










Identification of genomic variants of the SARS-CoV-2 Virus in patients admitted to a reference hospital in Curitiba/PR and the relationship with the clinical condition

Identificação de variantes genômicas do vírus SARS-CoV-2 em pacientes internados em um hospital de referência de Curitiba/PR e a relação com o quadro clínico

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ABSTRACT

Introduction: The coronavirus disease (COVID-19) has a variable clinical picture, ranging from patients with mild and nonspecific symptoms to severe symptoms such as respiratory distress syndrome and death. **Objectives:** To identify the genetic variant of the SARS-CoV-2 virus in patients with COVID-19 who were hospitalized at the Hospital *Universitário Evangélico Mackenzie* (HUEM), and to correlate the viral genetic variant and the presented symptoms with the development of the patient's clinical condition. **Methods:** A cross-sectional prospective study was performed with nasal swab samples from 219 SARS-CoV-2 positive patients. The patients were over 18 years old and were admitted to the HUEM between November 2021 and June 2022 for virus genotyping and analysis of medical records. **Results:** Of the 219 study participants, 66% had the delta variant and 33% had the omicron variant. The data obtained from deaths did not show significant relevance among the analyzed variables. The mean age was 61 years old, and the omicron variant affected older patients (65.5 years). The most prevalent comorbidities were SAH and DM in both genders, and the most relevant symptom was cough, which was observed mainly in those infected with the delta variant. Among the prognostic predictors, ground glass opacity on chest computed tomography was significantly more present in infections with delta variant. **Conclusion:** Delta variant affects the respiratory system more than omicron. In addition, despite of being collected in a similar time interval, the delta variant represented twice as many cases, which could demonstrate the effectiveness of the vaccine.

Keywords: COVID-19; SARS-CoV-2; Polymerase chain reaction.

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RESUMO

Introdução: A doença do coronavírus (COVID-19) apresenta um quadro clínico variável, indo desde sintomas leves e inespecíficos até sintomas graves como síndrome do desconforto respiratório e óbito. **Objetivos:** Identificar a variante genética do vírus SARS-CoV-2 em pacientes com COVID-19 internados no Hospital Universitário Evangélico Mackenzie (HUEM), e correlacionar a variante genética viral e os sintomas apresentados com o desenvolvimento da doença a condição clínica do paciente. **Métodos:** Foi realizado um estudo prospectivo transversal com amostras de swab nasal de 219 pacientes positivos para SARS-CoV-2. Os pacientes eram maiores de 18 anos e foram internados no HUEM entre novembro de 2021 e junho de 2022 para genotipagem viral e análise de prontuários. **Resultados:** Dos 219 participantes do estudo, 66% tinham a variante delta e 33% tinham a variante omicron. Os dados obtidos dos óbitos não apresentaram relevância significativa entre as variáveis analisadas. A média de idade foi de 61 anos, e a variante ômicron afetou pacientes mais velhos (65,5 anos). As comorbidades mais prevalentes foram HAS e DM em ambos os sexos, e o sintoma mais relevante foi a tosse, observada principalmente nos infectados pela variante delta. Entre os preditores prognósticos, a opacidade em vidro fosco na tomografia computadorizada de tórax foi significativamente mais presente nas infecções pela variante delta. **Conclusão:** A variante delta afeta mais o sistema respiratório do que o ômicron. Além disso, apesar de ter sido coletada em intervalo de tempo semelhante, a variante delta representou o dobro de casos, o que pode demonstrar a eficácia da vacina.

Palavras-chave: COVID-19; SARS-CoV-2; Reação em cadeia da polimerase.

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INTRODUCTION

A major challenge for global public health is the emerging of infectious diseases¹. In this context, a new type of coronavirus was identified in 2019, in Wuhan, China, causing severe acute respiratory syndrome, for which it became known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus demonstrated a high prevalence of infections and dissemination, culminating in the coronavirus (COVID-19) pandemic. COVID-19 had killed more than 666,000 Brazilians by May 2022, presenting as asymptomatic, with mild symptoms or with severe symptoms².

SARS-CoV-2 are enveloped viruses of the *Coronoviridae* family that have a crown of glycoprotein spikes external to the envelope for direct interaction with host cells. It is transmitted by droplets suspended in the air, by interpersonal contact and by contaminated objects and surfaces, with an incubation period that can vary from 1 to 14 days and transmissibility of up to 7 days after the appearance of

the first symptoms. The virus can even be transmitted by asymptomatic patients³.

The clinical condition is extremely variable, ranging from asymptomatic patients to mild and nonspecific flu symptoms, to fever, cough, sore throat, runny nose, anosmia, ageusia, diarrhea, abdominal pain, myalgia, fatigue and headache, to patients with severe symptoms that may progress to Acute Respiratory Distress Syndrome (ARDS) in which there is worsening of dyspnea, persistent pressure in the chest or oxygen saturation lower than 95% in room air, central cyanosis, and which may lead to death⁴.

This study aims to identify the genetic variant of the SARS-Cov-2 virus in patients with COVID-19 who were admitted to Hospital Universitário Evangélico Mackenzie (HUEM), in addition to correlate the detected genetic variant of the virus with different parameters: the development of the patient's clinical condition, the frequency of patients deaths, the frequency of the most common symptoms, and also patient's prognosis.

METHODS

This project was approved by the Ethics Committee and Research with Human Beings of *Faculdade Evangélica Mackenzie do Paraná* (CEP-FEMPAR) under reference n°. 5,021,398 (CAAE 46951921.4.0000.0103).

A cross-sectional prospective study was performed involving 219 COVID-19 positive individuals who were admitted to *Hospital Universitário Evangélico Mackenzie* (HUEM) from June 2021 to June 2022. All patients were over 18 years old.

Sample collection was performed using nasal swabs from patients who were positive for SARS-CoV-2, admitted to the HUEM between November 2021 and June 2022, for virus genotyping. Patients hospitalized before November 2021 were not genotyped, and thus an estimate of positive cases was performed, according to the work by Adamoski et al. (2022)⁵ who estimated the prevalence of viral variants by period of time (years 2020, 2021 and 2022) (Graph 1).

The collected nasal swab sample was stored in 15ml tubes containing 2ml of saline solution, being duly identified and transported in packaging at -20°C to the UFPR Human Cytogenetics and Oncogenetics laboratory, where the viral material was extracted and amplified by RT-PCR.

Total RNA was extracted using the RNA and viral DNA kit (MVXA-P096FAST) in an automatic nucleic acid extractor (Extracta 32, Loccus Biotecnologia, Brazil), using magnetic beads. The samples were then tested to confirm the presence of SARS-CoV-2 genetic material using the BIOMOL OneStep/COVID-19 KIT (IBMP, Curitiba, Brazil).

All confirmed positive samples were genotyped using the multiplex approach of Vogels et al. (2020)⁵ to detect Spike Δ69-70 and ORF1a Δ3675-3677 deletions in order to distinguish Alpha, Beta/Gamma, wild-type/Delta or Omicron (Ba.1, Ba.2 or Ba.4/Ba.5) variants. Assays were performed using the GoTaq Probe 1-Step RT-qPCR System (Promega) on a 7500 Fast or QuantStudio5 real-time

thermal cycler (ThermoFisher Scientific Inc., USA), as described by Adamoski et al. (2022)⁶.

Subsequently, the analysis of electronic medical records was performed to collect data such as age, gender, smoking or alcoholism, comorbidities, symptoms during hospitalization, imaging tests, vaccination and worsening of the condition during hospitalization regarding the need for orotracheal intubation and length of hospitalization, and data available in the HMED-HUEM, SIVESP-PR and “*Saúde Já Curitiba*” systems. These data were used for statistical tests.

Data analysis was performed using descriptive statistics with contingency tables and percentages for qualitative variables, and using calculation of mean, median and standard deviation for quantitative variables. In addition, the chi-square, Student’s t and Mann-Whitney U tests were performed to verify significant differences, which demonstrated significance when presenting results below 0.05.

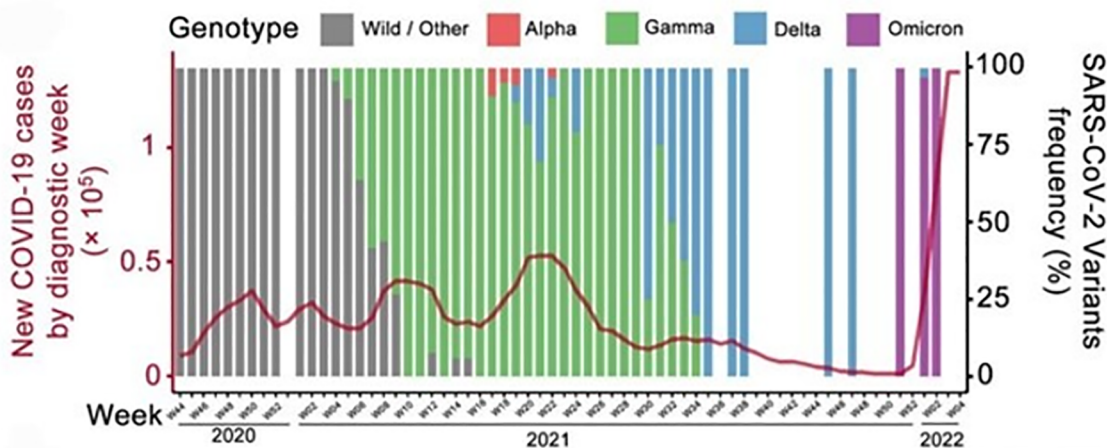
RESULTS

Of the 219 patients who participated in the study, 47% were women and 53% were men.

Of the 219 patients, 66% had the delta variant, 33% omicron and 1% had inconclusive results (Table 1). However, there was no significant difference in the number of hospitalized patients infected with delta and omicron variants ($p=0.313$).

When the sex of infected individuals was analyzed, there was no significant difference between the number of men and women with each type of variant ($p=0.471$).

Table 1 also shows that the mean age of hospitalized patients was 61 years old for both sexes. Still regarding the age of hospitalized patients infected by one of the genetic variants of the virus, there was a significant difference in involvement between ages ($p=0.004$). The omicron variant affected people with a higher mean age (65.5 years), while



Graph 1. Prevalence of viral variants by period of time. Source: Adamoski et al. (2022)⁵

Table 1. Number of cases per variant and average age between sexes and between variants.

| | | CASES | | |
|---------------------------|--------------|-------|-------|---------|
| | Delta | | | 145 |
| | Omicrom | | | 72 |
| | Inconclusive | | | 2 |
| | TOTAL | | | 219 |
| | Female | Male | Delta | Omicron |
| Mean of age | 61.2 | 61.1 | 58.9 | 65.5 |
| Standard deviation of age | 18.3 | 17.1 | 17.3 | 17.4 |

Source: Elaborated by author (2022).

the delta variant affected people with a mean age of 58.9 years.

Regarding mortality, of the 219 patients studied, 77 died, 53 were infected with the delta variant and 24 with the omicron variant, but there was no significant difference between the number of deaths comparing the two variants ($p=0.640$). Of the 77 patients who died, 16 were unvaccinated individuals, that is, almost 21%. Although no significant difference was observed regarding deaths between vaccinated and unvaccinated patients ($p=0.447$).

When comparing the vaccine status with percentage of deaths for each variant, it was observed that deaths were higher among vaccinated individuals infected with the delta variant (39%), while the unvaccinated had a percentage of deaths of 29%. Vaccinated individuals infected with the omicron variant had a percentage of deaths of 32%, while non-vaccinated individuals who died represented 40%. However, when comparing the number of deaths in vaccinated and unvaccinated individuals for each variant, no significant difference was observed ($p=0.549$).

Of the 77 individuals who died, 17 were smokers, but this aspect also showed no significant difference when comparing the number of deaths between smoker and non-smoker patients ($p=0.275$).

When the sex was compared with the number of deaths, no correlation was observed, therefore, there was

no significant difference on the number of deaths between females and males ($p=0.202$).

When analyzing the presence of comorbidities in hospitalized patients, among women there was a prevalence of SAH (Systemic arterial hypertension) followed by DM (Diabetes Mellitus) and vascular disease. In men SAH was also the most frequent comorbidity, followed by DM and kidney disease.

Another comorbidity analyzed was obesity, where a significant difference was observed between men and women, being present in 19% of women and in only 5% of men. A higher number of women with hypothyroidism and cardiovascular disease was also observed, with hypothyroidism present in 17% of women and only 4% of men and cardiovascular disease in 14% of women and 5% of men.

On the other hand, kidney disease was significantly more prevalent in men (23%) than in women (12%) (Table 2).

As for the symptoms presented by the patients at the time of admission, there was no significant difference between infections by the two variants.

When analyzing the 14 symptoms reported by the patients, only cough was significantly more prevalent in the delta variant in relation to the omicron variant, as shown in Table 3 ($p=0.038$).

One of the aspects that lead to the worsening of the clinical condition is pulmonary involvement, especially

Table 2. Number of individuals by comorbidity.

| | FEMALE | MALE | %F | %M | <i>p</i> |
|---------------------|--------|------|-----|-----|----------|
| SAH | 54 | 55 | 53% | 47% | 0.311 |
| Diabetes mellitus | 32 | 31 | 32% | 26% | 0.377 |
| Obesity | 19 | 6 | 19% | 5% | 0.001* |
| Respiratory disease | 18 | 14 | 18% | 12% | 0.213 |
| Renal disease | 12 | 27 | 12% | 23% | 0.033* |
| Hypothyroidism | 17 | 5 | 17% | 4% | 0.002* |
| Cardiac disease | 14 | 6 | 14% | 5% | 0.024* |
| Vascular disease | 20 | 20 | 20% | 17% | 0.649 |

Legend: * Significant difference – p less than 0.05.

Source: Elaborated by author (2022).

the presentation of ground-glass opacities observed on chest tomography. Regarding this finding, patients infected with the delta variant had a higher prevalence compared to those infected with the omicron variant, with a significant difference ($p=0.001$), as can be seen in Table 4.

However, no significant difference was noted regarding the presence of ground glass opacity on chest tomography between genders ($p=0.718$).

When the presence of ground glass opacity was compared with vaccination, there was no significant difference between vaccinated and unvaccinated patients who presented this characteristic ($p=0.254$), nor between vaccinated and unvaccinated patients of each variant who presented it ($p=0,072$). There was no statistical significance between ground glass opacity and the presence of comorbidities (Table 4).

One of the predictive aspects of prognosis is the hospitalization period, which can be evaluated according to the number of days the patient was hospitalized. The difference in the hospitalization period of patients between the two variants was not significant ($p=0.468$).

In addition, the number of deaths according to the hospitalization period for each variant also did not show significant difference ($p=0.915$).

Another predictor of prognosis is the need for Orotracheal Intubation (OTI) during hospitalization. The present study did not find a significant difference between the need for OTI in hospitalized patients infected with the delta variant and the omicron variant ($p=0.254$).

DISCUSSION

Although Nyberg et al. (2022)⁷ showed in their study that the omicron variant leads to a milder infectious condition when compared to the delta variant, the present study did not show significant difference between the length of hospital stay and the need for orotracheal intubation, two factors that suggest severity, between patients infected by both variants. However, when analyzing pulmonary involvement among hospitalized individuals, the presentation of ground-glass opacities observed on chest tomography was more frequent in those infected with the delta variant, corroborating data presented in the literature^{2,8-13}.

When analyzing the symptoms presented at the time of hospitalization, the results show that there was a significant difference only for cough in infections with delta variant, contrasting with the study by Cepeda et al. (2022)¹⁴, which highlights cough and loss of smell as less prevalent symptoms in delta variant infections, while the most frequent would be headache, sore throat, nasal discharge and fever. Still according to the authors, the most frequent symptoms of omicron variant infection are chills, myalgia, fever, cough, odynophagia, headache and tachycardia, while in the present study they were dyspnea, cough, asthenia and fever.

An interesting and alarming data that showed significant relevance in the present study was obesity among women. Studies indicate that the association of obesity with other diseases, such as infection by SARS-CoV-2 virus, is a risk factor for an unfavorable outcome¹⁵, and the association

Table 3. Number of patients per present symptoms.

| Symptoms | Delta | Omicron | %Delta | %Omicron | <i>p</i> |
|----------------------|-------|---------|--------|----------|----------|
| Nausea | 11 | 5 | 7.6% | 6.9% | 0.864 |
| Vomiting | 14 | 4 | 9.7% | 5.6% | 0.302 |
| Diarrhea | 16 | 4 | 11.0% | 5.6% | 0.188 |
| Abdominal pain | 10 | 3 | 6.9% | 4.2% | 0.424 |
| Asthenia/paresthesia | 27 | 16 | 18.6% | 22.2% | 0.530 |
| Dyspnea | 63 | 24 | 43.4% | 33.3% | 0.152 |
| Desaturation | 36 | 13 | 24.8% | 18.1% | 0.261 |
| Cough | 59 | 19 | 40.7% | 26.4% | 0.038* |
| Fever | 40 | 14 | 27.6% | 19.4% | 0.191 |
| Headache | 16 | 8 | 11.0% | 11.1% | 0.986 |
| Runny nose | 8 | 7 | 5.5% | 9.7% | 0.250 |
| Myalgia | 27 | 10 | 18.6% | 13.9% | 0.382 |
| Confusion | 9 | 5 | 6.2% | 6.9% | 0.835 |
| Tachypnea | 7 | 3 | 4.8% | 4.2% | 0.826 |

Legend: * Significant difference – *p* less than 0.05.

Source: Elaborated by author (2022).

Table 4. Prevalence of the ground-glass opacity appearance on chest tomography by variant and its relationship with comorbidities.

| GROUND-GLASS OPACITY | DELTA | OMICRON | %DELTA | %OMICRON |
|----------------------|-------|---------|--------|----------|
| No | 73 | 51 | 50% | 74% |
| Yes | 72 | 18 | 50% | 26% |
| Total | 145 | 69 | | |

| GROUND-GLASS OPACITY | | | | | | |
|----------------------|----|-----|-----|------|----------|--|
| Comorbidity | No | Yes | %No | %Yes | <i>p</i> | |
| SAH | 62 | 40 | 50% | 44% | 0.411 | |
| DM | 37 | 23 | 30% | 25% | 0.483 | |
| Obesity | 11 | 10 | 9% | 11% | 0.591 | |
| Hypothyroidism | 12 | 10 | 10% | 11% | 0.738 | |
| Renal disease | 9 | 11 | 7% | 12% | 0.221 | |
| Respiratory disease | 15 | 13 | 12% | 14% | 0.621 | |
| Cardiac disease | 11 | 7 | 9% | 8% | 0.771 | |
| Vascular disease | 16 | 5 | 13% | 5% | 0.073 | |
| Other | 19 | 11 | 15% | 12% | 0.513 | |
| No comorbidity | 21 | 17 | 17% | 19% | 0.719 | |

Source: Elaborated by author (2022).

of obesity with other comorbidities increases the risk of lethality, hospitalization and confirmed pneumonia, according to Gonçalves et al. (2022)¹⁶, although the gender at greatest risk, according to the study, was male.

Like other studies^{7,9}, this research shows a prevalence of SAH and DM for both genders¹⁷ and, corroborating the study by Colnago et al. (2022)¹⁷, there was a predominance of elderly people infected with the omicron variant, which may be related to the reduction of social isolation measures that occurred, mainly, due to the advance of vaccination in this period.

The present study did not find significant difference in terms of hospitalization period between patients infected by the two variants, which contradicts the study by Peralta-Santos et al. (2022)¹⁸, who reported that the omicron variant was associated with a shorter hospitalization period as well as a lower risk of hospitalization.

In addition, the most common comorbidities in hospitalized patients were SAH and DM in both sexes, which allows us to infer that it is necessary to observe these populations, prioritizing them in prevention and health promotion campaigns. One should also pay attention to the occurrence of obesity, since this comorbidity has increased significantly, becoming a public health problem nowadays, being a risk factor both for other diseases and for the bad outcome in cases of hospitalization and need for intensive care in patients with SARS-CoV-2.

Although data from the present study were collected at similar time intervals, the number of hospitalized patients infected by the delta variant (n=145) was more than twice the number of patients infected by omicron variant (n=72). This may represent an important vaccination factor in reducing cases of COVID-19, since during the collection period in which patients had the omicron variant, many people were

already vaccinated with more doses of the vaccine, which could demonstrate its effectiveness in combating the pandemic.

Among the 219 patients analyzed, 66% had the delta variant, 33% had the omicron variant and 1% had an inconclusive result, with no significant difference in the number of hospitalized patients who were infected with the delta and omicron variants.

Regarding the clinical status, patients infected with the delta variant had a higher prevalence of ground glass opacity when compared to those infected with the omicron variant, which corroborates data in the literature on a worse prognosis for delta variant infection.

Regarding mortality, 77 of the total number of patients died, 53 infected with the delta variant and 24 with the omicron variant. However, there was no significant difference between the number of deaths comparing the two variants, which may demonstrate an insignificance in the relationship between mortality and variant.

Furthermore, among the reported symptoms, only 1 of the 14 was significantly more prevalent in patients with the delta variant, contrary to what other publications say.

Finally, the two main predictors of prognosis analyzed were hospitalization period and need for OTI. When comparing the results of the two variants, both predictors showed insignificant differences, with hospitalization period and need for OTI.

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AUTHORS' CONTRIBUTION

We describe contributions to the papers using the taxonomy (CRediT) provide above. Maria Cecilia Neves Estephani and Laura Dos Anjos Bastos: Study design, Data acquisition and interpretation, Manuscript writing and revision - Naiara Bozza Pegoraro: Manuscript writing and revision - Eduardo Bolicenha Simm: Data acquisition and interpretation, Data analysis, Final version approval - João Otavio Ribas Zahdi, Maria Regina Pinheiro de Andrade Tizzot and Jaqueline Carvalho de Oliveira: Data acquisition and interpretation, Manuscript review, Approval of the final version - Camila Nemetz Kohler: Writing and revision of the manuscript, Approval of the final version - Liya Regina Mikami: Study design, Proposal of the study, Writing and revision of the manuscript, Approval of the final version.

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