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Original article

Factors associated with mortality, length of hospital stay and diagnosis of COVID-19: Data from a field hospital

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ABSTRACT

Background: During the pandemic of COVID-19, phylogenetic changes have been observed in the characteristics of the virus, in the diagnosis and treatment of the disease. The clinical course and the severe form of the disease depends on several factors. This study characterized the beginning setting for patient care of COVID-19 in a referral center in one of the main capital cities of Brazil. In addition, were evaluated the factors associated with mortality, length of stay, and diagnostic outcome.
Methods: A cross-sectional study was conducted during May 2020 (n = 1100). The association of the variables with outcome was evaluated by a multivariable logistic regression model, using odds ratios (OR) and 95 % confidence intervals (CI).
Results: Overall, 76 % of patients were COVID-19 positive, and 70 % were diagnosed by RT–qPCR. The majority were male (56 %), and over 52 years old (74 %), 68 % had hypertension, 44 % had diabetes mellitus, and 32 % were obese. The mean length of stay was 10 ± 8 days, which was higher in the 34 % who died (≥14; OR=2; 95 %CI=1.4–4) and who had hypertension (OR=2; 95 %CI=1.3–3) (P < 0.001). The mean length of stay was also higher (P = 0.008) for those patients with pulmonary impairment ≥ 50 % (10.72 ± 8.24), than those with < 50 % (8.98 ± 6.81). Age (> 62 and 65 years) was associated with longer hospitalization (OR=2; 95 %CI=1.4–3) and death (OR=6; 95 %CI=3–11). The time of sample collection for RT–qPCR was different between positive and negative tests (P = 0.001), with the time of 4–10 days showing a greater chance for virus detection (OR=2.9; 95 %CI=1.6–5).
Conclusion: Death was associated with age and pulmonary impairment. The length of hospitalization was associated with age, hypertension, pulmonary impairment and death. The time of sample collection to perform RT–qPCR and the rapid test was associated with a positive result for COVID-19. These results highlight the ongoing challenge of diagnosing, treating, and mitigating the effects caused by the COVID-19 pandemic.

Introduction

Worldwide, as of April 08, 2022, the World Health Organization (WHO) has reported 494,587,638 confirmed cases of COVID-19 and 6170,283 deaths [1]. In Brazil, from the first confirmed case (February 26, 2020) until April 07, 2022, 30,123,963 cases and 661,122 deaths, with a higher concentration of cases and deaths in the Southeast region. In Rio de Janeiro state, there have been 2108,417 cases and 73,039 deaths [2–4].

Immunization against COVID-19 in Brazil began almost a year after the first confirmed case (January 19, 2021), first restricted to priority groups. Thus far (April 08, 2022), in the state of Rio de

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Janeiro, 77 % immunization of the population over 5 years old with complete vaccination and 85 % immunization of the population over 12 years old with complete vaccination [5–7]. The vaccine protects against moderate and severe forms of the disease, reducing hospitalizations by 86 % and deaths by 95 % in addition to reducing the number of symptomatic cases by 80 % [8].

COVID-19 initially manifests with symptoms characteristic of a flu-like syndrome and can be confused with influenza and other seasonal viral infections of the upper respiratory tract [9]. However, some patients may to progress to the severe form of the disease. Therefore, a rapid diagnosis is essential for starting treatment and enabling social isolation, as it is a highly transmissible virus [9,10]. Despite limitations such as the long time it takes to release the results, and the possibility of false-negative results due to several factors, the gold standard is the quantitative real-time polymerase chain reaction molecular technique (RT–qPCR) using the reverse transcriptase assay [9]. In addition to the origin of the material collected, the result depends on the time elapsed between sample collection and the onset of symptoms, the fluctuation of viral load, and correct sample collection [9,11–17]. In addition to RT–qPCR, serology, based on the detection of immunoglobulin antibodies in blood, serum, or plasma samples, is also used because it provides rapid results; however, has low sensitivity (15–76 %) and must be performed 7 days after the onset of symptoms [9,11,17–20].

The clinical course of the disease depends on several factors, and the severe form is associated with some risk factors [21]. Thus, we conducted a descriptive study of the sociodemographic and clinical characteristics of the first individuals seen at a specialized field hospital of the Brazilian public health system for the care of COVID-19 patients. The influence of patient's characteristics on the length of hospital stay and clinical outcome was also evaluated along with the influence of the time of sample collection on the diagnostic result by RT–qPCR.

Methods

A cross-sectional study was conducted in a hospital cohort of patients seen from May 1–24, 2020, at Riocentro Campaign Hospital located in the west zone of the city of Rio de Janeiro/Brazil. The study was approved by the Research Ethics Committee (4.148.440).

Patients who underwent sample collection with sterile nasopharyngeal swabs were included. Diagnosis was through real-time RT–qPCR or, in the case of RT–qPCR with nondetectable results, the rapid antibody test for COVID-19 diagnosis. Patients with a positive result in one of the two diagnostic methods were classified as COVID-19 positive, and those with a negative result in both tests were classified as COVID-19 negative. The exclusion criteria were: patients transferred or discharged by default; inconclusive diagnosis for COVID-19, without confirmation by rapid testing; undefined diagnosis; and absence of data for statistical analysis.

Data were accessed from the patients' electronic medical records during their hospitalization. Sociodemographic (age, sex, BMI, and place of residence) and clinical data (dates of hospitalization, medical discharge or death, date of symptom onset, comorbidities, date of collection and result of RT–qPCR and rapid testing for COVID-19 diagnosis) were collected. According to the WHO [22], BMI was classified into two groups: nonobese (< 30 kg/m²) and obese (≥30 kg/m²). All information was double-checked by independent researchers for inclusion in this study.

Differences between means for continuous variables were evaluated using the Student's t-test, and data were expressed as mean, standard deviation, minimum and maximum values, and the number and frequency per variable. Categorical variables were described as percentages, analyzed using the Chi-square test or Fisher's exact test. The association of the variables with outcome was evaluated by a multivariable logistic regression model, using odds ratios (OR) and 95 % confidence intervals (CI), with adjustment for possible confounding factors. The adjustment model employed was determined by the variables that had a significance level less than or equal to 0,20 (P ≤ 0,20) in the univariate analysis but remained at a significance level of 0,05 (P < 0,05) after exiting the model.

Table 1
Demographic and clinical characteristics of the 761 patients.

Characteristics	n (%)	Characteristics	n (%)
Sex		**Diagnostics**	
Female	332 (43.6)	COVID-19	579 (76.1)
Male	429 (56.4)	Pneumonia	67 (8.8)
Age (years)		Suspected COVID-19	43 (5.7)
20–51	202 (26.5)	Influenza	31 (4.1)
52–64	196 (25.8)	Respiratory abnormalities[a]	14 (1.8)
65–73	173 (22.7)	Cardiac abnormalities	5 (0.7)
≥ 74	190 (25.0)	Tuberculosis	4 (0.5)
Comorbidities[b]		Other	18 (2.3)
Hypertension	493 (67.6)	**COVID-19 RT-qPCR**	
Diabetes Mellitus	323 (44.1)	Not detectable	229 (30.1)
Obesity	217 (31.7)	Detectable	530 (69.6)
Length of stay (days)		Inconclusive	2 (0.3)
0 – 5	254 (33.4)	**COVID-19 rapid test**[c]	
6 – 8	162 (21.3)	Negative	78 (60.0)
9 – 13	167 (21.9)	Positive	52 (40.0)
≥ 14	178 (23.4)	**COVID-19 outcome**[d]	
General Clinical Outcome		Discharge	385 (66.5)
Discharge	496 (65.2)	Death	194 (33.5)
Death	265 (34.8)		

[a] Other respiratory disorders: respiratory failure, asthma, dyspnea, and pulmonary obstruction.
[b] The same patient can present more than one comorbidity.
[c] Patients who had the rapid test for COVID-19 diagnosis in addition to RT-qPCR (n = 130).
[d] Patients diagnosed with COVID-19 confirmed by RT-qPCR or rapid test (n = 579).

Results

A total of 1100 electronic medical records of patients admitted to the field hospital were accessed from May 1 to May 24, 2020. A total of 339 patients were excluded, leaving 761 classified as COVID-19 positive (n = 579) and negative (n = 182), based on RT–qPCR and/or rapid antibody test results.

The demographic and clinical characteristics of the study population (n = 761) are described in Table 1, with the majority being male (56.4 %), over 52 years old (73.5 %), with a mean age of 62 ± 15 (20−101) years. In total, 67 % of patients (n = 493) had hypertension, 44.1 % (n = 323) had diabetes mellitus and 31.7 % (n = 217) had obesity (≥30 kg/m²). In addition to the information on the presence/absence of obesity, 275 patients had BMI information in their medical records, with a mean value of 27 ± 6 (13.5–50.7) kg/m².

According to the international classification of diseases (ICD-10), the main causes of hospitalization were COVID-19 (76.1 %), pneumonia (8.8 %) and influenza (4.1 %). Approximately 5 % of the patients had other respiratory, cardiac, or other types of diagnoses. In addition, 5.7 % (n = 43) of patients did not obtain a definitive diagnosis and were classified as suspected cases of COVID-19 and were also excluded from subsequent analyses. Thus, 579 patients had a diagnosis of COVID-19 confirmed by RT–qPCR or rapid antibody testing (Table 1).

Approximately 70 % of the COVID-19-positive patients were diagnosed by the technique considered the gold standard for disease diagnosis (RT–qPCR). Following the protocol of the institution's Hospital Infection Control Committee, patients with "non-detectable", "inconclusive" or delayed RT–qPCR results and patients who remained hospitalized with suspected SARS-CoV-2 infection were administered the rapid antibody test (17.1 %), of which 52 cases

Table 2
Association analysis between demographic and clinical characteristics and mean length of hospital stay for COVID-19 positive patients (n = 579).

Characteristics	≤ 10 days[a]	> 10 days[a]	p	OR_{crude} (IC 95 %)	$OR_{adjusted}$ (IC 95 %)[b]
Sex	**n (%)**	**n (%)**			
Female	159 (41.4)	86 (44.1)	0.54	1[c]	1[c]
Male	225 (58.6)	109 (55.9)		0.90 (0.63–1.27)	0.93 (0.61 – 1.42)
Age (years)					
≤ 62	208 (54.2)	68 (34.9)	**< 0.0001**	1[c]	1[c]
> 62	176 (45.8)	127 (65.1)		**2.21 (1.55–3.15)**	**1.99 (1.30 – 3.05)**
Hypertension					
No	143 (39.0)	40 (21.1)	**< 0.0001**	1[c]	1[c]
Yes	224 (61.0)	150 (78.9)		**2.39 (1.59 – 3.60)**	**2.62 (1.59 – 4.29)**
No information	17	5			
Diabetes Mellitus					
No	210 (57.4)	102 (53.4)	0.4	1[c]	1[c]
Yes	156 (42.6)	89 (46.6)		1.18 (0.83 – 1.67)	0.84 (0.54 – 1.30)
No information	18	4			
Obesity					
No	231 (67.7)	109 (61.6)	0.2	1[c]	1[c]
Yes	110 (32.3)	68 (38.4)		1.31 (0.90 – 1.91)	1.53 (0.96 – 2.43)
No information	43	18			
Pulmonary impairment					
< 50	171 (55.9)	66 (42.3)	**0.004**	1[c]	1[c]
≥ 50	135 (44.1)	90 (57.7)		**1.73 (1.17 – 2.55)**	**1.71 (1.13 – 2.58)**

[a] Groups determined according to the average length of stay of the 579 patients.
[b] Adjusted for age, pulmonary impairment, and hypertension, when applicable.
[c] Reference group.

were positive for COVID-19. In addition, 5 patients were diagnosed with COVID-19 by the rapid test due to delayed RT–qPCR results. Thus, 3 patients were positive for both tests, and 2 were diagnosed only by the rapid test (Table 1).

The mean hospital stay was 9 ± 8 (0–64) days, and most patients (66.6 %) were hospitalized for at least 6 days (Table 1). Regarding the clinical outcome of the general population, patients who died had a significantly (P < 0.001) longer length of stay (12 ± 9.2 days) than patients who were discharged (8.9 ± 7.5 days). Considering only COVID-19-positive individuals (n = 579), the mean length of stay was 10.1 ± 8.2 days, and among them, 194 (33.5 %) died. A longer mean length of stay (P < 0.001) was also observed among COVID-19-positive patients who died (12 ± 8.7 days) compared with those who were discharged (9.2 ± 7.8 days) (data not shown).

Table 2 describes the analyses of associations between length of stay and demographic and clinical characteristics of COVID-19-positive patients. A longer length of hospitalization was found to be associated with age over 62 years, the presence of hypertension and pulmonary impairment (> 50 %). The mean length of hospital stay among patients with hypertension was 10.8 ± 8.4 days, which was significantly longer (P = 0.001) than that among individuals who did not have this comorbidity (8.53 ± 7.8 days). Considering the presence of diabetes mellitus (10.1 ± 8.1 days) and obesity (10.8 ± 7.9 days), no significant difference was observed between groups regarding the mean length of stay (P = 0.664 and 0.126, respectively). On the other hand, when the presence of one or more comorbidities was evaluated, the mean length of stay was 10.5 ± 8.5 days, compared with 8.5 ± 7.1 in individuals without any of the three comorbidities (P = 0.01). For the pulmonary impairment, the mean length of hospital stay among patients with < 50 % was 8.98 ± 6.81, which was significantly shorter (P = 0.008) than that among ≥ 50 % individuals (10.72 ± 8.24) (data not shown).

The association analysis of demographic and clinical variables of COVID-19-positive patients (n = 579) in relation to clinical outcome is described in Table 3. An age over 52 years was associated with a higher chance of death (P < 0.001), reaching an almost 9-fold increase for patients older than 74 years. Length of hospitalization was also a significant factor for the clinical outcome of death (P < 0.001), with a 2-fold greater chance for patients hospitalized for more than 14 days. The pulmonary impairment was also associated with clinical outcome (P < 0.001), with patients with ≥ 50 % impairment showing a 3-fold greater chance of death. There was no significant association between the clinical outcome and sex, the presence of comorbidities or the timing of sample collection for RT–qPCR testing in the analysis adjusted for confounding factors (age and length of hospitalization) (Table 3).

There was a significant difference (P = 0.001) in the distribution of COVID-19-positive and -negative patients according to the time of sample collection for RT–qPCR testing (Fig. 1 A), with a predominance of positive patients (54.9 %) in the collection interval of 4–10 days after symptom onset. Sample collection between 4 and 10 days after symptom onset had a greater chance (2.9 times) of identifying the presence of the COVID-19 virus by RT–qPCR compared with the group that collected samples within 3 days (Table 4). Considering the method used in the diagnosis of COVID-19, the mean time elapsed between the onset of symptoms and sample collection for testing by RT–qPCR was 8.3 ± 4.9 days versus 11.9 ± 8.6 days in the group diagnosed by the rapid test (P < 0.0001). Furthermore, almost 45 % of patients diagnosed by the rapid test had the sample collected for RT–qPCR testing more than 10 days after symptom onset, while 72.5 % of patients diagnosed by RT–qPCR (n = 207) had samples collected within 10 days of symptom onset (Fig. 1B), however, no significant association was observed (OR= 2.14; 95 % CI = 0.99 – 4.61).

Discussion

This study describes the epidemiological and clinical profile of the first patients seen in a Brazilian field hospital according to the demand of the initial phase of the COVID-19 pandemic. In addition to reporting the number of deaths, which was associated with age, length of hospital stay, and pulmonary impairment, this study also observed that length of stay was associated with age and the presence of hypertension. The sample collection time for RT–qPCR and the rapid test were associated with positive results for COVID-19.

In February 2021, Brazil ranked 2nd in the number of new deaths, totaling 8244, behind only the United States, with 14,237 deaths [23]. The city of Rio de Janeiro, one of the largest urban centers in the country, had 1808 cases and 92 confirmed deaths by COVID-19 between March 6 and April 10, 2020, with the first death recorded only 11 days after the first case in Brazil. In this period, Rio de Janeiro was the second city with the highest number of cases of the disease [24].

Table 3
Association analysis between demographic and clinical characteristics and clinical outcome of the 579 COVID-19 positive patients.

Characteristics	Medical Discharge (n = 385)	Death (n = 194)	*p*	OR_{crude} (IC 95 %)	$OR_{ajusted}$ (IC 95 %)[a]
Sex	**n (%)**	**n (%)**			
Female	162 (42.1)	83 (42.8)	0.9	1[b]	1[b]
Male	223 (57.9)	111 (57.2)		0.97 (0.69–1.38)	1.25 (0.78 – 1.99)
Age (years)					
20–51	137 (35.6)	20 (10.3)	**< 0.001**	1[b]	1[b]
52–64	113 (29.3)	43 (22.2)		**2.61 (1.45–4.68)**	**3.22 (1.54 – 6.72)**
65–73	72 (18.7)	65 (33.5)		**6.18 (3.47–11.01)**	**6.52 (3.18 – 13.37)**
≥ 74	63 (16.4)	66 (34.0)		**7.18 (4.01–12.85)**	**9.14 (4.39 – 19.02)**
Hypertension					
No	141 (38.0)	42 (22.6)	**< 0.001**	1[b]	1[b]
Yes	230 (62.0)	144 (77.4)		2.10 (1.41 – 3.14)	1.21 (0.69 – 2.11)
No information	14	8			
Diabetes Mellitus					
No	217 (58.5)	95 (51.1)	0.1	1[b]	1[b]
Yes	154 (41.5)	91 (48.9)		1.35 (0.95 – 1.92)	1.33 (0.83 – 2.11)
No information	14	8			
Obesity					
No	220 (65.3)	120 (66.3)		1[b]	1[b]
Yes	117 (34.7)	61 (33.7)	0.8	0.96 (0.65 – 1.40)	1.07 (0.64 – 1.79)
No information	48	13			
Time to RT-qPCR collection (days)					
0–3	37 (13.9)	25 (21.0)	0.17	1[b]	1[b]
4–10	148 (55.4)	64 (53.8)		0.64 (0.36 – 1.15)	0.75 (0.35 – 1.59)
≥ 11	82 (30.7)	30 (25.2)		0.54 (0.28 – 1.05)	0.53 (0.23 – 1.21)
No information	118	75			
Length of hospital stay (days)					
0 – 5	130 (33.8)	51 (26.3)	**< 0.001**	1[b]	1[b]
6 – 8	101 (26.2)	30 (15.5)		0.76 (0.45–1.27)	0.72 (0.36 – 1.43)
9 – 13	87 (22.6)	42 (21.6)		1.23 (0.75–2.01)	0.92 (0.48 – 1.77)
≥ 14	67 (17.4)	71 (36.6)		**2.70 (1.70–4.30)**	**2.73 (1.49 – 5.02)**
Pulmonary impairment					
< 50	196 (58.9)	41 (31.8)	**< 0.001**	1[b]	1[b]
≥ 50	137 (41.1)	88 (68.2)		**3.07 (1.99 – 4.72)**	**3.38 (2.11 – 5.43)**

[a] Adjusted for age, length of hospitalization, and pulmonary impairment, when applicable.
[b] Reference group.

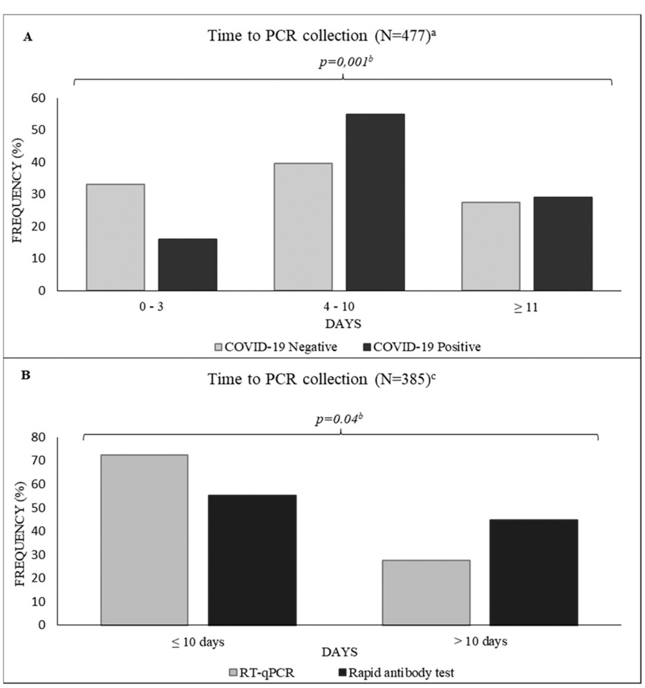

Fig. 1. Time of sample collection for the RT-qPCR technique according to (A) COVID-19 positive and negative patients and (B) the diagnostic method (rapid antibody test or RT-qPCR). [a]Number of patients after exclusion of those with "Suspected COVID-19" diagnosis (n = 43) and those without information of symptom onset or swab collection date (n = 241). [b]P value obtained using Pearson's chi-square test. [c]Number of COVID-19 patients diagnosed only on RT-qPCR (n = 527) or rapid antibody test (n = 49), excluding those without information of symptom onset or swab collection date (n = 191).

Table 4
Association analysis between collection time for RT-qPCR testing and Covid-19 diagnosis (n = 477).

Collection time (days)	Negative (n = 91)[a]	Positive (n = 386)[a]	p	OR (IC 95 %)
	n (%)	**n (%)**		
0–3	30 (33.0)	62 (16.1)	0.001	1[b]
4–10	36 (39.6)	212 (54.9)		**2.85 (1.63 – 4.99)**
≥ 11	25 (27.5)	112 (29.0)		**2.17 (1.17–4.01)**

[a] 241 patients had no information on symptom onset and/or swab collection date.
[b] Reference group.

Of the 761 patients seen at the field hospital in May 2020, approximately 76 % had COVID-19 confirmed by RT–qPCR and/or rapid testing, 15 % had pneumonia or inconclusive results for COVID-19, and approximately 9 % had other diagnoses. These numbers underscore the importance of care and investment in effective disease diagnosis. The B.1.1.33 strain, identified in 80 % of the genomic sequences of COVID-19-positive patients in Rio de Janeiro, reached a prevalence of 90 % in April 2020 [3]. In samples collected between May and November 2020 in Brazil, a phylogenetic reconstruction of 116 genomes was performed, with 87 % belonging to three genetic clusters of the strains B.1.1.33 and B.1.1.28 [25], the likely strains that infected the patients included in the present study.

Most patients were male and over 60 years old and had a high frequency of comorbidities, corroborating the profile of COVID-19-positive patients described elsewhere [24,26–30]. The prevalence of hypertension, diabetes mellitus and obesity in the patients analyzed exceeds the prevalence of these comorbidities in the general population [31,32], indicating the need for COVID-19 hospitalization and the high mortality rate in patients with previous comorbidities [33].

In the present study, the presence of hypertension was associated with higher risk of staying longer than 10 days in hospital, in agreement with a previous study that observed that patients admitted to ICU had a higher probability (78 %) of prior hypertension compared with those admitted to general practice and who stayed less time in the hospital [29]. It is known that length of hospital stay is age dependent, increasing up to 34 days in individuals 80 years of age or older [28]. Furthermore, there is a linear increase in the COVID-19 mortality rate after the age of 30 years, according to published data from 45 countries [34]. A significant increase in the risk of death has been observed in patients over 70 years of age compared with those aged 50–59 years [35]. The association between death and long hospital stay could be due to the severity of illness, however, the pulmonary impairment was considered as a confounding variable, and even then, it remained statistically significant. Together, these results reinforce the need for specialized medical care for male patients with advanced age and associated comorbidities, as they require longer hospitalization and a greater chance of death.

Despite advances in diagnosing the disease, RT–qPCR testing is still considered the gold standard, especially in hospital settings [36], and samples collected from the nasopharyngeal mucosa are more efficient for COVID-19 diagnosis [15]. In this reference center for COVID-19 treatment, nasopharyngeal RT–qPCR was also prioritized for diagnosis; however, 30 % of the tests were negative. It was observed that the number of positive results for COVID-19 was higher when the sample collection was performed within 4–10 days after symptom onset when compared with patients who collected within 3 days, as previously observed for studies conducted in the same period [37]. Data from Rio de Janeiro between February and April 2020 indicate that the mean time between symptom onset and definitive COVID-19 diagnosis was 8 days [38]. A review study conducted with data collected up to June 2020 described that the positive RT–qPCR result decreased from 96 % to 75 % when the nasopharyngeal sample was collected 10 days after symptom onset [39]. Parmar and colleagues identified patients with typical COVID-19 signs and/or symptoms with repeatedly negative RT–qPCR results, however seropositive for IgG and IgM [13]. These findings corroborate the management performed at the field hospital, as the highest number of rapid tests (44.8 %) were performed on inpatients who were COVID-19 negative on RT–qPCR and who already had 10 days or more of symptom onset. Before the seventh day of symptom onset, the number of antibodies may be insufficient for the detection and diagnosis of COVID-19 [20]. Therefore, patients presenting with clinical criteria for COVID-19, even those with negative RT–qPCR results, should also receive treatment for acute disease [11].

Some considerations and limitations should be noted for the interpretation of the results described here, especially regarding the improvement of disease diagnostic techniques, the time of sample collection after the onset of symptoms, and the result of the diagnosis by RT–qPCR, as the study was performed with data obtained in May 2020. During the pandemic, phylogenetic changes have been observed in the characteristics of the virus [2] and consequently in the diagnosis of the disease by RT–qPCR. Currently, it is recommended that a nasopharyngeal sample be collected up to 8 days after the onset of symptoms [40]. Another limitation of the present study is that despite the short time of onset of symptoms and onset of care at the field hospital, the risk of memory bias should be considered, as the patients were referred from other care centers and the date of symptom onset was self-reported by the patient. However, the results of the present study reflect the beginning of the Brazilian setting for the diagnosis and treatment of COVID-19 in a public referral center in one of the main capital cities of the country. Furthermore, the present observations are relevant for understanding the impact of the pandemic, which was probably not specific to the situation in Brazil. The results of this study can contribute as a database for future studies to understand the course of the disease and develop useful diagnostic tools in clinical practice and to identify individuals at risk of presenting the severe form of the disease.

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Authors' contribution

VCS and JAP conception and design of the study. VCS acquisition of data. MCS, MPM and JAP analysis and interpretation of data. VCS, MCS, and JAP drafted the article, JAMG and JAP revised it critically for important intellectual content. All authors reviewed and approved the final version of the manuscript before submission.

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