cross-sectional research. This research had been recognized by the ethical committee and conformed with the principles of the Helsinki declaration. From December 1st, 2020 to January 30th, 2021, we consecutively selected COVID-19 patients in Dr. Wahidin Sudiro Husodo General Hospital, Mojokerto, East Java, Indonesia. We included all COVID-19 confirmed cases hospitalized in Dr. Wahidin Sudiro Husodo General Hospital. We excluded the patient with incomplete data. The confirmed case was defined as patients who had a positive result of real-time fluorescent reverse transcription-polymerase chain reaction (RT-PCR). All important information about the patients was collected from the medical record. Hypertension was the documented systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg at least two
the patients had a blood sodium level less than 135 mmHg.7

2.2. Statistical analysis

All statistical analysis process was conducted using SPSS 23.0 (IBM) software. The baseline characteristic of the patients was showed in the table. The number and percentage were used to describe the categorical data. For continuous data, the mean and standard deviation (SD) were used to show the continuous data with normal distribution. The comparison between 2 continuous variables was assessed using Mann Whitney test for abnormally distributed data and the independent t-test for normally distributed data. The comparison between the two categorical variables was tested using the Fisher’s exact test or the Chi-squared test. An odds ratio (OR) was calculated to measure a correlation between hypertension and hyponatremia in COVID-19 patients. The statistically significant was considered if p-value <0.05.

3. Results

A total of 116 COVID-19 patients were identified from our registry system. Of those, a total of 18 patients were excluded because of incomplete data. Finally, a total of 98 COVID-19 confirmed cases were involved in the data analysis. Patients were grouped into hypertension group (n = 54) and no hypertension group (n = 44) (Figure 1). The prevalence of hypertension among COVID-19 patients was 55.1%. The mean age in the hypertension group and no hypertension group was 56.3 ± 11.3 and 54.8 ± 13.6 years old, respectively. Overall, we did not find the significant differences in age, gender, and the prevalence of comorbid conditions such as chronic kidney disease, diabetes mellitus, heart failure, or coronary artery disease in both groups. Baseline characteristics information of the included patients are summarized in Table 1.

| Comorbid disease                  | Hypertension (n = 54) | No Hypertension (n = 44) | P-value |
|-----------------------------------|-----------------------|--------------------------|---------|
| Male sex                          | 26 (48.2)             | 24 (54.5)                | 0.529   |
| Age, years old                    | 56.3 ± 11.3           | 54.8 ± 13.6              | 0.356   |
| Coronary artery disease           | 26 (48.1)             | 17 (38.6)                | 0.345   |
| Diabetes mellitus                 | 1 (1.85)              | 1 (2.2)                  | 0.883   |
| Heart failure                     | 25 (46.2)             | 21 (47.7)                | 0.888   |
| Chronic kidney disease            | 4 (7.4)               | 5 (11.3)                 | 0.500   |
| Blood Pressure                    |                       |                          |         |
| SBP, mmHg                         | 170 (90 - 250)        | 112.5 (90 - 135)         | 0.398   |
| DBP, mmHg                         | 103 (36 - 170)        | 77.5 (70 - 85)           | 0.624   |

The prevalence of hyponatremia among COVID-19 all patients was 79.6%. The prevalence of hyponatremia was greater in the hypertension group than no hypertension group patients. From the Chi-square test, it pointed out that hypertension increased the risk of hyponatremia in COVID-19 patients (90.7% vs. 65.9%; OR = 5.06; 95% CI = 1.66 - 15.4; p = 0.002) (Figure 2). The mortality rates in COVID-19 patients suffered from hypertension were 57.4 %, whereas the mortality rates in COVID-19 patients without pressure were 54.5 %, respectively (OR 1.36; 95% CI = 0.51 - 3.65; p = 0.17)

4. Discussion

Our current study confirmed that hypertension was associated with hyponatremia in covid 19 patients COVID-19 patients. The prevalence of hyponatremia was greater in the hypertension group than no hypertension group patients. It was related to a higher risk of hyponatremia, about 5.06-fold.

Several previous studies have discussed hypertension, hyponatremia in COVID-19 patients. A pooled analysis study about hypertension in patients with COVID-19 by Lippi et al. suggested that high blood pressure may be correlated with an up to 2.5-fold higher risk of fatal or severe COVID-19. It was also confirmed from a pooled analysis that COVID-19 severity is correlated with lower serum concentrations of potassium, calcium, and sodium.8 Another study by Huang et al. reported that hypertensive patients tend to show higher severity and mortality, from OR of hypertension were 1.562 (95% CI: 0.929 - 2.625; P=0.092) and 1.262 (95% CI: 0.683 - 2.332; P=0.458).9
spike protein receptor-binding domain, thus allowing virus entry.11 ACE-2 has a role as an entrance receptor by attachment to the virus's spike protein, permitting the invasion of SARS-CoV-2 into target cells. Transmembrane protease serine subtype 2 (TMPRSS2) facilitates the spike protein to permit the attachment with ACE-2, allowing SARS-CoV-2 invasion.3 In 2000, ACE-2, a novel ACE isoform, was found. It take an essential part in the non-classical RAS pathway, ACE-2/angiotensin-(1-7)/Mas receptor axis, which opposes the classical RAS pathway. Angiotensin-(1-7) stimulates G protein-coupled receptor Mas. Then, Mas receptor counteracts the destructive impacts of classical RAS pathway by induction of vasodilatation, anti-inflammatory, and cardioprotection, mainly in pathological conditions.12,13 ACE-2 and ACE play essential roles in maintaining the balance in both RAS pathways. When SARS-Cov-2 infected the human body, RAS activation was altered by downregulated ACE-2. During SARS-CoV-2 virus entrance and replication, ACE-2 is depleted and downregulated.14 This leads loss of the antagonist function of ACE-2 against the classical RAS pathway. This situation leads the RAS equilibrium towards the ACE/Angiotensin II pathway. As a result, Angiotensin II will activate the AT2 receptors that impact vasodilatation and cause an increased natriuresis.15 The natriuresis cause depletion of sodium levels that leads to hyponatremia.16 Hyponatremia is also the most frequent electrolyte imbalance in COVID-19 patients. It is caused by inappropriate antidiuretic hormone secretion. SIADH probably a result of the marked elevation of inflammatory cytokines, especially interleukin-6.6

Our study has several drawbacks. First, it was a single-center cross-sectional study. Second, the sample size was small. However, this study provided preliminary data about the correlation between hypertension and hyponatremia in hospitalized COVID-19 patients.

5. Conclusion

Based on this single-center cross-sectional study, we revealed that hypertension was correlated with a higher risk of hyponatremia in COVID-19 patients. We suggested further multi-center study with a better design larger size of study participants.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

Data used in our study were presented in the main text.

6.4. Competing interests

Not applicable.

6.5. Funding source

Not applicable.

6.6. Authors contributions

Idea/concept: APW. Design: APW. Control/supervision: DTWN. Data collection/processing: APW. DTWN. Extraction/Analysis/interpretation: APW. DTWN. Literature review: DTWN. Writing the article: APW. Critical review: DTWN. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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