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Is the behavior of vital signs in the first days of hospitalization associated with clinical outcomes in patients with COVID-19? A retrospective study

O comportamento dos sinais vitais nos primeiros dias da hospitalização está associado aos desfechos clínicos em pacientes com COVID-19? Um estudo retrospectivo

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Abstract

Background: The trajectory of vital signs, especially at the beginning of hospitalization, can result in answers about clinical outcomes. **Aim:** To evaluate the behavior of vital signs/derived variables and blood pressure variability (BPV) during the early phase of hospitalization for COVID-19 and its association with clinical outcomes, in addition to identify the cut-off point for these vital signs/derived variables to predict clinical outcomes. **Methods:** Retrospective analysis of 100 patients hospitalized for COVID-19, allocated into: negative outcome group (NOG; n=56) and positive outcome group (POG; n=44). Vital signs [heart rate, systolic (SBP), diastolic and mean blood pressure (MAP), temperature, respiratory rate (RR) and peripheral oxygen saturation]/derived variables [pulse pressure (PP) and double product (DP)] and VPA were assessed in the first five days of hospitalization. ROC curves were used to identify cut-off points for predicting clinical outcomes. **Results:** Compared to the 1st day of hospitalization, POG showed a reduction in PP on the 3rd and 5th days, RR from the 3rd day, DP from the 4th day and SBP on the 5th day ($p<0.05$). Additionally, POG presented lower PP on the 2nd and 4th days ($p<0.05$), lower RR on the 4th day and lower variability of SBP and MAP ($p<0.05$) in relation to NOP. The ROC curve was able to predict negative outcomes when PP ≥ 40 mmHg on the 5th day of hospitalization (AUC: 0.63; p=0.02). **Conclusion:** Patients with a positive clinical evolution showed better behavior of signs/derived variables and BPV in the early phase of hospitalization. Furthermore, PP ≥ 40 mmHg on the 5th day of hospitalization was considered as a cut-off point to predict negative results.

Keywords: SARS-CoV-2; Vital Signs; Blood Pressure; Inpatients.

Resumo

Introdução: A trajetória dos sinais vitais, principalmente no início da hospitalização, pode resultar em respostas sobre desfechos clínicos. **Objetivo:** Avaliar o comportamento dos sinais vitais/variáveis derivadas e da variabilidade da pressão arterial (VPA) durante a fase precoce de hospitalização por COVID-19 e sua associação com desfechos clínicos, além de identificar o ponto de corte dos sinais vitais/variáveis derivadas para prever desfechos clínicos. **Métodos:** Análise retrospectiva de 100 pacientes hospitalizados por COVID-19, alocados em: grupo desfechos negativos (GD-; n=56) e grupo desfecho positivo (GD+; n=44). Sinais vitais [frequência cardíaca (FC), pressão arterial sistólica (PAS), diastólica e média (PAM), temperatura, frequência respiratória (FR) e saturação periférica de oxigênio]/variáveis derivadas [pressão de pulso (PP) e duplo produto (DP)] e VPA foram avaliadas nos primeiros cinco dias de hospitalização. Curvas ROC foram utilizadas para identificar pontos de corte na predição dos desfechos clínicos. **Resultados:** Comparado ao 1.º dia de internação, o GD+ apresentou redução na PP no 3.º e 5.º dias, FR a partir do 3.º dia, DP a partir do 4.º dia e PAS no 5.º dia ($p<0,05$). Adicionalmente, o GD+ apresentou menor PP no 2.º e 4.º dias, menor FR no 4.º dia e menor VPA (PAS e PAM) em relação ao GD- ($p<0,05$). A curva ROC foi capaz de predizer desfechos negativos quando PP ≥ 40 mmHg no 5.º dia de internação (AUC: 0,63; p=0,02). **Conclusão:** Pacientes com desfecho clínico positivo apresentaram melhor comportamento dos sinais vitais/variáveis derivadas e da VPA na fase precoce de

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hospitalização. Adicionalmente, PP ≥ 40 mmHg no 5º dia de hospitalização foi considerada como ponto de corte para prever desfechos negativos.

Palavras-chave: SARS-CoV-2; Sinais Vitais; Pressão Arterial; Pacientes Internados.

INTRODUCTION

In addition to the typical respiratory manifestations of COVID-19, the multisystemic impact caused by the disease is evident, including the cardiovascular system[1]. Although most patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present mild to moderate symptoms[2], some underlying conditions such as the presence of chronic diseases, obesity, and others may require hospitalization due to the greater risk of progression to severe forms of COVID-19[3].

Thus, to better understand the disease and obtain more assertive care strategies, using simple clinical parameters, such as vital signs and their changes at the bedside before clinical deterioration, can be valuable with the potential to anticipate health outcomes[4]. Commonly, heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), temperature (T), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) are considered essential signs in the monitoring of patients hospitalized for acute illness[4].

A retrospective study of 8,770 confirmed cases of COVID-19 showed that high HR and RR, as well as low SpO_2, were identified as risk factors for mortality from COVID-19[5]. Furthermore, the trajectory of individual vital signs during the seven days preceding the negative/positive outcome of patients hospitalized for COVID-19 was able to differentiate their worsening more quickly than in patients with viral pneumonia[6].

In addition to vital signs, BP variability (BPV) is another method of clinical relevance and applicability that characterizes the continuous and dynamic fluctuations that occur in BP levels over some time [7] and can stratify cardiovascular risk[8]. Methods for assessing BPV include standard deviation, coefficient of variation (CV), and average real variability (ARV)[9]. A retrospective study showed that greater daily variability of in-hospital SBP can independently predict acute respiratory distress syndrome in COVID-19 patients with hypertension[10].

From a prognostic point of view, a systematic review gathered studies that showed that a daily increase in 24-hour BP, regardless of the average BP level, is a predictor of the development, formation, and evolution of damage to the heart, blood vessels and kidneys that promote an increased risk of fatal and non-fatal cardiovascular events in the adult population[11].

Although vital signs in patients hospitalized for COVID-19 have gained attention as a potential early marker of outcome, surprisingly few attempts have been made to understand their association with clinical outcomes early in hospitalization, especially in daily variables. Furthermore, we are not aware of any study that has defined a cutoff point for vital signs to predict easily identifiable clinical outcomes.

Thus, this study aimed to evaluate vital signs, variables derived from vital signs, and BPV during the early phase of hospitalization for COVID-19 and verify their association with different clinical outcomes, in addition to identifying whether there is a cutoff point for each vital sign/derived variable to predict clinical outcomes for this population. Our hypothesis is that patients with negative clinical outcomes will be associated with worse behaviors of vital signs/derived variables and BPV in the first days of hospitalization for COVID-19. Furthermore, vital signs/derived variables will have good discrimination, through cutoff points, in the risk stratification for negative and positive outcomes.

METHODS

Study design and population

This was a retrospective study that followed the STROBE recommendations and was approved by the Research Ethics Committee of the Federal University of São Carlos (number 4,601,278; CAAE: 42877521.8.3001.8148) with the consent of the *Irmandade Santa Casa de Misericórdia de São Carlos*. Medical records were screened and data were extracted from March 2020 to October 2021. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study.

The inclusion criteria were: adult patients (≥ 18 years old), of both genders, diagnosed with COVID-19 and hospitalized in a ward or Intense Care Unit (ICU). The exclusion criteria were: patients transferred from an external unit to the aforementioned hospital or vice versa, hospital discharge on request or by evasion, hospitalization period < five days, patients whose medical records did not present the necessary information, patients in orotracheal intubation (OTI) from the days analyzed (1st to 5th day of hospitalization) and those in palliative care.

Data collection

Demographic and anthropometric data, smoking history and self-reported diseases, antihypertensive medications in use, clinical data at admission, such as main symptoms, vital signs, laboratory test values, pharmacological and non-pharmacological treatments for COVID-19, and data related to the period of hospitalization of each patient (including clinical outcomes) were collected from each patient's electronic medical record. The severity

of COVID-19 was based on clinical symptoms, following previous recommendations[12]. Two previously trained individuals performed data extraction from the medical record to perform a standardized and careful extraction concerning the details of the medical record.

To characterize negative and positive clinical outcomes, information such as date of hospital discharge, length of hospital stays, need for OTI during hospitalization, and/or date of hospital death were obtained. Negative outcomes were defined according to the following sequence of occurrence: 1) hospital death; 2) OTI after the 5th day of hospitalization; and 3) prolonged hospitalization, defined as a length of hospitalization ≥ the mean length of hospitalization of the total sample[13], which was 7.5 ± 2.3 days for our total sample (n=100), and therefore, we adopted the value of ≥ 7 days as the cutoff point. Each patient was classified into a single negative outcome. The positive outcome was defined as: 1) hospital discharge < the mean length of hospitalization of the total sample[13], that is, < 7 days.

According to clinical outcomes during hospitalization, patients were allocated into: 1) a negative outcome group (OG-); and 2) a positive outcome group (OG+).

Vital signs, derived variables and BPV

The following vital signs were obtained from the patient's medical records: 1) HR in bpm; 2) SBP in mmHg; 3) DBP in mmHg; 4) mean arterial pressure (MAP) in mmHg, calculated using the formula MAP = SBP + 2x DBP)/3; 5) T in ºC; 6) RR in rpm; and 7) SpO_2 in %. Three daily measurements were recorded (morning, afternoon, and evening) considering the 1st to 5th day of hospitalization. Then, the mean value of the three periods was considered for all variables. Additionally, the following derived variables were calculated: 1) pulse pressure (PP) in mmHg, given by the difference between SBP and DBP[14]; and 2) double product (DP) in mmHg.bpm, obtained by multiplying SBP by HR[15].

Finally, the BPV (SBP, DBP and MAP) was calculated from the 1st to the 5th day of hospitalization using the following methods: 1) Standard deviation in mmHg, with distribution of values around the mean of the days; 2) CV in %, which is the standard deviation divided by the corresponding mean multiplied by 100[15]; and 3) ARV in mmHg, with the mean of the absolute differences between consecutive BP readings[11,15] (Figure 1).

Statistical analysis

The study sample was a convenience sample, and all medical records of patients hospitalized in the ward or ICU due to COVID-19 (n=482) were evaluated during the period. However, data from n=100 patients were included due to the exclusion criteria. All analyses were performed using SigmaPlot® software, version 14.5 (Systat Software Inc., San Jose, CA, United States). The Kolmogorov-Smirnov test assessed the normality of continuous variables. Quantitative data are presented as mean ± standard deviation/standard error, while categorical variables are presented as absolute frequency (%). Comparison of quantitative variables between groups was performed using the unpaired Student's t-test or Mann-Whitney U test, as appropriate. A comparison of categorical variables between groups was performed using Fisher's exact test. Two-way ANOVA (Tukey's post-hoc) was applied to compare vital signs/derived variables between and within groups. For all comparisons, the probability of type I error occurrence was set at 5%. ROC curves were used to identify possible cutoff values for vital signs/derived variables (HR, SBP, DBP, MAP, T, RR, PP and DP) in predicting clinical outcomes, and the area under the curve (AUC) was identified, with the respective sensitivity and specificity values.

RESULTS

A total of 482 medical records were assessed for eligibility. Of these, 382 were excluded as they did not meet the inclusion criteria. Finally, the sample consisted of n=100 patients, with n=56 patients allocated to OG- and n=44 patients to OG+ (Figure 2).

Table 1 shows patient characteristics, COVID-19 severity, self-reported medical history, main symptoms, vital signs/derived variables, and laboratory tests at admission for all patients and by clinical outcome. The groups were similar except for age, with OG- being older than OG+ (58 ± 15 vs. 49 ± 15 years old; p<0.01).

Days	Collection period	Value considered	Vital signs obtained	Derived variables	BPV
1st, 2nd, 3rd 4th, 5th	Morning Afternoon Evening	Mean	HR, SBP, DBP, MAP, T, RR and SpO_2	PP and DP	Standard deviation, CV and ARV

Figure 1. Summary of assessment of vital signs, derived variables, and blood pressure variability (BPV). HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; T: temperature; RR: respiratory rate; SpO_2: peripheral oxygen saturation; PP: pulse pressure; DP: double product; CV: coefficient of variation; ARV: average real variability.

Table 1. Patient characteristics, COVID-19 severity, self-reported illness history, main symptoms, vital signs/derived variables, and laboratory tests at hospital admission for all patients and by clinical outcome.

	Total (n=100)	OG- (n=56)	OG+ (n=44)	p=value
Age, years old	54 ± 15	58 ± 15	49 ± 15	<0.01*
Male, n (%)	50 (50)	31 (55)	19 (43)	0.31
Smoking status (former/current), n (%)	16 (16)/ 3 (3)	11 (20)/3 (5)	5 (11)/ 0	0.28/0.25
Body mass index, kg/m^2	29,6 ± 5,7	29,9 ± 5,7	29,2 ± 6,0	0.68
COVID-19 severity				
Moderate/Severe	28 (28)/ 72 (72)	17 (30)/ 39 (70)	11 (25)/ 33 (75)	0.65
Self-reported diseases, n (%)				
Hypertension	40 (40)	27 (48)	13 (29)	0.06
Diabetes mellitus	29 (29)	20 (36)	9 (20)	0.12
Coronary artery disease	8 (8)	5 (9)	3 (7)	1.00
COPD	5 (5)	3 (5)	2 (4,5)	1.00
Chronic kidney disease	5 (5)	4 (7)	1 (2)	0.38
Main symptoms, n (%)				
Dyspnea	72 (72)	39 (70)	33 (75)	0.65
Cough	53 (53)	31 (55)	22 (50)	0.68
Fever	38 (38)	18 (32)	20 (45)	0.21
Myalgia	17 (17)	8 (14)	9 (20)	0.43
Headache	14 (14)	7 (12,5)	7 (16)	0.77
Diarrhea	12 (12)	8 (14)	4 (9)	0.54
Nausea or vomiting	8 (8)	6 (11)	2 (4,5)	0.46
Odynophagia	7 (7)	5 (9)	2 (4,5)	0.46
Vital signs/derived variables				
HR, bpm	86.3 ± 14.7	85.2 ± 15.0	87.7 ± 14.5	0.42
SBP, mmHg	128.1 ± 16.3	128.0 ± 17.5	128.6 ± 14.6	0.77
DBP, mmHg	78.6 ± 12.1	76.0 ± 11.2	80.5 ± 13.1	0.17
PAM, mmHg	90.8 ± 17.2	88.2 ± 17.9	94.1 ± 2.5	0.10
T, ºC	36.5 ± 0.7	36.6 ± 0.7	36.5 ± 0.7	0.60
FR, rpm	20.8 ± 4.7	20.3 ± 3.9	21.4 ± 5.5	0.24
SpO_2, %	93.9 ± 2.4	93.9 ± 2.5	93.9 ± 2.2	0.90
PP, mmHg	55.7 ±18.6	57.8 ± 20.3	52.8 ± 15.8	0.19
DP, mmHg.bpm	11064 ± 2275	10874 ± 2348	11304 ± 2183	0.36
Exames laboratoriais				
Glóbulos vermelhos, milhões/mm^3	4.6 ± 0.7	4.6 ± 0.7	4.6 ± 0.8	0.91
Hemoglobina, g/dL	13.6 ± 2.2	13.6 ± 2.2	13.5 ± 2.3	0.91
Hematócrito, %	40.8 ± 6.6	40.9 ± 6.6	40.7 ± 6.8	0.90
Leucócitos, cells/mm^3	10260 ± 8386	9993 ± 4773	10600 ± 11542	0.75
Linfócitos, cells/mm^3	1,192 ± 1167	1385 ± 1440	925 ± 540	0.10
Neutrófilos, cells/mm^3	4574 ± 2129	4983 ± 2055	4053 ± 2204	0.28
Plaquetas, k/µl	212 ± 80	214 ± 89	208 ± 68	0.77
CRP, mg/dL	1.4 ± 1.2	1.4 ± 1.3	1.4 ± 1.1	0.96
D-dimero, ng/mL	2600 ± 4500	2200 ± 3800	3500 ± 5700	0.43
Creatinina, mg/dL	0.9 ± 0.8	0.9 ± 0.9	0.8 ± 0.4	0.35
Uréia, mg/dL	39.2 ± 21.9	42.8 ± 24.8	34.5 ± 16.8	0.10
Sódio, mEq/L	133.9 ± 13.4	134.8 ± 3.8	132.8 ± 19.8	0.52
Potássio, mEq/L	3.9 ± 0.6	3.9 ± 0.6	3.8 ± 0.5	0.36
pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	0.92
PaO_2, mmHg	71.0 ± 26.6	70.8 ± 26.6	71.3 ± 27.0	0.93
PCO_2, mmHg	38.5 ± 7.3	38.7 ± 8.4	38.3 ± 5.5	0.82
HCO_3, mEq/L	26.4 ± 3.8	26.4 ± 3.9	26.4 ± 3.6	0.98
BE, mEq/L	2.3 ± 3.5	2.3 ± 3.6	2.3 ± 3.6	0.94
SaO_2, %	89.2 ± 13.7	88.2 ± 15.1	90.5 ± 11.9	0.49
Lactato, mmol/L	2.2 ± 2.1	1.9 ± 2.3	2.5 ± 2.7	0.41

Data expressed as mean ± SD or absolute values (percentage). OG-: negative outcome group; OG+: positive outcome group; n: number of patients. HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; T: temperature; RR: respiratory rate; SpO2: peripheral oxygen saturation; PP: pulse pressure; DP: double product; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; pH: potential of hydrogen; PaO_2: partial pressure of oxygen; PCO_2: partial pressure of carbon dioxide; HCO_3: sodium bicarbonate; BE: base excess; SaO_2: arterial oxygen saturation. *Significant difference between OG+ and OG- (p<0.05). Unpaired Student's t-test or Fisher's exact test were applied.

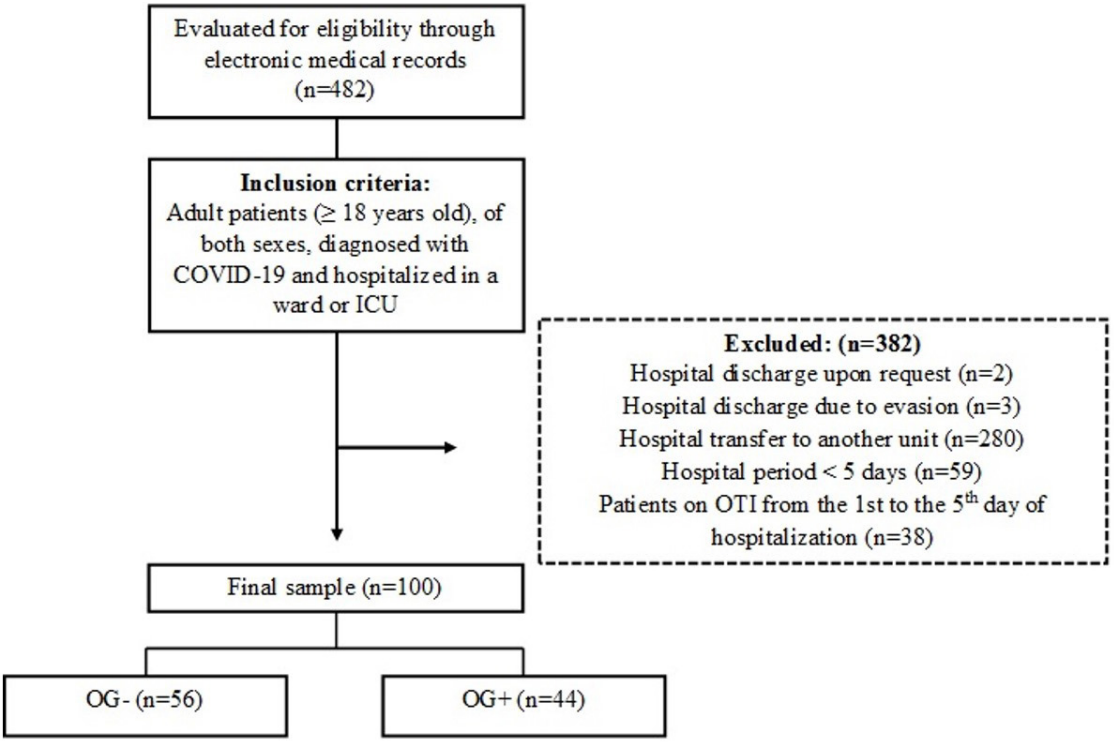

Figure 2. Flowchart of patient inclusion in the study. ICU: Intensive Care Unit; OTI: orotracheal intubation; OG-: negative outcome group; OG+: positive outcome group.

The groups were similar regarding the use of antihypertensives and pharmacological and non-pharmacological treatments for COVID-19 (p>0.05). On the other hand, OG- had a longer hospital stay compared to OG+, which was expected (8.9 ± 2.1 vs. 5.6 ± 0.5; p<0.01), with this being the most common negative outcome (50%) (Table 2).

Only OG+ showed a significant reduction in the 1st day of hospitalization in the following variables: PP on the 3rd and 5th days, RR from the 3rd day, DP from the 4th day, and SBP on the 5th day (p<0.05). In addition, OG+ showed a lower PP value on the 2nd and 4th days of hospitalization and a lower RR on the 4th day compared to OG- (p<0.05) (Figure 3).

Regarding BPV, OG- presented a greater standard deviation of SBP and MAP variability about OG+ (10.0 ± 5.1 vs. 7.7 ± 3.6; p=0.03 and 8.1 ± 4.8 vs. 7.0 ± 6.1; p=0.04, respectively) (Table 3).

ROC curve analyses revealed a cut-off value for PP on the 5th day of hospitalization, being ≥ 40 mmHg to predict negative outcomes, with a sensitivity of 83% and specificity of 69% [AUC: 0.63 (0.52-0.74); p=0.02] (Figure 4).

DISCUSSION

This study retrospectively investigated the behavior of vital signs/derived variables and BPV of patients with COVID-19 in the early phase of hospitalization and their association with different clinical outcomes; in addition, it sought to identify a cutoff value for vital signs/derived variables to differentiate clinical outcomes for this population. The main findings of the study were: 1) Significant reduction in PP, RR, DP and SBP considering the 1st day of hospitalization as described: PP on the 3rd and 5th days, RR from the 3rd day, DP from the 4th day and SBP on the 5th day only for OG+. In addition, this group presented lower PP on the 2nd and 4th day of hospitalization and lower RR on the 4th day compared to OG-; 2) OG- presented a greater standard deviation of SBP and MAP variability with the evolution of the days; and 3) a cutoff point for PP ≥ 40 mmHg was identified, capable of discriminating patients with negative outcomes on the 5th day of hospitalization.

When observing the vital signs/derived variables at hospital admission, we found that our sample presented elevated values of RR, PP, and DP[14,16,17] (20.8 ± 4.7, 55.7 ± 18.6, and 11,064 ± 2,275, respectively), regardless of the clinical outcome. The elevated RR present in our sample may be a condition consistent with impairment and damage to the respiratory system in the early days of COVID-19[18]. Increased values of PP (greater than 40 mmHg)[19] and DP (> 6000 mmHg.bpm)[17] suggest impairment of the elastic properties of the arterial wall and cardiac volume[20] and increased cardiac workload[17], respectively, as a consequence of the disease.

Regarding the hospital admission data, the results of laboratory tests showed that the total sample presented high values of C-reactive protein (CRP) and D-dimer

Table 2. Use of antihypertensive medications, pharmacological and non-pharmacological treatment for COVID-19 and clinical outcomes during hospitalization for all patients and by clinical outcome.

	Total (n=100)	OG- (n=56)	OG+ (n=44)	p-value
Use of hypertensive drugs, n (%)				
Beta blockers	8 (8)	6 (11)	2 (4,5)	0.46
ACE inhibitors	11 (11)	7 (12,5)	4 (9)	0.75
Calcium channel blockers	9 (9)	6 (11)	3 (7)	0.72
ARA II	12 (12)	8 (14)	4 (9)	0.54
Diuretics	5 (5)	2 (4)	3 (7)	0.65
Treatment for COVID-19, n (%)				
Antivirals	7 (7)	5 (9)	2 (4,5)	0.46
Antibiotics	28 (28)	18 (32)	10 (23)	0.37
Antithrombotics	81 (81)	45 (80)	36 (82)	1.00
Glucocorticoids	66 (66)	36 (64)	30 (68)	0.83
Benzamides	69 (69)	38 (68)	31 (70)	0.83
NSAIDs	85 (85)	45 (80)	40 (91)	0.16
Oxygen supplementation	76 (76)	43 (77)	33 (75)	1.00
Noninvasive ventilation	3 (3)	2 (4)	1 (2)	1.00
Clinical outcomes, n (%)				
Hospital deaths	5 (5)	5 (9)	-	-
OTI after 5th day of hospitalization	1 (1)	1 (2)	-	-
Prolonged hospital stay (≥ 7 days)	50 (50)	50 (89)	-	-
Hospital discharge < 7 days	44 (44)	-	44 (100)	-

Data expressed in absolute values (percentage). OG-: negative outcome group; OG+: positive outcome group; n: number of patients; ACE: angiotensin-converting enzyme; ARA II: angiotensin II receptor antagonists; NSAIDs: nonsteroidal anti-inflammatory drugs; -: not applicable; OTI: orotracheal intubation. Fisher's exact test was applied.

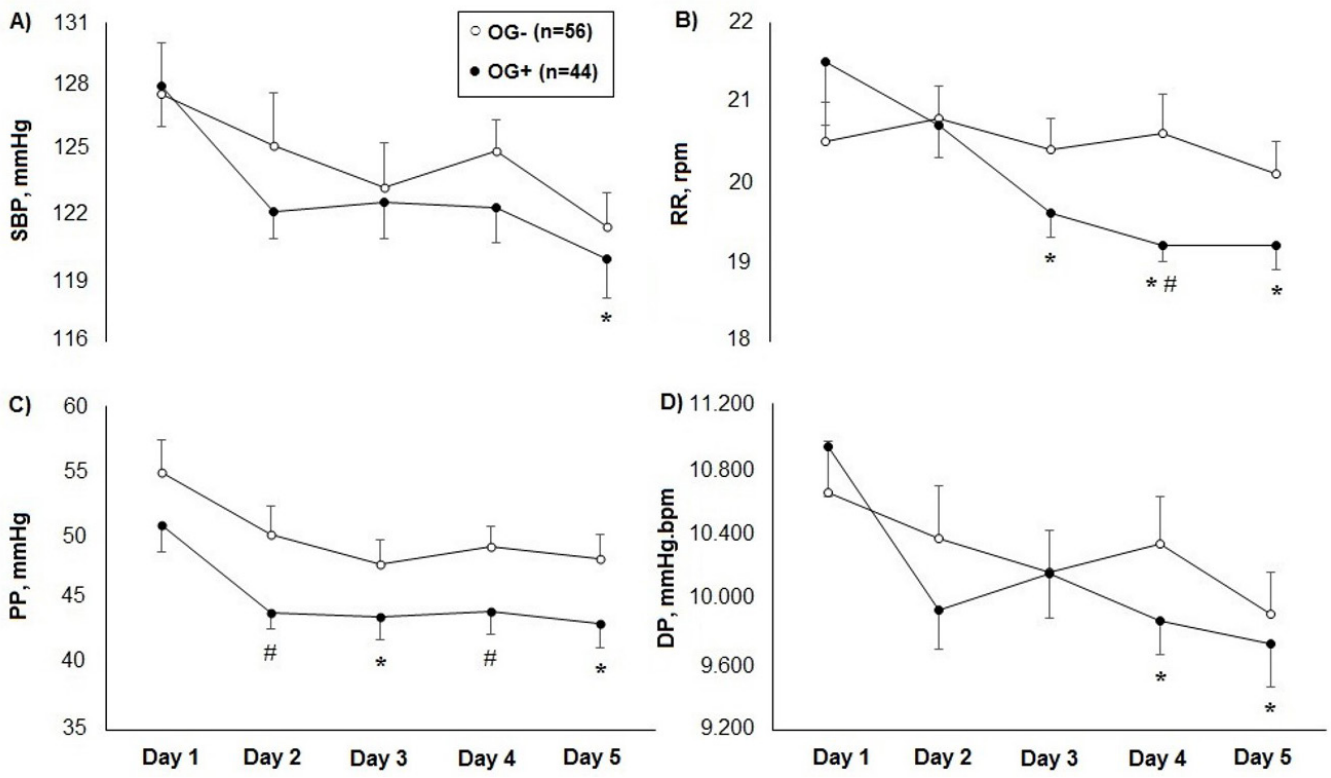

Figure 3. Illustration of the behavior of vital signs (SBP and RR) and derived variables (PP and DP) from the 1st to the 5th day of hospitalization of OG- (negative outcome group) and OG+ (positive outcome group). Data expressed as mean ± SE. A) SBP: systolic blood pressure; B) RR: respiratory rate; C) PP: pulse pressure, obtained by the difference between SBP and diastolic blood pressure; D) DP: double product, obtained by multiplying SBP by heart rate. *Significant difference compared to Day 1 ($p<0.05$). #Significant difference between OG- and OG+ on the same day ($p<0.05$).

Table 3. Blood pressure variability of all patients and by clinical outcome.

	Total (n=100)	OG- (n=56)	OG+ (n=44)	p-value	Difference of means (95% CI)
SBP, mmHg					
Standard deviation, mmHg	9.1 ± 4.6	10.1 ± 5.1	7.8 ± 3.6	0.03*	-2.3 (-4.1; -0.5)
CV, %	7.2 ± 3.6	8.0 ± 3.8	6.3 ± 2.9	0.06	-1.7 (-3.2; -0.3)
ARV, mmHg	11.9 ± 9.7	10.8 ± 6.7	13.2 ± 12.5	0.96	2.4 (-1.5; 6.3)
DBP, mmHg					
Standard deviation, mmHg	6.2 ± 2.9	6.4 ± 2.8	5.9 ± 3.1	0.30	-0.5 (-1.6; 0.6)
CV, %	8.4 ± 3.9	8.6 ± 3.8	7.8 ± 4.3	0.29	-0.8 (-2.5; 0.9)
ARV, mmHg	8.7 ± 6.5	8.2 ± 5.4	9.4 ± 7.7	0.75	1.2 (-1.4; 3.9)
MAP, mmHg					
Standard deviation, mmHg	7.6 ± 5.5	8.2 ± 4.9	7.0 ± 6.1	0.04*	-1.2 (-3.3; 1.0)
CV, %	7.8 ± 3.8	9.2 ± 5.6	8.3 ± 8.6	0.13	-0.9 (-3.8; 2.1)
ARV, mmHg	9.2 ± 7.6	8.7 ± 5.8	10.0 ± 9.3	0.92	1.3 (-1.7; 4.8)

Data expressed as mean ± SD. Difference of means (95% confidence interval - CI). OG-: negative outcome group; OG+: positive outcome group; n: number of patients; SBP: systolic blood pressure; CV: coefficient of variation; ARV: average real variability; DBP: diastolic blood pressure; MAP: mean arterial pressure. *Significant difference between OG+ and OG- (p<0.05). Mann-Whitney U test applied.

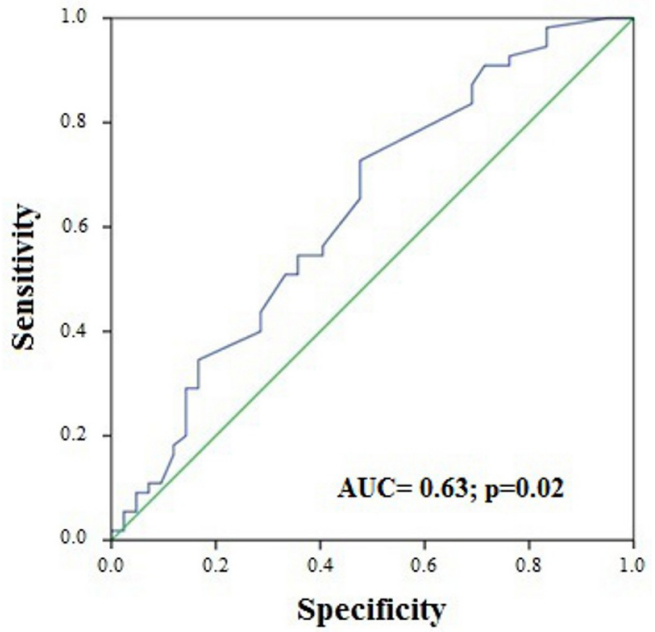

Figure 4. ROC curve. Predictive value of pulse pressure (PP) on day 5 of hospitalization for COVID-19 to discriminate negative outcomes.

(1.4 ± 1.2 mg/dL and 2,600 ± 4,500 ng/mL, respectively), in addition to low levels of partial oxygen pressure and arterial oxygen saturation obtained through arterial blood gas analysis (71.0 ± 26.6 mmHg and 89.2 ± 13.7%, respectively). Moderate elevation of CRP, i.e., > 1 mg/dL, demonstrates ongoing systemic inflammatory inflammation[21], and as in a previous study, levels between 1–3 mg/dL represent a moderate risk for the development of cardiovascular disease[22]. Regarding the elevated D-dimer value, previous data revealed that a concentration greater than 2,590 ng/mL in patients hospitalized for COVID-19 could predict the risk of pulmonary embolism[23]; in addition, a level > 2.14 mg/L, i.e., > 2,140 ng/mL, can identify patients with COVID-19 at higher risk of in-hospital mortality[24]. In this study, we did not observe an association between negative outcomes and CRP and D-dimer concentrations (data not shown). Regarding low levels of partial oxygen pressure and arterial oxygen saturation, i.e., <80 mmHg and <95%[25] respectively, a possible pathophysiological mechanism has been the hypothesis of low elastance and high pulmonary compliance, low ventilation-perfusion and low pulmonary recruitment as a consequence of systemic inflammation due to SARS-CoV-2[26]. This result explains the need for oxygen supplementation during hospitalization in 76% of patients.

Our results showed that the mean length of hospital stay for the total sample was 7.5 ± 2.3 days, as already mentioned. This period was shorter than that observed in the study by Gu et al., carried out in China, in which the authors found a mean length of hospital stay of 17 days (ranging from 4 to 34 days) for 75 patients hospitalized for COVID-19 [13]. A systematic review showed differences between the mean length of hospital stay in China and abroad, with a shorter mean length of stay described in the latter [14 days (10–19) vs. 5 days (3–9), respectively][27], possibly due to different hospital admission and discharge criteria and the distinction between local capacity and pressure on the health system.

In the present study, only OG+ showed a significant reduction in some vital signs/variables derived in the early

phase of hospitalization for COVID-19. Furthermore, we identified that OG-, compared to OG+, presented a greater standard deviation of SBP and MAP variability. Thus, we can infer that patients who evolved with a positive clinical outcome presented better behavior of the cardiovascular profile (PP, DP, and SBP) and respiratory demand (RR) in the first days of hospitalization compared to those with negative clinical outcomes.

It is important to highlight that when our sample was allocated according to the clinical outcome, OG- was older than OG+. The literature shows that during aging, physiological changes occur in all systems, directly reflecting on vital signs[28,29], and the increase in the severity of COVID-19 with increasing age of patients has been widely highlighted[30,31]. In addition to age, male patients, smokers, obese patients, and those with some comorbidity, mainly hypertension, diabetes mellitus, and cardiovascular diseases, are more likely to develop severe cases[32]. However, in our study, different clinical outcomes were not associated with these characteristics.

Vital signs have great relevance in the clinical outcomes of patients hospitalized for COVID-19 but great emphasis has been placed on the vital signs at admission as predictors of outcomes, without covering subsequent days. Furthermore, to our knowledge, no study has evaluated variables derived from vital signs related to the cardiovascular profile, such as PP and DP, in clinical outcomes during the early phase of hospitalization for COVID-19. Elevated SBP at hospital admission for COVID-19, but not hypertension, is significantly associated with the risk of developing severe disease leading to worse outcomes. Also, low SpO_2 and DBP, and elevated RR at hospital admission for COVID-19 were observed to be significantly associated with in-hospital mortality[33].

Regarding BPV, our results are similar to those of Li et al.[34] who investigated the daily clinical variability of BP [3 to 47 days (median of 18 days)] and its association with clinical outcomes in patients hospitalized for COVID-19; the authors found that critically ill patients (transferred to other hospitals for treatment, admitted to the ICU, or who died) presented increased variability in SBP and DBP, which was associated with worse clinical outcomes.

One of the main points of our study was to identify a cutoff point for each vital sign/derived variable to predict outcomes for patients hospitalized for COVID-19. Using the ROC curve, we found a cutoff point for the PP variable, i.e., a PP ≥ 40 mmHg on the 5th day of hospitalization that predicted a negative outcome during hospitalization in these patients. In this context, these results may be clinically useful to refine the ability to discriminate unfavorable outcomes in this population. The association of high PP with adverse cardiovascular outcomes is a well-documented correlation in the literature. Also, the effect of this elevation on clinical outcomes and overall morbidity and mortality has been highlighted[19].

Our results have relevant clinical implications since the analysis of the evolution of vital signs, derived variables, and BPV in this population contributes to the early warning of deteriorating patients. Thus, it is possible to use this care tool in the hospital routine, contributing to the identification of patients with increased risk for negative outcomes, to allow early interventions and more precise support.

Despite the positive aspects presented, the study has some important limitations. The main limitation of the study is the relatively small number of patients from only one hospital in one country. A larger sample of patients hospitalized for COVID-19 in several centers and countries would allow expanding our findings. In addition, the retrospective nature of the study presents less control over the vital signs obtained by different professionals and equipment. Finally, the hospitalization period of less than 5 days and the OTI of many patients that occurred within 5 days after hospital admission resulted in the exclusion of patients, reducing the external validity of the study.

CONCLUSION

Patients hospitalized for COVID-19 and with a positive clinical outcome showed better evolution of vital signs/derived variables and BPV in the early phase of hospitalization. Furthermore, a PP ≥ 40 mmHg on the 5th day of hospitalization was a relevant cutoff point to predict negative outcomes (in-hospital death, OTI after the 5th day of hospitalization and prolonged hospitalization).

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CONFLICT OF INTEREST

None

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