Original Article

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Determining Extracellular Water Effects in Mild and Severe COVID-19 Pneumonia Clinical Course by using the Bioimpedance Method

Zuhal Cavus, Ayse Vahaboglu, Ulku Aygen Turkmen, Habibe Vural, Dondu Genc Moralar

University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital, Clinic of Anaesthesiology and Reanimation, Istanbul, Turkey

Abstract

Aim: Coronavirus disease-2019 (COVID-19) pneumonia is characterized by a clinical picture showing similar features in severe patients. Some studies evaluate the pathophysiology, prognosis, and treatment of COVID-19 pneumonia. Different laboratory tests have been used to assess the severity and prognosis of rigorously ill COVID-19 patients in addition to clinical and radiological findings. There is no precise indicator for predicting prognosis. We aimed to analyze disease severity by using extracellular water (ECW) measurements.

Methods: Extracellular water values and cardiac parameters as cardiac output (CO), and stroke volume (SV) measurements of patients were performed using a non-invasive, easy-to-use, validated device non-invasive cardiac system (NICaS) within the first 2 h after admission. Hemodynamic parameters and ECW values were measured by connecting the NICaS device to make 12 measurements for 2 h at 5 min intervals during admission to service and intensive care patients.

Results: Comparing the ward and intensive care groups, there was not any statistically significant difference found between demographic data and ECW, SV, and CO measurements.

Conclusion: Although we could not find a statistically significant difference between our measurements, we believe that the NICaS device can play a significant role in the fluid treatment of COVID-19 patients.

Keywords: COVID-19, extracellular water, non-invasive monitorization

Introduction

Since 2020, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has affected many countries worldwide. These symptoms differ from asymptomatic to severe pneumonia and respiratory distress syndrome. Almost 14% of the patients worsen to severe respiratory distress and need admission to the intensive care unit (ICU). Although there are many studies in the literature to determine the factors affecting disease severity, there is not any proper prognostic marker yet (1).

Although Coronavirus disease-2019 (COVID-19) pneumonia has different characteristics, it demonstrates a clinical picture similar to acute respiratory stress syndrome (ARDS), which is determined by the Berlin definition from many perspectives, especially in severe patients. Lung injury due to coronavirus SARS-CoV-2 is similar to other causes of ARDS, yet its early clinical characteristics demonstrate more sincere hypoxemia and absence of dyspnea with less radiologically evident lung injury, which is a pattern that has not been defined in ARDS previously (2-4). The main pathology in ARDS is the accumulation of extravascular lung fluid (EVLW) (both the interstitium and alveoli) due to disrupted alveolar-capillary permeability. This causes edema formation and leads to reduced alveolar clearance and collapse/de-recruitment, impaired gas exchange, and increased pulmonary vascular resistance.

Extracellular edema is a risk factor and a predictor of mortality in various medical conditions, such as heart, lung, and kidney failure. Various studies have shown that the extracellular water (ECW) in the lung is efficient in determining the severity of the disease in ARDS too.

Address for Correspondence: Zuhal Cavus, University of Health Sciences Turkey, Gaziosmanpasa Training and Research Hospital, Clinic of Anaesthesiology and Reanimation, Istanbul, Turkey
Phone: +90 532 632 31 66 E-mail: zuhalcavus74@gmail.com ORCID: orcid.org/0000-0002-7588-5240
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Fluid excess in the lung can be defined as EVLW or ECW and can be determined with invasive (hemodilution) or non-invasive (bioimpedance) methods (5,6).

Besides the clinical and radiological findings, different tests have been used to assess the severity and prognosis of COVID-19 patients. In the literature to determine prognostic factors for morbidity and mortality of SARS-CoV-2 researchers focused on blood biochemical, comorbidities, drugs, and basic clinical variables [O_2 saturation, temperature, or heart rate (HR)]. In a recent study, a correlation was detected between platelet-monocyte aggregates and the severity of the COVID-19 pneumonia clinical course (7). Several observational reports identify fluid accumulation, and sacral and pulmonary edema (8). ECW, as a marker of hydration status, is easy to use and proven as a predictor of survival in ICU patients. Although there are many studies on COVID-19 in the literature, limited studies are comparing extracellular fluid accumulation and prognosis (9,10).

Depending on compliance, Gattinoni et al. (11) mentioned COVID ARDS in two different types: H and L; nevertheless, compliance is not a predictor of the severity of illness. In our study, we predicted disease severity by using ECW measurements.

Materials and Methods

Compliance with Ethical Standards

The Institutional Ethical Committee approved this study (protocol no: 76; 28/05/2020), which was performed in accordance with the Second Declaration of Helsinki. Clinical Trials approved this study with protocol number NCT04416009. This prospective, observational, longitudinal cohort study was performed at a single tertiary medical center. Consent forms were taken from all patients.

Study Design and Participants

The inclusion criteria for the study were patients who were diagnosed with COVID-19 infection by applying real-time reverse transcriptase-polymerase chain reaction assays in patients older than 18. Arrhythmia and patients under 18 years of age were exclusion criteria for this study.

ICU or service admission decisions were made according to standard hospital protocols due to clinical assessments and laboratory findings. Oxygen saturation (SpO_2) lower than 85% and/or dyspnea and/or mental confusion were eligible criteria for ICU admission; patients not displaying these criteria were accepted to the ward with non-invasive cardiac system (NICaS) monitorization.

Measurements

ECW values and cardiac parameters such as cardiac output (CO) and stroke volume (SV) measurements of patients were performed using a non-invasive, easy-to-use, validated device NICaS within the first 2 h after admission. Hemodynamic parameters and ECW values were measured by connecting the NICaS device to make 12 measurements for 2 h with 5 minutes intervals during admission to ward and intensive care patients.

The NICaS device is a laptop, consisting of two electrodes and software that calculates cardiac parameters, elastic resistance, and ECW. These electrodes are similar to electrocardiogram electrodes, and the measurements can be done by sticking one of them on the wrist and the other on the other ankle or on both of the wrists.

Measurements were assumed using the NICaS (Kfar Malal, Israel), which evaluates EBW and hemodynamic parameters, including SV, HR, cardiac index, CO, and total peripheral resistance with the whole-body bioimpedance system. Total body water, ECW, and intracellular water can be measured by electrical bioimpedance. EBW calculation can be performed with an electrical current of 1.4 mA with a 32-kHz-frequency wave that passes through the patient via two pairs of tetrapolar electrodes placed at both wrists (12,13).

SV can be calculated by the Frinerman formula using the measurements of changes in electrical strength, which is a result of volume changes in the arterial system. HR is measured from an electrocardiograph, and CO is calculated as CO= SV.HR. The blood pressure is measured non-invasively and manually inserted at every time point.

NICaS has FDA approval and stands within its obligations in comparison with the pulmonary artery catheter-determined CO thermodilution techniques. And it is CE-marked in many countries (14,15).

Sample Size Calculation

We predicted the impact of ECW in the clinical course of COVID-19. The sample size is calculated based on the findings of Tagami and Ong (6) Gpower 3 for the Mac Os. program was used. Among-group Power analysis was performed a priori based on the t-test between independent groups (effects size: 0.6; power: 0.8; alpha error: 0.05). It was calculated that a total of 52 people, 26 people in each group, should be included in the study for the total sample size to generate a power of 0.8.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows 15.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normality assumption. Normally, distributed continuous variables were expressed as mean ± standard deviation, whereas the continuous variables that do not have a normal distribution were expressed as median (minimum-maximum). Categorical variables are summarized as counts (percentages). The significance of the difference between the 2 groups was investigated using the Student t-test or Mann-Whitney U test. Nominal variables were evaluated by the Pearson χ^2 test. A two-sided $p<0.05$ was considered statistically significant.

Results

We enrolled 65 hospitalized patients with a diagnosis of COVID-19 pneumonia. Patients in the wards were evaluated as a mild clinical course (Group 1, n=33) and patients in the ICU were considered a severe clinical course (Group 2, n=32).

A statistically significant difference was not found between the groups based on the demographic data of the patients. Results were: Group 1: 59.1±18.9 years, Group 2: 58.8±16.6 years and gender Group 1 male: 16 (49) and Group 2 male: 19 (59); Group 1 female: 17 (51) and Group 2 female: 17 (51) (Table 1).

Both groups were evaluated in terms of CO and SV values. CO was in Group 1 (5.2121±5.2121 L/min) and in Group 2 (5.1344±2.00252 L/min), and SV was in Group 1 (63.1242±25.94214 mL) and Group 2 (57.3562±20.92284 mL). Even though the SV values were above average, no statistically significant difference was detected (Table 1) (Figure 1, 2).

The results of the ECW values were in Group 1 (39.7758±2.58772) and Group 2 (58.78±16.648). Because of the statistical analysis performed by calculating the averages of measured values, there was not any significant difference was found between the hemodynamic parameters and ECW measurements between the groups (Figures 1-3).

Discussion

Previous studies demonstrated that excessive-volume load is a factor that increased mortality in patients with ARDS with COVID-19 pneumonia. And peripheral and pulmonary edema are often present in COVID-19 patients (16). Because of the measurements we made in the general wards and intensive care units of our hospital, we did not find a significant difference between the cardiac functions and ECW values of the patients. There is not any significant difference in the age and gender comparisons of the patients.

An increase in plasma volume is an important consequence of fluid retention. With the increase in plasma volume, the SV and CO increase significantly. There are studies in which both ECW and hemodynamic parameters are measured and correlated with non-invasive methods, especially in patients with a significant increase in fluid loads such as cesarean section, or pregnancy. In our study, we also made measurements to evaluate the correlation between cardiac parameters and fluid deficit, and we found a correlation between the measured parameters, similar to previous studies (17-19).

In BIAC-19 (bioelectric impedance analysis body composition) studies, Moonen et al. (20) determined body composition by the bioimpedance method in COVID-19 patients admitted to general wards and the ICU. They measured fat-free mass, soft lean mass, mineral mass, bone mineral content, percentage of body fat, visceral fat area, skeletal muscle mass, and protein mass using this method. They concluded that there was not any association between body composition and complications, mortality, or severity of COVID-19 infection. Similarly, we did not find any correlation between ECW values and disease severity (21).

In our study, since the measurements were performed in the first 2 h of hospitalization, the results of the evaluation with the bioimpedance method were not statistically significant. Simultaneously, we did not interfere with fluid therapy and other treatments during the hours of measurements. All patients were treated using restrictive fluid therapy strategies and COVID-19 Guidelines. In a recent study, the authors attempted to make bioelectrical impedance vector analysis measurements to evaluate the hydration status until the 72nd h of hospital admission. They claimed that hydration may be a prognostic factor for COVID-19 patients and that the non-invasive impedance method can be used to determine fluid therapy strategies, especially in the ICU. They argued that overhydration is an indicator of poor prognosis and predicted that restrictive

Table 1. Demographic and clinical characteristics

	Grup 1 (n=33)	Grup 2 (n=32)	p-value
Age*	59.1±18.9 years	58.8±16.6 years	0.944[a]
Gender, n (%) Man Woman	 16 (49) 17 (51)	 19 (59) 17 (51)	0.379[c]
ECW (%)**	40.1 (34.5-46.2)	38.2 (34.1-56.2)	0.138[b]
CO (L/min.)**	4.1 (1.7-12.1)	4.5 (2.1-10)	0.604[b]
SV (mL)**	63.1 (30.1-112.7)	50.8 (26.4-106.7)	0.679[b]

[a] Student t-test, [b]Mann-Whitney U test, [c]Pearson chi-square, *Mean ± standard deviation, **Median (minimum-maximum), ECW: Extracellular water compartment, CO: Cardiac output, SV: Stroke volume

fluid protocols are more appropriate in these patients. Overhydration assessment could be an extra parameter to follow-up COVID-19 patients. Therefore, the fluid load measured by the bioimpedance method is important in determining the course of fluid therapy. Contrary to our expectations, we did not detect any change in ECW due to pneumonia during the first hours of hospitalization to be substantial, in our study. Although our purpose was not to determine mortality, in their previous study they found not only ECW but whole-body composition at admission is a single predictor for mortality in COVID-19 (22,23). It is obvious that fluid status is important in COVID-19, so fluid therapy should be done carefully. Our intention was not to monitor the handicaps brought by fluid therapy or to monitor fluid therapy. It was to determine whether the extracellular fluid existence at admission influences the clinical course and whether ECW accumulation has a role in basic pathology, just like in ARDS. According to our results, the mechanisms in COVID-19 patients with ARDS are different from classical ARDS. Many studies in the literature have suggested that there are different ARDS mechanisms in COVID-19, supporting this idea (24,25)

Zhang et al. (26) claimed that demographic factors and treatment strategies perform a role in the prognosis of the disease. In this study, medical and mechanical ventilation treatments were prioritized. Older age, obesity, comorbidities, and some laboratory findings such as changes in blood cell counts, lactate dehydrogenase,

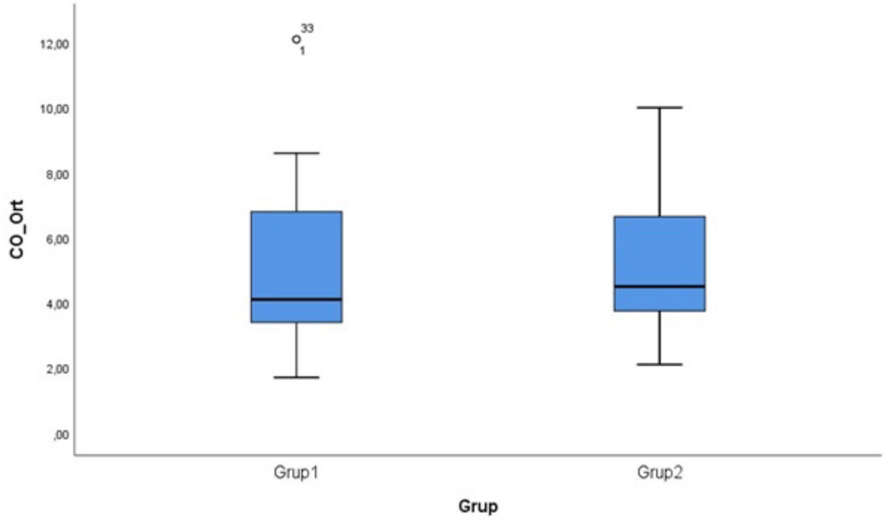

Figure 1. In the analysis using the mean values, no significant difference was found between the groups in terms of CO
CO: Cardiac output

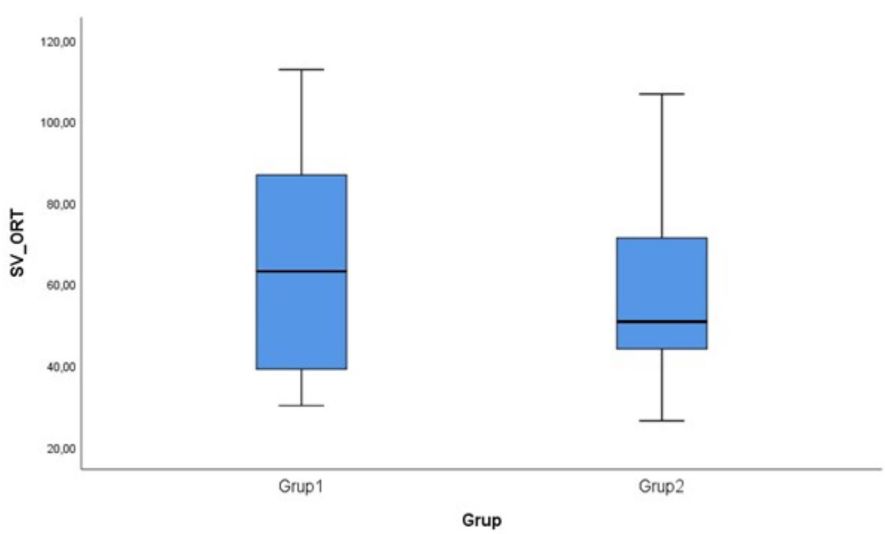

Figure 2. In the analysis using the mean values, no significant difference was found between the groups in terms of SV
SV: Stroke volume

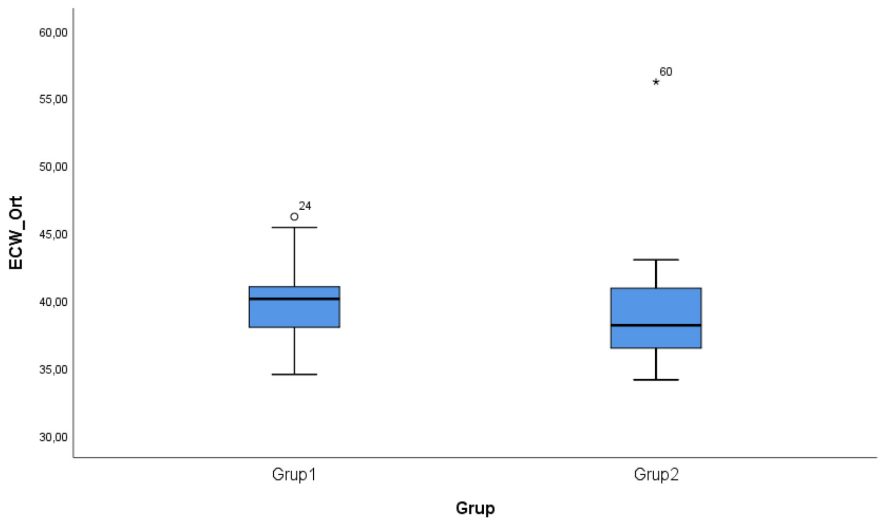

Figure 3. In the analysis using the mean values, no significant difference was found between the groups in terms of ECW
ECW: Extracellular water compartment

procalcitonin, aspartate aminotransferase, alanine aminotransferase, and blood urea nitrogen are discussed in the foreground. According to the study to perform new treatment strategies, further studies are needed. They did not mention fluid therapy, but we believe that extravascular lung volume is important so fluid management must have a majority in treatment.

There are limited studies that have focused on ECW in COVID-19 patients. In a study conducted by 7 patients in the prone position, it was found that extracellular lung water (EVLW) was increased and associated with increased mortality. A statistically significant decrease in EVLW was detected 18 h after patients were placed in the prone position, and it was emphasized that it could make a difference in the clinical management of severe patients requiring a prone position, especially in terms of pulmonary edema (27). In another study, COVID ARDS and non-COVID ARDS were compared, and EVLW was found to be higher in COVID patients, which was associated with disease severity and mortality. In this study, in which the transthoracic thermodilution method was used, hemodynamic parameters were found to be statistically similar between the groups. They claimed that due to the difference between EVLW and hemodynamic parameters, fluid therapy should be determined as restrictive but should be performed patient-specifically (28). Similar to these studies, hemodynamic changes did not differ between the groups in our study. Whether changes in the ECW depend on the severity of the disease or fluid therapy strategies has not been determined, but its importance has been noted in the follow-up.

In studies directed during the pandemic, COVID-19 pneumonia was classified as type 1 (non-ARDS) and type 2 (ARDS) by Gattinoni et al. (11). While the diagnosis was mostly made with computerized tomography images and clinic appearance, he argued that the treatment method was different between the groups. He also attributed the decrease in compliance in the ARDS group primarily to the natural course of the disease, not pulmonary edema. In support of Gattinoni et al.'s (29) idea, our study showed that the main pathology was not due to pulmonary edema.

Study Limitations

The major limitation of our study is to take measurements within 2 h of hospital admission and not continue for longer. Hence, we could not determine the effects of treatments and fluid management on patients. Probably, the patient's fluid status during treatment will provide findings that will support us to have an idea about mortality and prognosis.

We did not consider the comorbidities of the patients. Even dough the ECW values in the ICU Group were mildly higher, it was not statistically different. If we included arrhythmic patients, which were our exclusion criteria, the results would be different.

Conclusion

Based on the fact that we did not find a significant difference between the groups in terms of ECW and cardiac parameters, we can state that ECW may be an indicator of the ineffectiveness of pulmonary edema in the initial stage of the disease. However, the evaluation of hemodynamic parameters with NICaS, with clinical and biochemical parameters, may provide meaningful ideas about hydration. We believe that NICaS is a comfortable and non-invasive method to help manage fluid therapy, especially during the pandemic. Further studies are needed to support this idea.

Information: Has been presented as oral presentation in TARK 2022.

Ethics

Ethics Committee Approval: The Institutional Ethical Committee approved this study (protocol no: 76; 28/05/2020), which was performed in accordance with the Second Declaration of Helsinki. Clinical Trials approved this study with protocol number NCT04416009. This prospective, observational, longitudinal cohort study was performed at a single tertiary medical center.

Informed Consent: Consent forms were taken from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.C., A.V., Concept: Z.C., H.V., Design: U.A.T., H.V., Data Collection or Processing: A.V., H.V., Analysis or Interpretation: D.G.M., Literature Search: Z.C., H.V., Writing: Z.C., D.G.M.

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