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Observational Study

Septic shock 3.0 criteria application in severe COVID-19 patients: an unattended sepsis population with high mortality risk

Abstract

BACKGROUND

COVID-19 can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring ICU admission, respiratory and vasopressor support. Therefore, clear clinical criteria are pivotal to early recognition of patients more likely to need prompt organ support. Although most patients with severe COVID-19 meet the Sepsis-3.0 criteria for septic shock, it has been increasingly recognized that hyperlactatemia is frequently absent, possibly leading to an underestimation of illness severity and mortality risk.

AIM

To identify the proportion of severe COVID-19 patients with vasopressor support requirements, with and without hyperlactatemia, and describe its clinical outcomes and mortality.

METHODS

We performed a single-center prospective cohort study. All adult patients admitted to ICU with COVID19 were included in the analysis and were further divided into three groups: Sepsis group, without both criteria; Vasoplegic Shock group, with persistent hypotension and vasopressor support without hyperlactatemia; and Septic Shock 3.0

group, with both criteria. COVID-19 was diagnosed using clinical and radiologic criteria with a SARS-CoV-2 positive RT-PCR test.

RESULTS

118 patients (mean age 63 years, 87% males) were included in the analysis (n = 51 Sepsis group, n = 26 Vasoplegic Shock group, and n = 41 Septic Shock 3.0 group). SOFA score at ICU admission and ICU length of stay were different between groups (P < 0.001). Mortality was significantly higher in vasoplegic shock and septic shock 3.0 when compared with sepsis group (P < 0.001) without difference between the former two groups (P = 0.713). Log rank test of Kaplan-Meier survival curves were also different (P = 0.007). Ventilator-free days and vasopressor-free days were different between sepsis vs vasoplegic shock and septic shock 3.0 groups (both P < 0.001), and similar in the last two groups (P = 0.128 and P = 0.133, respectively). Logistic regression identified the maximum dose of vasopressor therapy used (AOR 1.046; 95%CI: 1.012-1.082, P = 0.008) and serum lactate level (AOR 1.542; 95%CI: 1.055-2.255, P = 0.02) as the major explanatory variables of mortality rates (R^2 0,79).

CONCLUSION

In severe COVID-19 patients, the Sepsis 3 criteria of septic shock may exclude around one third of patients with a similarly high risk of poor outcomes and mortality rate, that should be equally approached.

Key Words: COVID-19; Critical care; SARS-CoV-2; Septic shock; Lactate; Sepsis 3.0 criteria

Core Tip: COVID-19 can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring ICU admission, respiratory and vasopressor support. Although most patients with severe COVID-19 meet the Sepsis-3.0 criteria for septic shock, it has been increasingly recognized that hyperlactatemia is frequently absent. Our data clearly shows that one third of patients characterized as Sepsis by Sepsis 3.0 criteria present a risk of poor outcomes and mortality rate similar to those characterized as Septic shock and that should be equally approached.

INTRODUCTION

COVID19 can be associated with life-threatening organ dysfunction due to septic shock, frequently requiring ICU admission, respiratory and vasopressor support[1]. Surviving Sepsis Campaign guidelines for the management of critically ill adults with COVID-19 document a highly variable prevalence of septic shock in these patients ranging from 1 to 35%[2,3].

Clear clinical criteria of septic shock in this population are, therefore, pivotal to early recognition of patients more likely to have poor outcomes and high mortality.

Since its publication in 2016, Sepsis 3.0 criteria for septic shock have been validated in several studies, as a superior predictor for in-hospital mortality, with an association with greater than 40% hospital mortality rate[3-5]. A vasopressor requirement in the absence of hypovolemia and serum lactate level greater than 2 mmol/L (> 18 mg/dL) have been recommended to be used as a clinical marker combination for risk stratification in patients with infection[3-6].

Although patients with severe COVID-19 frequently meet the Sepsis 3.0 criteria for septic shock, it has been increasingly recognized that, in this population, hyperlactatemia is frequently absent, even in markedly hypotensive patients requiring high doses of vasopressors. This potentially underrecognized population might still conserve a high illness severity and mortality risk, indicating the need for a similar close

clinical surveillance and prompt organ support as COVID septic shock patients defined by Sepsis 3.0 criteria.

This study aimed to identify the proportion of patients with severe COVID-19 with hypotension despite adequate volume resuscitation, needing vasopressor support to have a MAP > 65 mmHg, with and without hyperlactatemia, in ICU, and describe its clinical outcomes and mortality rate.

MATERIALS AND METHODS

Study design and population

A single-center prospective observational cohort study was conducted over a 9-month consecutive period between March 2020 and January 2021. Data were collected from consecutive adult patients, admitted to ICU, using patient's electronic medical records, in Centro Hospitalar Lisboa Ocidental, in Lisbon, Portugal. The study was approved by the National Ethics Committee for Clinical Research (reference REC: 2020_EO_02).

Eligibility criteria included age equal to or above 18 years old and admission to an intensive care unit with multiorgan failure secondary to COVID-19 pneumonia, described as the development of potentially reversible physiological derangement involving two or more organ systems or change in baseline of SOFA score of 2 points or more. COVID-19 respiratory infection was diagnosed using clinical and radiological criteria of pulmonary involvement with a SARS-CoV-2 positive RT-PCR test. Subjective complaints of dyspnea, fatigue, loss of taste or smell, fever, chest pain, nausea and diarrhea were considered as clinical criteria and interstitial opacities, alveolar opacities, consolidations and/or pleural effusions were considered as radiological criteria of SARS-CoV-2 pneumonia.

Patients included in the analysis were further divided according to the presence of hyperlactatemia (lactate > 2 mmol/L) and persistent hypotension with vasopressor support, and 3 groups were identified: Sepsis group, without both criteria; Vasoplegic Shock group, with persistent hypotension with vasopressor support without hyperlactatemia; and Septic Shock 3.0 group, with both criteria.

Data Collection and End-points

Patient demographic characteristics were recorded at baseline for all patients including comorbidities, days of symptoms of SARS-CoV-2 infection and SOFA score at admission. Daily measurements of vital signs (including minimum mean arterial pressure and maximum respiratory rate), ventilation variables (including minimum ratio partial pressure arterial oxygen and the fraction of inspired oxygen, time of ventilation in prone position and duration of neuromuscular blockade), hemodynamic support (including the use of vasopressor therapy and maximum dosage of vasopressor support), renal function (including rate of replacement therapy and maximum creatinine level registered), laboratory variables (including hemoglobin, troponin I, lactate, C-reactive protein, and procalcitonin), prescribed therapies (remdesivir and dexamethasone) and outcomes (discharge alive or death in ICU) were also collected for every admitted patient to statistical analysis.

The number of secondary infections per patient was also collected in the three groups. The association of (1) clinical suspicion of new onset infection, (2) with persistent or increased inflammatory serum biomarkers, (3) requiring antibiotic therapy, (4) in a patient with a length of ICU stay of at least 48h were the criteria used for secondary infection definition. Positive microbiological cultures or microbial identification were not used as exclusion criteria for this definition.

Primary outcomes included 28-day mortality rate. As secondary outcomes, in-hospital mortality rate, ventilator-free days and vasopressor-free days at day 28 were determined.

Statistical analysis

All Gaussian distributed variables were expressed as mean SD), and nonnormally distributed variables as median [interquartile range (IQR)]. Categorical variables were expressed as numbers and percentages.

Chi-square test was used for categorical variables, and t-test and Kruskal-Wallis were used on continuous variables for statistical assessment of outcomes between groups. Kaplan-Meier survival curve and log-rank test were also obtained to ascertain and compare survival between groups.

Multiple logistic regression modeling for in-hospital mortality rate was made considering minimum blood pressure registered, maximum dose of vasopressor therapy, maximum serum lactate level, maximum troponin level, minimum hemoglobin level, and maximum C-reactive protein and procalcitonin levels as variables to fit the model. The model was further adjusted for patients' gender, age, and SOFA score at admission.

To assess the ability of the "serum lactate level" and "maximum vasopressor therapy used" variables in predicting the primary endpoints, diagnostic performances were calculated and receiver operating characteristic (ROC) curves were constructed in order to ascertain the corresponding area under the ROC curve (AUROC).

In all the hypothesis tests, a p-value of less than 0.05 was considered for statistical significance and usual confidence intervals of 95% were chosen.

RESULTS

In total, 118 patients were included during the study period, 51 (43,2%) in the Sepsis group, 26 (22%) in the Vasoplegic Shock group, and 41 (34,8%) in the Septic Shock 3.0 group. No patient with hyperlactatemia and normal arterial blood pressure was identified. Patients' baseline characteristics are summarized in Table 1.

The mean age was 63 (± 13,1) years with a statistical difference between the three groups and with an older subset of patients being found in the Septic Shock 3.0 group. There was no difference in gender or in the patient's body mass index distribution.

SOFA score at admission, respiratory support, hemodynamic support, maximum creatinine, C-reactive protein and maximum procalcitonin levels registered, showed in Table 1, were different between the 3 groups, but without statistical difference between Vasoplegic Shock and Septic Shock 3.0 groups. In addition, maximum serum lactate

level was not different between Sepsis and Vasoplegic Shock groups (1,64 ± 0,56 mg/dL *vs* 1,39 ± 0,35 mg/dL, respectively, *P* = 0,134). Similarly, secondary infection rates, per patient, were different between the three groups (*P* < 0.0001) without differences between Vasoplegic Shock and Septic Shock 3.0 groups (*P* = 0.041).

The analysis of the primary outcomes revealed overall in-hospital mortality of 23,7%. The mortality rate was significantly higher in Vasoplegic Shock (26,9%) and Septic Shock 3.0 groups (46%) when compared to the Sepsis group (3,9%) (*P* = 0,026 and *P* = 0,0003, respectively) without difference between the former two groups (*P* = 0.713). 28-day mortality rate was also not statistically different between Vasoplegic Shock and Sepsis 3.0 shock groups (*P* = 0,619) (see Figure 1).

Secondary outcomes are presented in Table 2. Ventilator free-days and vasopressor free-days at day 28 were statistically different between the Sepsis group and Vasoplegic Shock (*P* < 0.001, in both tests) and Septic Shock 3.0 groups (*P* < 0.001, in both tests), without statistical differences between the last two groups (*P* = 0,128 and *P* = 0,133, respectively).

Multivariable logistic regression adjusted to gender, age, and SOFA score at admission, identified the maximum dose of vasopressor therapy used (AOR 1.046; 95%CI: 1.012-1.082, *P* = 0.008) and serum lactate level (AOR 1.542; CI 95%: 1.055-2.255, *P* = 0.02) as the major explanatory variables of mortality rates (R^2 0.79).

The AUROC curves for prediction of 28-day mortality rate, by serum lactate level and maximum vasopressor therapy dosage used, were constructed and are present in Figure 2. The highest AUROC was for the maximum vasopressor therapy dosage used (0.81; 95%CI: 0.696-0.922) when compared to serum lactate level (0.645; 95%CI: 0.491-0.799).

DISCUSSION

Despite the general acceptance of the Sepsis-3 Task Force update of the defining criteria for septic shock, several lines of investigation have questioned its clinical sensitivity to reliably perform clinical decision-making and identification of patients with a high risk

of complications and mortality[7-12]. This was further questioned when its criteria were preferably indicated for a coding and epidemiological application, and not intended as a clinical screening tool.

Our study clearly shows that using the sepsis 3 criteria there is a proportion of hypotensive patients with vasopressor support without hyperlactatemia (n = 26; 22%), that, despite being classified as "Sepsis", present outcomes that are clearly different to those found on that group and superimposable to those of Septic shock 3.0 group. This potential discriminative inaccuracy favors patients to be diagnosed as Sepsis, despite an illness severity and mortality like Septic Shock 3.0 patients, and that should be equally treated.

Furthermore, COVID-19 patients' mortality rates have been strongly and positively associated with ventilation and hemodynamic support, especially when critically ill and in the need of ICU care[13,14], depending on reliable criteria to institute prompt and adequate organ support and improve outcomes.

Our data shows that the use of hyperlactatemia as criteria to clinically classify COVID-19 patients as having septic shock may undermine the sensitivity of our assessment of patients' severity and prognosis in this population. This evidence is in accordance with previously published studies describing the existence of different ICU patients' profiles, within the definition of Sepsis with concomitant different outcome and mortality rates[15,16].

The overlap in Ventilator and Vasopressor free-days values and In-hospital mortality rate and 28-day mortality rates (see Table 2), in Vasoplegic Shock and Septic Shock 3.0 groups, provides evidence that further supports the premise of a similar illness severity between those two groups. This data might indicate that occult hypoperfusion may still be present in COVID-19 patients[17], even with normal serum lactate levels, accounting for its systemic dysfunction and compromising patients' survivability. This is reinforced by the fact that the maximum dose of vasopressor therapy used was one of the major explanatory variables of mortality rates across the three groups when adjusted to lactate levels.

Moreover, COVID-19 patients belonging to Septic shock 3.0 group presented with higher values of SOFA at ICU admission, higher needs of mechanical ventilation, poorer respiratory severity indexes, and higher dosages of vasopressor support, when compared to patients in Vasoplegic shock group. However, no statistical differences were found between these two groups regarding the mentioned indexes. These results are similar to those previously ascertained by Verboom *et al*[18] 2019, which demonstrated a high percentage of agreement in mortality between patients with and without hyperlactatemia, under septic shock conditions.

Our study provides evidence that the use of Sepsis 3.0 criteria can undervalue severely ill COVID-19 patients. According to their clinical requirements and prognosis, a group of patients, equally severe to Septic Shock 3.0, are being classified as Sepsis. It is clear that it would be safer that these patients (those with persistent hypotension with vasopressor support without hyperlactatemia) should have a different classification, to account for their increased mortality risk and poor prognosis, and their subsequent need for close clinical monitoring, prompt diagnosis, and adequate resuscitation. This is in concordance with significantly better accuracy of hypotension with vasopressor support when compared to hyperlactatemia, to predict the mortality rate of COVID-19 patients.

This study strengthens its results with a robust structure and data prospectively collected. Furthermore, the homogeneity of supportive care across the compared groups limits some potential biases on the analyzed outcomes. However, it is not without some limitations. Although COVID-19 pneumonia was necessary for eligibility to statistical analysis, it lacks information about potential confounders of co-infections or other shock causes, before ICU admission. On the other hand, the potential complications during ICU stay that could justify hyperlactatemia, not directly related to COVID-19 infection, were also not registered.

CONCLUSION

In severe COVID19 patients, the Sepsis 3 criteria of septic shock may exclude around one-third of patients with a similarly high risk of poor outcomes and mortality rate, which should be equally approached. Considering the importance of early recognition of septic shock COVID-19 patients to improve their survival, the presence of hypotension with vasopressor support, even without hyperlactatemia, demonstrated a strong prognostic accuracy for mortality.

ARTICLE HIGHLIGHTS

Research background

The Sepsis 3.0 criteria of sepsis and septic shock have been extensively used in the definition of severe patients, admitted to hospital care and intensive care, in order to adequately define a subset of patients with poor prognosis and higher mortality rates.

Since its publication in 2016, its use has been presented as a good diagnostic tool to define these patients and to promptly initiate organic support.

COVID-19 patients present a strong association with life-threatening organ dysfunction due to septic shock and frequently requiring ICU admission and organ support

Research motivation

The population of COVID-19 patients frequently lacks hyperlactatemia, a necessary clinical criteria to define septic shock by the Septic shock 3.0 criteria. Therefore, this could potentially lead to an unrecognized subset of these patients that conserve a high illness severity and mortality risk, and that is being inaccurately misclassified as sepsis.

Research objectives

This study aimed to identify the proportion of patients with severe COVID-19 with vasopressor requirements without hyperlactatemia and describe its clinical outcomes and mortality rate.

Research methods

A single-center prospective observational cohort study was conducted in a tertiary hospital in Portugal, analyzing adult patients, admitted to ICU, with COVID-19 pneumonia.

The data collection was extensive, providing data about comorbidities, clinical status, severity indexes, respiratory, haemodynamic, and renal dysfunctions and outcomes of these COVID-19 patients.

Research results

A proportion of 22% of the analyzed COVID-19 patients was found to have persistent hypotension despite adequate volume resuscitation, needing vasopressor support, and without hyperlactatemia.

This "Vasoplegic Shock" group was found to retain a high 28-day and hospital mortality rates, and low vasopressor-free days and ventilator-free days, without differences to those presented in the "Septic shock 3.0" group, but statistically different to those in the Sepsis group.

Multivariable logistic regression identified the maximum dose of vasopressor therapy used and serum lactate level as the major explanatory variables of mortality rates. However, the highest AUROC was for the maximum vasopressor therapy dosage used when compared to serum lactate level.

Research conclusions

The Sepsis 3.0 criteria of septic shock may exclude around one-third of patients with similar clinical severity, poor outcomes, and mortality rate, which should be equally approached.

Research perspectives

Further studies are needed to identify a subset of these COVID-19 patients, who were not initially admitted to ICU care, despite persistent hypotension with vasopressor

requirements, and describe its clinical course and outcomes, further demonstrating a potential need to redefine our septic shock criteria in COVID-19 patients in order to maximize its early recognition and prompt adequate surveillance and support.

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