Clinical and epidemiological aspects of patients infected with SARS-CoV-2 variants: a case-control study

Aspectos clínicos e epidemiológicos de pacientes infectados com variantes do SARS-CoV-2: um estudo caso controle

Aspectos clínicos y epidemiológicos de pacientes infectados con variantes del SARS-CoV-2: un estudio de casos y controles

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Abstract
Objective: To compare the clinical outcomes of patients infected with SARS-CoV-2 variants with patients infected with the original strain. Methods: This is a case control study comparing cases of COVID-19 patients infected with SARS-CoV-2 variants of concern identified by genomic sequencing, with a control group of 62 patients randomly selected from a COVID-19 database of patients diagnosed prior to the emergence of these variants. Findings: In the 40 patients infected with variants, the predominant (52.5%) was P.1 variant. The variant group presented more arthralgia (p=0.015), hyporexia (p=0.006), nausea/vomiting (p=0.048), and mental confusion (p=0.029), the last not identified in the control group. There were no significant differences in comorbidities or demographic data between the groups. Severe disease, according to the WHO Clinical Progression Scale, was identified only in those infected with the variants, as well as high-flow oxygen therapy and ICU admission (p=0.05). The two deaths reported in the study were in patients infected with the variants. Conclusions: The worst outcomes were observed in the group infected with SARS-CoV-2 variants, although no significant differences in comorbidities or demographics date were observed between the groups.
Keywords: Case-control studies; Signs and symptoms; Virus infection, COVID-19.

Resumo
Objetivo: Comparar os desfechos clínicos de pacientes infectados com variantes dos SARS-CoV-2 com pacientes infectados com a cepa original. Métodos: Este é um estudo caso controle que compara casos de pacientes com COVID-19 infectados com variantes de preocupação do SARS-CoV-2, identificadas por sequenciamento genômico, com um grupo controle de 62 pacientes selecionados aleatoriamente de um banco de dados de pacientes com COVID-19 diagnosticados previamente ao surgimento dessas variantes de preocupação. Resultados: Nos 40 pacientes infectados com as variantes, a forma predominante foi a variante P.1 (52,5%). O grupo infectado por variantes apresentou mais artralgia (p=0,015), hiporexia (p=0,006), náusea/vômito (p=0,048) e confusão mental (p=0,029), sendo esta última não identificada no grupo controle. Não houve diferenças significativas entre os grupos quando comparados comorbidades ou dados geográficos. Forma grave da doença, de acordo com a Escala de Progressão da OMS, foi identificada somente naqueles infectados com as formas variantes, assim como o uso de oxigenoterapia de alto fluxo e admissão na UTI (p=0,05). As duas mortes reportadas no estudo foram em pacientes infectados com formas variantes do vírus. Conclusões: Os piores desfechos foram observados no grupo infectado com variantes do SARS-CoV-2, apesar de não haver diferenças significativas nas comorbidades ou dados demográficos entre os grupos.
Palavras-chave: Estudos de casos e controles; Sinais e sintomas; Infecção viral COVID-19.

Resumen
Objetivo: Comparar los resultados clínicos de los pacientes infectados con variantes del SARS-CoV-2 con los pacientes infectados con la cepa original. Métodos: Se trata de un estudio de casos y controles que comprende casos de pacientes con COVID-19 infectados con variantes de la preocupación por SARS-CoV-2, identificados por secuenciación genómica, con un grupo control de 62 pacientes seleccionados aleatoriamente de una base de datos de pacientes con COVID-19 diagnosticados antes de la aparición de estas variantes de preocupación. Resultados: En los 40 pacientes infectados con las variantes, la forma predominante fue la variante P.1 (52,5%). El grupo infectado con variantes presentó más artralgia (p=0,015), hiporexia (p=0,006), náuseas/vómitos (p=0,048) y confusión mental (p=0,029), no identificándose esta última en el grupo control. No hubo diferencias significativas entre los grupos cuando se compararon las comorbilidades o los datos geográficos. La forma grave de la enfermedad, según la Escala de Progresión de la OMS, se identificó solo en aquellos infectados con formas variantes, así como el uso de oxigenoterapia de alto flujo y el ingreso en la UCI (p = 0,05). Las dos muertes reportadas en el estudio fueron en pacientes infectados con formas variantes del virus. Conclusiones: Los peores resultados se observaron en el grupo infectado con variantes del SARS-CoV-2, aunque no hubo diferencias significativas en las comorbilidades ni en los datos demográficos entre los grupos.
Palabras clave: Estudios de casos y controles; Signos y síntomas; Infección por el virus de la COVID-19.

1. Introduction

The SARS-CoV-2 virus was identified in December 2019 in Wuhan province, China, being responsible for cases of mild disease to atypical and potentially fatal pneumonia, especially in the elderly (Leung, 2020). The unrestrained worldwide spread of SARS-CoV-2 has allowed the emergence of several mutations and new dominant variants, some of them have been designated as Variants of Concern (VOC) (Guo et al., 2021). The first VOC identified was B.1.1.7 in United Kingdom, with the rapid spread of this variant around the world being remarkable (Tang et al., 2021). The second one, B.1.351, emerged in South Africa and bring concern about increased infectivity (Tegally et al., 2021). In Brazil, the uncontrolled spread of SARS-

CoV-2 led to emergence of two VOC, VOC P.1 and the VOC P.2 (Castro et al., 2021). Both variants were associated with cases of reinfection, decrease of efficiency of some vaccines and severe cases, contributing with the devasting second wave in Brazil (Faria et al., 2021; Zeiser et al., 2022). Due to the ongoing pandemic situation, other SARS-CoV-2 variants continues to be identified and related to increase of infectivity and disease severity (Aleem et al., 2021).

COVID-19 continues to be a challenge worldwide. Analysis of clinical presentation, especially in cases of infection with the virus variants, provides subsidies for greater knowledge of the disease, both by raising data for clinical suspicion, as well as to guide possible treatments and control measures to be adopted by the administrators (Ong et al., 2021).

The present study reports the clinical-epidemiological profile of 40 COVID-19 patients infected by variants, comparing the clinical course and outcomes of these cases with a control group of 62 patients randomly selected from a COVID-19 database of patients diagnosed prior to the emergence of these variants.

2. Methodology

Ethical aspects

This study was approved by the research ethical board of the Federal University of Sergipe (CAAE 31079720.5.0000.5546) and followed the recommendations of Resolution 466/2012 from the National Health Council, Ministry of Health, Brazil.

Study design and clinical sampling

This is a case-control, clinical-epidemiological study, including patients who were RT-qPCR positive for SARS-CoV-2. The paper organization was based in guidelines of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Due to social distancing and the difficulties to face-to-face care during the critical period of the pandemic, the 'Monitora Corona' project was created to follow-up patients by daily telephone calls. In this study, the control group was composed of individuals who were infected by the original strain of SARS-CoV-2, during April to July 2020, before the emergence of variants, randomly extracted from Monitora Corona project. Meanwhile, the case group was selected from patients with RT-qPCR positive to SARS-CoV-2, during September to October 2021, and diagnosed by the Central Public Health Laboratory of Sergipe (LACEN-SE), reference and certified for diagnosis of COVID-19 in the State. The identification of virus variants was made by viral genome sequencing by the Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, the National laboratory of reference and certified for diagnosis of COVID-19. The methods and techniques for laboratorial diagnostic and sequencing are from national network of surveillance of COVID-19 and were previously published (Faria et al., 2021; Lamarca et al., 2021; Naveca et al., 2021).

To minimizing possible discrepancies in clinical manifestations, all patients are from same state, Sergipe, Brazil, aiming a more homogeneous genetic population. Demographical, epidemiological, and clinical data were collected from these patients by a semi-structured interview, using the same questionnaire for both case and control groups. Both groups were also submitted to the same classification during the interviews, according to the WHO Clinical Progression Scale, registered on the WHO International Platform (Marshall et al., 2020).

Statistical analysis

Statistical analysis was performed using the SPSS statistical program (version 26.0 for Windows). Different tests were used, according to the obtained data, including Bootstrap. For continuous variables: Gaussian distribution was evaluated by Pearson's and Shapiro-Wilk normality tests and groups were compared by Student T test or Mann-Whitman U test. For

categorical data: the association was tested using a 95% confidence interval (CI) using Fisher's Exact Test with data considered statistically significant with values of $p \leq 0.05$.

3. Results

The present study recruited a total of 102 patients with positive RT-qPCR for SARS-CoV-2 from April 2020 to June 2021. The CT values found in the RT-qPCR analyzed in the study, range from 11 to 29, confirming the positivity for the coronavirus with a high viral load. Most samples (80.0%) were collected between days 1 and 5 of the disease, the most suitable period for estimating the viral load.

Most patients were female (N=63, F=61.8%), 14 to 73 years old (average of 41.8 years, ± 12.3 DP), and work in industry and commerce sector (N=47, F=46.0%). The most common comorbidities found were Systemic Arterial Hypertension (N=23, F=22.5%) and Obesity (N=21, F=20.6%). The most prevalent blood type was O+ (N=37, F=36.2%) followed by A+ (N=16, F=16.7%). Azithromycin and systemic corticotherapy were used in more than half of the patients (N=54, F=52.9% for Azithromycin and N=53, F=51.9% for systemic corticoids). The epidemiological and clinical characteristics found in patients infected with variants of SARS-CoV-2 are like the total group described.

Table 1 shows differences in epidemiological and clinical aspects on admission and clinical outcome according to the WHO progression scale between case group, patients with SARS-CoV-2 variants, and control group, patients infected with the original strain. There is a statistical relevant higher frequency of healthcare professionals in the control group. As for associated diseases, dyslipidemia was more frequent in the case group, from the variants (p=0.011). No statistical significance was identified between the groups in respect to the treatments used.

Table 1. Comparison of demographic, clinical data on admission and clinical outcome according to the WHO progression scale between COVID-19 patients infected by SARS-CoV-2 variants and a control group infected with the original variant from a state of Northeast, Brazil.

Variables	Variant Group (n=40) % (n)	Control Group (n=62) % (n)	p value[a]
Age (Mean ± SD)	42.8 ± 11.9	41.1 ± 12.5	0.922
Females	60.0 (24)	62.9 (39)	0.836
Healthcare workers	15.0 (6)	40.3 (25)	0.001
Blood type A	21.6 (8)	19.4 (12)	0.873
Blood type O	47.5 (19)	43.6 (27)	0.873
Associated diseases (Systemic Arterial Hypertension, Diabetes, Obesity and Asthma)	32.5 (13)	21.0 (13)	0.206
Dyslipidemia	35.0 (14)	14.5 (9)	0.011
Azytromycin treatment	65.0 (26)	45.2 (28)	0.050
Corticoid treatment	45.0 (18)	56.5 (35)	0.258
Clinical Manifestations			
Musculoskeletal system			
Asthenia	57.5 (23)	58.1 (36)	0.955
Myalgia	67.5 (27)	59.7 (37)	0.425
Arthralgia	**47.5 (19)**	**24.2 (15)**	**0.015**
Digestive system			
Odynophagia	50.0 (20)	37.1 (23)	0.198
Dysgeusia	65.0 (26)	64.5 (40)	0.960
Anosmia	65.0 (26)	59.7 (37)	0.589
Hyporexia	**60.0 (24)**	**32.3 (20)**	**0.006**
Diarrhea	35.0 (14)	30.6 (19)	0.646
Abdominal pain	35.0 (14)	19.4 (12)	0.077
Nausea/vomiting	**35.0 (14)**	**17.7 (11)**	**0.048**
Respiratory system			
Dry cough	75.0 (30)	74.2 (46)	0.927
Productive cough	27.5 (11)	12.9 (8)	0.065
Dyspnea	40.0 (16)	29.0 (18)	0.251
Sneeze/runny nose	57.5 (23)	46.8 (29)	0.290
Nervous system			
Headache	72.5 (29)	87.1 (54)	0.065
Dizziness	37.8 (14)	19.4 (12)	0.077
Mental confusion	**7.5 (3)**	**0 (0)**	**0.029**
Others			
Fever	65.0 (26)	50.0 (31)	0.136
Skin lesions	7.5 (3)	11.4 (7)	0.530
WHO Clinical Progression Scale			
Ambulatory mild disease	91.9 (37)	100 (62)	0.050
Moderate disease	2.7 (1)	0 (0)	0.374
Severe disease	5.4 (2)	0 (0)	0.050
Clinical evolution and outcome			
Hospitalization	10.0 (4)	4.8 (3)	0.271
Oxygen therapy high flow	7.5 (3)	0 (0)	0.050
Intensive care unit admission	7.5 (3)	0 (0)	0.050
Mechanical ventilation	5.0 (2)	0 (0)	0.146
Death	5.0 (2)	0 (0)	0.137

[a] Fisher's Exact Test. Source: Authors.

Patients infected with the new variants presented a higher frequency of symptoms associated with the central nervous system. The symptom of dizziness was observed in 37.8% of patients infected with variants versus 19.4% in the control group, although not statistically significant (p = 0.077). However, mental confusion was only identified in patients infected with variants, as compared to the control group (7.5 vs 0, p = 0.029). The variant group had also higher frequency of arthralgia (47.5

vs 24.2%, p = 0.015), hyporexia (60 vs 32.3%, p = 0.006), Nausea/vomiting (35 vs 17.7%, p = 0.048). Although not statistically significant, the variant group also presented higher frequency of important respiratory symptoms, such as productive cough (27.5 vs 12.9%, p = 0.065). There were no asymptomatic cases in this study.

Clinical outcomes, according to the WHO Clinical Progression Scale criteria, it was observed moderate to severe cases only in the group of patients infected with the variants, including the two deaths identified in the study. Seven cases of hospitalization were identified in the studied patients, four (10%) in the variant group and three (4.8%) in the control group. However, these 3 patients from the control group that were hospitalized were classified as mild disease but were hospitalized to perform exams due to comorbidities. From these, only three of the case group (7.5%) evolved to high-flow oxygen therapy and admission to the Intensive Care Unit, and 2 (5.0%) evolved to mechanical ventilation and death. These 2 deceased patients had obesity and dyslipidemia in common.

The frequency of the SARS-CoV-2 variants found by the viral genome sequencing was analyzed and some of the major symptoms presented by the patients, according to the virus variant is shown in Table 2. Higher frequency of the P.1 variant was observed, representing more than half of the virus samples analyzed (52.5%). When the main clinical manifestations were analyzed, according to the type of variant, the patients infected with the P.1 variant presented a higher frequency of hyporexia, nausea/vomiting and arthralgia. The symptom of mental confusion was not present in patients infected by the P.1 variant, but it was more frequent in variant P.2.

Table 2. Frequency of clinical manifestations, evolution and outcome observed in the group infected with variants

Clinical manifestations, evolution, and outcome	P.1 (Gamma) N=21 (52.5%)	P.2 (Zetta) N = 7 (17.5%)	B.1.617.2 (Delta) N = 3 (7.5%)	Other variants N = 9 (22.5%)	p value[a]
Arthralgia, % (n)	27.5 (11)	5.0 (2)	0 (0)	15.0 (6)	0.015
Hyporexia, % (n)	30.0 (12)	12.5 (5)	5.0 (2)	12.5 (5)	0.006
Nausea/vomiting, % (n)	15.0 (6)	7.5 (3)	5.0 (2)	7.5 (3)	0.048
Mental confusion, % (n)	0 (0)	5.0 (2)	0 (0)	2.5 (1)	0.029
Oxygen therapy high flow	5.0 (2)	0 (0)	0 (0)	2.5 (1)	0.795
Intensive care unit admission	5.0 (2)	0 (0)	0 (0)	2.5 (1)	0.795
Mechanical ventilation	5.0 (2)	0 (0)	0 (0)	0 (0)	0.928
Death	5.0 (2)	0 (0)	0 (0)	0 (0)	0.928

[a] Fisher's Exact Test. Source: Authors.

4. Discussion

The present study reports the clinical-epidemiological profile of 40 patients infected with SARS-CoV-2 variants, comparing the clinical course and outcome of these cases with a control group of 62 patients infected previously to the variants emerged. Our analyzes found similar epidemiological profiles in the control and in the case group. Both groups have a higher frequency of women, and a similar average of age. The prevalence of health professionals in the control group may be related to the fact that they were more exposed at the beginning of the pandemic. The frequency of comorbidities is like what it is expected in the general population, portraying no selection bias, and no differences were observed in respect to comorbidities between the groups. It was found a lower frequency of obesity than in the last census, when an average of 40% of obese adults was detected (Ministério da Saúde, 2020). This factor can have an impact on the analysis of outcomes, since it is known to be a group with greater aggravation and higher mortality, that may overcome the virus variant aspect itself (Graham et al., 2021).

The greater infectivity of one variant in relation to another may be connected to the ability of the virus to escape from the immune system, which can also cause a change in clinical presentation. But it is still unclear how is the impact of such

differences in the viral behavior, pathophysiology, and the mortality, in relation to the original genome (Tao et al., 2021). The study of clinical presentation and outcome is essential as a strategy to investigate the capacity of variants to escape acquired immunity and the possible response of discovered vaccines (Hemmer et al., 2021).

No evidence of an association between variant infection and the total number of symptoms reported by patients was found, as well as no relationship between differences in disease duration. This pattern was also evidenced in other studies in the literature (Graham et al., 2021; Tao et al., 2021). In the case group, it was observed more atypical manifestations compared to those reported in the first cases of Wuhan, such as abdominal pain, arthralgia, hyporexia and mental confusion, which may suggest virus adaptations to human being and infect of new cell groups, causing new clinical manifestations (Hemmer et al., 2021). A meta-analysis study with reports from different countries found neurological manifestations of COVID in 73% of hospitalized patients (Correia et al., 2020). Dizziness and mental confusion were symptoms reported in all of them (Espíndola et al., 2020). In our study, mental confusion was a symptom reported only in the variant group, even with a lower number of patients.

Regarding to clinical evolution and outcome, it is noteworthy that in both groups we found a hospitalization rate, although the hospitalization of the control group was not related to COVID-19 severity, since they were all classified as mild disease, and moderate to severe cases were present only in the case group. The need of oxygen and a lethality rate were observed only in the patients infected by the variants. However, these numbers were below the national (Lamarca et al., 2021) and international average for COVID-19 (Graham et al., 2021), which may be connected to the access and quality of the healthcare provided to the patients from this study, who were monitored daily by phone.

Studies in other countries have shown the association of infection by variants with an increased risk of mortality (Aleem et al., 2021). However, in Brazil, this association was not evidenced (Naveca et al., 2021). Although there were no significant differences in comorbidities or demographic data between the groups in the present study, maybe because of the low number of patients included, it is not possible to define the role of the variants itself in the induction of the most severe cases, including in the deaths. Both deaths reported in this study, occurred in patients with severe obesity and dyslipidemia.

The study of the genetics of SARS-CoV-2 brings a look at the capacity of each variant to become dominant through adaptations (Maury et al., 2021). The number of analyzed cases are still limited due to the few virus samples isolated that are submitted to genomic analysis. However, efforts to make correlation of genomics with the analysis of clinical data can provide subsidies for the study of the behavior of new viruses and guide treatments and vaccine efficacy (Chakraborty et al., 2021). Moreover, genomic data available are necessary to better comprehension of pandemic, but data accuracy is also important (Abbud & Castilho, 2022).

5. Conclusion

Therefore, this study reports differences between the clinical course and outcome of patients infected with SARS-CoV-2 variants compared to patients infected with the original strain. Some symptoms were predominant in patients infected by variants, as arthralgia, hyperoxia, nausea/vomiting and mental confusion. There was no significant difference in comorbidities or demographic data between the groups. These results, besides their limitation, contributes to better comprehension of viral behavior and disease management.

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