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Temporal progression of sepsis on critical care COVID-19 patients: a retrospective cohort study

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SUMMARY

OBJECTIVE: This study aimed to describe sepsis progression in critical COVID-19 patients using the SOFA score and investigate its relationship with mortality.

METHODS: Three researchers collected and analyzed retrospective clinical and laboratory data found in electronic health records from all patients admitted to a severe COVID-19 exclusive intensive care unit from March 2020 to October 2020. Mixed-effect logistic regression was used to evaluate SOFA (Sepsis-3) score variables as mortality prediction markers, while Kaplan-Meier survival curves were used to compare mortality between groups of patients. Cox proportional hazard models were used to further stratify mortality association between variants.

RESULTS: A total of 73 patients were included. Temporal COVID-19-related sepsis progression analysis indicates difference in degrees and timing between different organ dysfunction over time. Sepsis-3 Cardiovascular Dysfunction characterized by severe hypotension added to the use of any vasopressor drugs was the only parameter associated with in-hospital death during the first 5 days of hospital admission (OR 2.19; 95%CI 1.14-4.20; p=0.01).

CONCLUSION: Increased Sepsis-3 Cardiovascular Dysfunction score, characterized as hypotension associated with the use of vasopressor drugs in the first days of intensive care unit stay, is related to higher mortality in COVID-19 patients and may be a useful prognostic prediction tool.

KEYWORDS: Sepsis. COVID-19. SaRS-CoV-2. Critical care.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, which started in December 2019, has claimed over 6 million lives in more than 192 countries[1] and yet its physiopathology is poorly understood. Acute respiratory distress syndrome was described as a major complication[2], but symptoms may present as a spectrum ranging from asymptomatic to multisystemic, and some patients do not even develop respiratory distress – instead, they develop other symptoms unrelated to respiratory distress, which may be valuable prognostic markers[3].

In these critical patients, multiorgan damage, manifested as sepsis, has been described since early reports[4,5]. The most recent systematic review and meta-analysis about the prevalence of sepsis in COVID-19[6] have explored the hypothesis of COVID-19 as the direct cause of viral sepsis and described a prevalence as high as 77.9% in affected patients.

However, after more than 2 years of the beginning of the COVID-19 pandemic and a wide description of multiple variants, as of April 2022, as few as nine systematic reviews could be found on the PubMed indexing website referring to a search combining "sepsis" and "covid-19" as MeSH terms, which suggests that the correlation between sepsis and COVID-19 is yet underestimated.

Given the lack of studies focusing on the multi-organic aspect of COVID-19 critical care, the continuous spread of the pandemic, and overall sub-notification of sepsis cases, it is necessary to describe and analyze the temporal evolution of systemic organ failure in intensive care patients, in order to accurately identify risk factors, hallmarks, and evidence of prognosis that can help the development of better treatment and reduce morbimortality.

This study aimed to describe sepsis progression in critical COVID-19 patients using the SOFA score and investigate its relationship with mortality.

METHODS

This is a retrospective cohort study based on the analysis of a COVID-19-positive sample of patients from Santa Clara Hospital, Porto Alegre, Brazil, admitted between May 2020 and

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October 2020 with available data on the local electronic health records system. Ethical approval for this study was obtained from Irmandade da Santa Casa de Misericórdia de Porto Alegre Review Board (approval number 4.237.991).

Eligibility criteria for data inclusion were as follows:

1. having an RT-PCR method confirmed diagnostic of COVID-19;
2. having 2 and more days of intensive care unit (ICU) stay; and
3. availability of minimal data for patient identification, including age, sex, and comorbidities.

Sample size calculation using a 95% of confidence level with a margin of error of 5% and considering a 3% mortality rate for COVID-19 cases yielded a minimum necessary of 45 measurements to meet statistical constraints. This was exceeded using a convenience sampling drawn from the hospital setting chosen.

Our choice comprises the total number of patients in a COVID-19 exclusive ICU from the beginning to the end of the so-called the first wave of the pandemic in Brazil. After that, as disease treatment progressed and mortality was reduced as a result of vaccination and public health efforts, fewer examinations became available. Therefore, our sample displays abundant data for qualitative analysis and stratification while also readily representing disease progression with minimal confounding factors.

Data were collected by an independent researcher and checked by two researchers, while a fourth settled on differences in interpretations. Right censored data included patients who were

1. lost to follow-up;
2. lost due to evasion from healthcare complex facilities, and
3. transferred to another healthcare complex.

The sample was divided and compared between groups of deceased versus recovered patients. The primary outcome under analysis was death. The predictors of mortality were SOFA (Sepsis-3) score[7] values, which progressively rate organ dysfunction from 1 to 4, with 4 being the most severe, as follows:

- Respiratory system (PaO_2/FiO_2 ratio) from <400 (1) to <100 (4)
- Coagulation system (serum platelets in cell/mm^3) from <150,000 (1) to <20,000 (4)
- Liver function (serum bilirubin in mg/dL) from 1.2–1.9 (1) to >12.0 (4)
- Cardiovascular system (mean arterial pressure in mmHg) <70 (1) or use of vasopressor drug >15 mcg/kg/min (4)
- Renal system (serum creatinine in mg/dL) from 1.2–1.9 (1) to >5.0 (4)

Exposure was considered as RT-PCR confirmed SARS-CoV-2 infection. Tertiary medical care by ICU staff was considered a major potential confounder and modifier. Since it is impossible to distinguish its effects from those of usual COVID-19 progression, our time frame was defined as a 10-day analysis after ICU admission and then subdivided into two 5-day analyses, to reduce confounding effects.

Statistical analysis

We verified normality in data distribution using Shapiro-Wilk test. Our plot (Figure 1) was generated by using LOWESS (Locally Weighted Scatterplot Smoothing) to fit a smooth curve to nonparametric data points. LOWESS weight function gives the most weight to the data points nearest the point of estimation and the least weight to the data points that are furthest away.

To analyze the association between increasing sepsis score and mortality, a mixed-effect logistic regression model was applied by using the lme4 package, available for R Studio software. The odds ratio was calculated by taking the exponential coefficient output. Our model aimed to estimate binary outcome variables (death vs. survival) ratios, with SOFA score variables as patient-level continuous predictors, days since admission as a patient-level categorical predictor (0–10), and a random intercept by patient ID. Cox proportional hazard models were used to further stratify mortality association between variants.

A p-value <0.05 was adopted as a cutoff value for statistical significance. All data were extracted and cleaned using R Studio version 4.1.2 for macOS.

RESULTS

Our sample yielded a total of 73 patients, of which 37 (50.3%) were deceased. The majority were 60 years or older (53%), and 38 (52%) were females. Hypertension was the most common comorbidity (58%), while kidney disease was the least common (4%). On admission, dyspnea was the most common symptom (67.5%), while tachycardia was present in only 1 patient. Median time from symptom onset until ICU admission was 10.17 days. Detailed clinical characteristics during admission can be observed in Table 1.

Figure 1 shows the LOWESS plot for our data. Detailed results for mixed-effect logistic models and hazard models can be observed in Table 2. Complete data have been submitted as Supplementary file. On the first 4 days of ICU admission, the

Table 1. Patient characteristics on admission.

	Total (n=73)	Survivors (n=36)	Fatal (n=37)
Median age in years (IQR)	61.5 (47.25–73.0)	52.0 (43.0–66.0)	66.0 (56.0–79.0)
<40	7	6	1
40–60	28	17	11
≥60	38	13	25
Sex			
Female	38	17	21
Male	35	19	16
Weight in kg (IQR)	80.0 (70.0–95.0)	83.5 (70.0–100)	74.50 (66.75–90.5)
Previous hospitalization	40	21	19
Comorbidities			
Hypertension	41	17	24
Diabetes	29	12	17
Obesity	19	10	9
Smoking history	9	3	6
Respiratory diseases	9	4	5
Cardiovascular disease	5	2	3
Gastrointestinal diseases	5	2	3
Central nervous system diseases	11	4	7
Liver diseases	7	2	5
Chronic kidney diseases	3	0	3
Surgery history	10	4	6
Chronic heart disease	14	6	8
Cancer	9	5	4
Signs and symptoms on ICU admission			
Fatigue	10	4	6
Fever	29	15	14
Dyspnea	50	23	27
Tachycardia	1	0	1
Cough	32	18	14
Coryza	7	2	5
Myalgia	11	7	4
Chest pain	6	3	3
Pharyngalgia	5	2	3
Diarrhea	9	2	7
Nausea and vomiting	6	2	4
Median (IQR) time from onset of symptom to hospital admission, days	10 (2–16)	12 (6–15)	8 (2–16)
Median (IQR) time from hospital admission to outcome, days	9 (2–16)	8 (2–15)	10 (3.0–16.5)
Mean SOFA scores			
Respiratory System Score	1.48	1.53	1.42
Coagulatory System Score	0.25	0.1	0.42
Liver Function Score	0.02	0.4	0
Cardiovascular System Score	0.89	0.21	1.54
Renal Function Score	0.53	0.26	0.78
Total SOFA score	2.71	1.94	3.45
Other			
Days from symptom onset until ICU admission (mean)	9.0	10.0	5
Days hospitalized (IQR)	12	8.5	10.0
Sepsis diagnostic by ICU team (total)	14	4	10

IQR: interquartile range; ICU: intensive care unit; SOFA: systemic organ failure.

odds of in-hospital death was associated with increased cardiovascular dysfunction (OR 2.19; 95%CI 1.14-4.20; p=0.01). On days 5–10, no statistically significant relationship was detected. Cox proportional hazard model adjusted for multivariate analysis demonstrated increased risk for Cardiovascular Dysfunction score = 3 (OR 2.87; 95%CI 1.05–7.8; p=0.04), but reduced risk for Respiratory Dysfunction score = 1 (OR 0.3; 95%CI 0.092–1.0; p=0.04) when compared to score = 0 (no organ dysfunction).

DISCUSSION

Our study demonstrates that the progression of dysfunction has a different timing of worsening for each system evaluated. Regarding risk factors, cardiovascular dysfunction, characterized by Sepsis-3 as hypotension added to the use of vasopressor drugs[7], is the only factor evaluated with a positive correlation for mortality in the first 5 days of hospitalization. Respiratory dysfunction, characterized by a low PaO_2/FiO_2 ratio ranging from <400 – <100, showed no positive association.

There are three reasons for our choice of a time frame of 10 days of analysis. First, we considered that after 5 days, too many confounding factors could be included in the patient's profile after intensive care symptomatic management. Second, we found no previous studies in which a time series analysis had been done in ICU patients for sepsis progression. One of the first reports pointed to a median time from disease onset to death of 16 days but did not stratify this number as a subset of ICU admission time[8]. Third, our data displayed evident inflection points in which the parameter would behave differently, i.e., organ dysfunction would decrease.

The difference in observable trends implies that the primary mechanism behind clinical symptoms in critical patients does not involve only the lung, although it does not explain when the adjacent organ damage initially happens. Current evidence[9] implies that the exudative and proliferative phases of alveolar

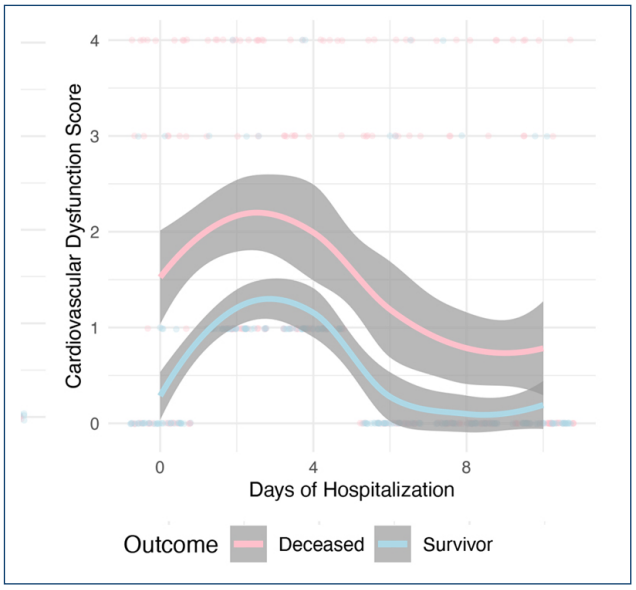

Figure 1. SOFA Cardiovascular Dysfunction Score progression over time comparing deceased and recovered patients in a COVID-19 exclusive intensive care unit.

Table 2. Sepsis-3 score hazard models and mixed-effect logistic regression.

Cox proportional hazard models		
Cardiovascular Dysfunction score	**Odds ratio (95%CI)**	**p-value**
3	2.87 (1.05–7.8)	0.04*
4	1.69 (0.65–4.4)	0.283
Coagulation Dysfunction score		
1	2.34 (0.48–11.5)	0.295
2	2.42 (0.67–8.8)	0.178
3	1.18 (0.15–9.6)	0.875
Respiratory Dysfunction score		
1	0.30 (0.092–1.0)	0.049*
2	0.92 (0.332–2.5)	0.867
3	0.81 (0.217–3.0)	0.751
4	0.30 (0.062–1.5)	0.135
Mixed-effect logistic regression		
Days 0–4		
Respiratory	1.08 (0.37–3.34)	0.83
Coagulation	3.62 (0.08–152.55)	0.5
Cardiovascular	2.19 (1.14–4.20)	0.01*
Liver	2.31 (0.27–19.44)	0.44
Renal	1.20 (0.44–3.29)	0.71
Days 5–10		
Respiratory	1.28 (0.3–5.3)	0.73
Coagulation	0.21 (0.01–3.65)	0.63
Cardiovascular	1.73 (0.31–9.48)	0.52
Liver	NA	NA
Renal	1.12 (0.45–2.74)	0.8

Cox proportional hazard model adjusted for multivariate analysis for each category of systemic organ failure score and odds for in-hospital death associated with an increase of 1 point in systemic organ dysfunction score (systemic organ failure-3) using mixed-effect logistic regression using a generalized linear mixed model fit by maximum likelihood (Adaptive Gauss-Hermite Quadrature) and Sepsis-3 reference values. The data show that a greater Cardiovascular Dysfunction score, which is characterized by the use of any vasopressor drug added to increased hypotension, is related to overall increased mortality. The odds ratio for liver dysfunction is nonavailable (NA) due to insufficient data from patients in a 10-day time frame.

damage should happen within the first 10 days. However, respiratory dysfunction peaks around day 6 in our data, and platelets still seem to be within normal levels in our sample (although COVID-19 has been described as a coagulopathy[10,11].

A negative correlation of respiratory system distress also corresponds to that reported for the first wave in China, where the use of invasive mechanical ventilation ranged could go as low as 13.46%[12], strengthening the hypothesis that multiple organ damage, which in turn may evolve into sepsis, does not derives uniquely from lung damage.

These data also confirm considerably reliable evidence, suggesting that patients with higher risk can be identified early in the hospitalization process. Cardiovascular disease and hypertension were already described as strong predictors[13] since cardiac involvement is 13 times higher in critical patients[14]. The same dynamic applies to kidney injury[15], a major correlate with ICU mortality[16]. Many biomarkers have been pointed out as predictors in previous systematic reviews[17], as well as genetic factors, such as overexpression of ADAM9 metalloprotease, which have also been suggested as a "signature" of critically ill patients[18], since it directly influences the uptake and replication of SARS-CoV-2 in lung intraepithelial cells.

In terms of novelty and study similarity, to the best of our knowledge, our study is the first to analyze sepsis progression over a defined time frame by using the SOFA (Sepsis-3) score as a prognostic prediction tool for sepsis in intensive care COVID-19 patients. Our study adds further knowledge to the field of critical care by pointing out which parameters should be observed with additional attention on COVID-19 patients during intensive care admission to precociously differentiate which patients have a higher chance of worsening. Such knowledge is crucial considering each day in ICU may decrease mean survival probability by 3.27% per day[19].

Sepsis is still a major mortality cause in a hospital setting and further studies are necessary to increase survival rates through early detection and treatment. Nonetheless, our data provide evidence that supports the idea that cardiovascular system dysfunction might be an important parameter to be observed during the hospital admission process to distinguish between patients with good or bad chances of recovery before a major adverse event occurs.

Limitations

This study has some limitations. A larger sample could be used in the same study design to yield undetectable results. Also, the use of retrospective data from electronic health records in a hospital setting may result in a lack of uniformity of clinical data availability subjected to each patient's profile. This may have impaired further clinical analysis by underestimating SOFA score results or impairing data analysis, such as in the case of renal system function, which had scarce data.

Finally, this is a study with data from patients of an exclusive ICU during the second half of the year 2020, and since then, multiple variants have been described and may display slightly different disease severity onset.

CONCLUSIONS

Increased Sepsis-3 Cardiovascular Dysfunction score, characterized as hypotension associated with the use of vasopressor drugs in the first days of ICU stay, is related to higher mortality in COVID-19 patients and may be a useful prognostic prediction tool.

AUTHORS' CONTRIBUTIONS

PL: Conceptualization, Data curation, Writing – original draft. **FBN:** Supervision, Writing – review & editing. **GB:** Supervision, Writing – review & editing. **JAH:** Data curation, Writing – review & editing.

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