FRANCISCO TOMAZ MENESES DE OLIVEIRA

PERFIL DE PACIENTES COM COVID-19 E DOENÇA CEREBROVASCULAR EM UM CENTRO DE REFERÊNCIA DE NEUROLOGIA EM SÃO PAULO, BRASIL.

Tese apresentada ao Curso de Pós-graduação da Faculdade de Ciências Médicas da Santa Casa de São Paulo para obtenção do Título de **Doutor** em **Ciências da Saúde**.

SÃO PAULO
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Área de Concentração: **Ciências da Saúde**

Orientador: **Rubens José Gagliardi**

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1. Acidente vascular cerebral 2. Isquemia cerebral 3. AVC isquêmico 4. AVC hemorrágico 5. COVID-19

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DEDICATÓRIA

A Deus, por me proporcionar o sobrenatural.
À minha família, exemplos de amor e carinho.

Aos meus mestres Dr. Sanvito, Dr. Rubens, Dr. Augusto, Dr. Sidney,
através dos seus ensinamentos consegui ver a neurologia e o mundo com olhos mais vivos,
vibrantes, e por sempre me encorajarem nos momentos mais desafiadores.

Ao Hospital e à Faculdade da Santa Casa de São Paulo,
por serem meu mundo nos últimos 15 anos,
onde descubro o nosso mundo todo dia, outra vez.

Aos meus amigos, que me ensinaram o que é a lealdade,
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que tanto nos desafiam e emocionam, o verdadeiro significado da vocação.
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Aos pacientes, razão maior deste estudo.

EPÍGRAFE

“Obrigado” — Carlos Drummond de Andrade

Clara manhã, obrigado.
O essencial é viver.
Viver, e ver, e crer,
e, de repente,
saber que o mundo
não é só meu,
mas de todos,
e que a vida
é um presente
sem preço,
e que a gente,
só de existir,
já faz sentido.
Obrigado a quem?
A tudo, a todos.
Ao sol, ao vento,
ao mar, à flor,
ao pão, ao trabalho,
ao amigo, ao inimigo,
ao que foi, ao que é,
ao que virá.
O essencial
é ser grato.
A gratidão
dá sentido ao passado,
traz paz ao presente,
cria visão para o futuro.
Simplesmente, obrigado.

ABREVIATURAS

ACE2 – *Angiotensin-Converting Enzyme 2* (Enzima Conversora de Angiotensina 2)

ADC – *Apparent Diffusion Coefficient* (Coeficiente Aparente de Difusão)

ALS – *Acute Lung Syndrome* (Síndrome Pulmonar Aguda)

AM – Amazonas

AVC – Acidente Vascular Cerebral

AVCH – Acidente Vascular Cerebral Hemorrágico

AVCI – Acidente Vascular Cerebral Isquêmico

BMC – *BioMed Central*

CEP – Comitê de Ética em Pesquisa

CK – *Creatine Kinase* (Creatinoquinase)

COVID-19 – *Coronavirus Disease 2019*

CRP – *C-Reactive Protein* (Proteína C Reativa)

CT – *Computed Tomography* (Tomografia Computadorizada)

CVT – *Cerebral Venous Thrombosis* (Trombose Venosa Cerebral)

DNA – *Deoxyribonucleic Acid* (Ácido Desoxirribonucleico)

DWI – *Diffusion-Weighted Imaging* (Imagem Ponderada em Difusão)

ECA2 – Enzima Conversora de Angiotensina 2

EEG – Eletroencefalograma

ELISA – *Enzyme-Linked Immunosorbent Assay* (Ensaio Imunoenzimático)

EM – Esclerose Múltipla

FLAIR – *Fluid-Attenuated Inversion Recovery* (Sequência de RM com Supressão de Líquor)

Gd – Gadolínio

HE – *Hemagglutinin Esterase* (Hemoaglutinina Esterase)

HIV – *Human Immunodeficiency Virus* (Vírus da Imunodeficiência Humana)

IC – Intervalo de Confiança

ICU – *Intensive Care Unit* (Unidade de Terapia Intensiva)

IgG – Imunoglobulina G

IgM – Imunoglobulina M

IQR – *Interquartile Range* (Intervalo Interquartil)

LDH – *Lactate Dehydrogenase* (Desidrogenase Lática)

LCR – Líquido Cefalorraquidiano

MERS-CoV – *Middle East Respiratory Syndrome Coronavirus*

MRI – *Magnetic Resonance Imaging* (Ressonância Magnética)

OMS – Organização Mundial da Saúde

PCR – *Polymerase Chain Reaction* (Reação em Cadeia da Polimerase)

PCT – *Procalcitonin* (Procalcitonina)

RM – Ressonância Magnética

RNA – *Ribonucleic Acid* (Ácido Ribonucleico)

RT-PCR – *Reverse Transcriptase Polymerase Chain Reaction* (Reação em Cadeia da Polimerase por Transcriptase Reversa)

SARS – *Severe Acute Respiratory Syndrome* (Síndrome Respiratória Aguda Grave)

SARS-CoV – *Severe Acute Respiratory Syndrome Coronavirus*

SARS-CoV-2 – *Severe Acute Respiratory Syndrome Coronavirus 2*

SNC – Sistema Nervoso Central

SNP – Sistema Nervoso Periférico

SPSS – *Statistical Package for the Social Sciences*

SWI – *Susceptibility Weighted Imaging* (Imagem Ponderada por Suscetibilidade)

TC – Tomografia Computadorizada

TCLE – Termo de Consentimento Livre e Esclarecido

UTI – Unidade de Terapia Intensiva

WHO – *World Health Organization* (Organização Mundial da Saúde)

SUMÁRIO

1. INTRODUÇÃO

1.1. SARS-CoV-2

Os coronavírus são vírus integrantes da ordem *Nidovirales*, família *Coronaviridae*, subfamília *Coronavirinae*, divididos em três gêneros: *Alphacoronavírus*, *Betacoronavírus* e *Gammacoronavírus* (1). Seu nome deriva de sua aparência morfológica observada por microscopia eletrônica, devido ao fato de ser envolto por um halo de espículas semelhante a uma coroa solar (2).

Este vírus tem o genoma composto por um RNA de fita simples e polaridade positiva, envolto por um envelope formado por três proteínas principais: a proteína de envelope (E), a hemoaglutinina esterase (HE) e a proteína de espícula (S). A proteína S é responsável não só pelas espículas características dos coronavírus, como também pelo reconhecimento de receptores ACE-2 (3,4).

Em dezembro de 2019, na cidade de Wuhan, na China, foi observado o surgimento de um novo vírus da família *Coronaviridae*, altamente patogênico. Esse vírus se espalhou rapidamente pelo mundo, causando uma doença aguda caracterizada por pneumonia potencialmente letal e sintomas clínicos semelhantes aos relatados na síndrome respiratória aguda grave (SARS-CoV) e na síndrome respiratória do Oriente Médio (MERS-CoV) (5,6). A doença foi nomeada pela Organização Mundial da Saúde como COVID-19, e o novo vírus denominado SARS-CoV-2, devido à sua homologia com o SARS-CoV e provável ação sobre o mesmo receptor celular (7,8).

1.2. COVID-19

Os coronavírus são vírus de RNA que, normalmente, causam infecções entéricas e respiratórias. O tropismo viral depende da distribuição tecidual dos receptores nos hospedeiros. A entrada do SARS-CoV na célula humana é mediada pela enzima conversora de angiotensina 2 (ECA2), expressa no epitélio das vias aéreas, parênquima pulmonar, endotélio vascular, células renais e intestino delgado (6,9).

O cérebro também expressa receptores ECA2 em neurônios e células da glia, tornando-o um alvo potencial da COVID-19 (10). Assim como o SARS-CoV, o SARS-CoV-2 utiliza a proteína de pico S1 para interagir com o receptor ECA2, apresentando afinidade de ligação de 10 a 20 vezes superior à do SARS-CoV (8,11).

O neurotropismo é uma característica reconhecida dos coronavírus. O envolvimento cerebral pode ocorrer por disseminação hematogênica ou via olfatória através da placa cribriforme, nas fases iniciais ou tardias da infecção (12). Na microcirculação, a proteína de

pico interage com ECA2 no endotélio capilar, e rupturas endoteliais podem levar a hemorragias cerebrais e consequências fatais (13,14).

1.3. Manifestações neurológicas associadas à COVID-19

Em um estudo com 214 pacientes em Wuhan, China, manifestações neurológicas ocorreram em 36,4% dos infectados (15). As manifestações foram classificadas em três grupos:

- Envolvimento do sistema nervoso central (tontura, cefaleia, alteração de consciência, crise convulsiva, AVC agudo, ataxia);
- Envolvimento do sistema nervoso periférico (anosmia, ageusia, distúrbios visuais, neuralgias);
- Lesão muscular esquelética.

Os sintomas neurológicos foram mais prevalentes em casos graves, com destaque para tontura (16,8%) e cefaleia (13,1%) (15). Outros estudos apontam manifestações como encefalopatia necrosante hemorrágica, meningoencefalite, síndrome de Guillain-Barré e síndrome de Miller Fisher (16–18).

O envolvimento do tronco cerebral, descrito em autópsias e modelos experimentais, sugere possível relação com insuficiência respiratória central (19,20).

1.4. Doenças cerebrovasculares e COVID-19

A pandemia de COVID-19 impôs carga sem precedentes aos sistemas de saúde (21). Estudos indicam associação entre infecção por SARS-CoV-2 e aumento da incidência de doenças cerebrovasculares, inclusive em pacientes jovens e previamente hígidos (22–24).

Acredita-se que o vírus possa induzir disfunção endotelial e estado pró-trombótico, favorecendo AVCs isquêmicos e hemorrágicos (25–27). Comorbidades como hipertensão arterial sistêmica, diabetes mellitus e dislipidemia agravam o risco e o prognóstico (28,29).

Diante da relevância epidemiológica e da alta morbimortalidade das complicações neurológicas da COVID-19, é essencial compreender o perfil dos pacientes acometidos, visando estratégias preventivas e terapêuticas mais eficazes (30).

2. OBJETIVOS

2.1. Objetivo Geral

Avaliar e caracterizar o perfil clínico, epidemiológico, laboratorial e radiológico de pacientes com diagnóstico de doença cerebrovascular associada à infecção pelo SARS-CoV-2, atendidos em um hospital terciário de referência em neurologia na cidade de São Paulo, Brasil.

2.2. Objetivos Específicos

- **Descrever o perfil demográfico e clínico** dos pacientes acometidos por eventos cerebrovasculares durante ou após a infecção por SARS-CoV-2, considerando idade, sexo, comorbidades e gravidade da doença.
- **Identificar os principais tipos de eventos cerebrovasculares** observados na amostra, com ênfase na prevalência de acidente vascular cerebral isquêmico, acidente vascular cerebral hemorrágico e trombose venosa cerebral.
- **Analisar os parâmetros laboratoriais e de neuroimagem** associados aos casos, destacando achados compatíveis com processos inflamatórios, endoteliais e trombóticos relacionados à infecção viral.
- **Avaliar os desfechos clínicos** dos pacientes com doença cerebrovascular associada à COVID-19, incluindo tempo de internação, necessidade de ventilação mecânica, permanência em unidade de terapia intensiva e mortalidade hospitalar.
- **Investigar potenciais fatores prognósticos** e correlações entre a gravidade da infecção pelo SARS-CoV-2 e a ocorrência de eventos cerebrovasculares, contribuindo para o melhor reconhecimento e manejo clínico dessas complicações.

3. MÉTODOS

3.1. Delineamento do Estudo

Trata-se de um **estudo observacional, prospectivo e descritivo**, realizado com o objetivo de analisar as características clínicas, laboratoriais, radiológicas e desfechos de pacientes com diagnóstico de doença cerebrovascular associada à infecção pelo SARS-CoV-2.

Os dados foram obtidos a partir de avaliações clínicas presenciais e de informações contidas em prontuários eletrônicos, seguindo protocolo padronizado de coleta. O estudo faz parte de um projeto institucional sobre manifestações neurológicas relacionadas à COVID-19 conduzido no Hospital da Santa Casa de Misericórdia de São Paulo.

3.2. Período do Estudo

A coleta de dados foi realizada entre **dezembro de 2020 e dezembro de 2023**, período que abrange diferentes ondas de incidência da infecção por SARS-CoV-2 no Brasil. Foram incluídos casos diagnosticados tanto durante a fase aguda da infecção quanto até **60 dias após o evento infeccioso inicial**, de modo a contemplar manifestações cerebrovasculares subagudas e tardias.

3.3. Local do Estudo

O estudo foi desenvolvido no **Hospital Central da Irmandade da Santa Casa de Misericórdia de São Paulo**, instituição terciária de referência em neurologia e doenças cerebrovasculares, localizada na cidade de São Paulo, Brasil. Todos os exames laboratoriais, de imagem e acompanhamentos clínicos foram realizados de acordo com as rotinas assistenciais e protocolos institucionais da instituição.

3.4. Seleção da Amostra

3.4.1. Critérios de Inclusão

Foram incluídos pacientes que atenderam aos seguintes critérios:

- Diagnóstico confirmado de infecção por SARS-CoV-2, comprovado por RT-PCR e/ou sorologia positiva;
- Presença de evento cerebrovascular agudo (isquêmico, hemorrágico ou trombose venosa cerebral) durante a infecção ou até 60 dias após;
- Idade igual ou superior a 15 anos;

- Atendimento em qualquer unidade do Hospital da Santa Casa de São Paulo durante o episódio neurológico.

3.4.2. Critérios de Exclusão

Foram excluídos pacientes que apresentaram:

- Testes laboratoriais negativos para SARS-CoV-2 sem soroconversão subsequente;
- Diagnóstico alternativo que explicasse o evento neurológico;
- Dados clínicos ou de imagem incompletos impossibilitando análise;
- Recusa em participar ou ausência de consentimento livre e esclarecido.

3.5. Coleta de Dados

A coleta foi conduzida por neurologistas e médicos pesquisadores previamente treinados, utilizando formulário padronizado. Os pacientes foram avaliados em três momentos:

- **Avaliação inicial**, até uma semana após o início dos sintomas neurológicos;
- **Reavaliação de 30 dias** (±15 dias);
- **Reavaliação de 90 dias** (±15 dias).

Foram registradas variáveis sociodemográficas, clínicas e laboratoriais, incluindo:

- Idade, sexo, comorbidades e uso prévio de medicamentos;
- Tipo de evento cerebrovascular e tempo entre o diagnóstico de COVID-19 e o início dos sintomas neurológicos;
- Necessidade de internação, ventilação mecânica e uso de corticoterapia;
- Tempo de hospitalização, permanência em UTI e mortalidade hospitalar.

3.6. Neuroimagem

Todos os pacientes com suspeita clínica de evento cerebrovascular realizaram **tomografia computadorizada (TC) e/ou ressonância magnética (RM)** do encéfalo, conforme disponibilidade e condições clínicas.

- **TC**: realizada em cortes axiais, sagitais e coronais;

- **RM**: sequências T1 axial e sagital, T2 axial, FLAIR, DWI/ADC, SWI, e pós-contraste (T1 Gd e FLAIR Gd).

Os exames foram revisados por radiologistas e neurologistas experientes. Foram classificados conforme o tipo de evento (isquêmico, hemorrágico ou venoso) e sua topografia.

3.7. Dados Laboratoriais

Foram analisados os seguintes parâmetros:

- **Hemograma**, **ureia**, **creatinina**, **eletrólitos**, **função hepática** e **marcadores inflamatórios** (PCR, D-dímero, LDH, ferritina, lactato);
- **Sorologia** e/ou **RT-PCR** para SARS-CoV-2;
- **Sorologias complementares** para descartar causas infecciosas concomitantes (sífilis, HIV, hepatites).

Os resultados foram comparados entre os diferentes tipos de evento cerebrovascular para identificação de possíveis marcadores prognósticos.

3.8. Planejamento da Análise Estatística

A análise estatística foi realizada com o software **IBM SPSS Statistics® (versão 25.0)**. As variáveis contínuas foram expressas como **medianas e intervalos interquartis (IQR)**, e as variáveis categóricas, como **frequências absolutas e percentuais**.

As comparações entre grupos (por tipo de evento e gravidade clínica) foram realizadas com testes não paramétricos (Mann–Whitney e Kruskal–Wallis) e testes de **Qui-quadrado** ou **Exato de Fisher** para variáveis categóricas. Valores de $\mathbf{p < 0,05}$ foram considerados estatisticamente significativos.

3.9. Aspectos Éticos

O estudo foi aprovado pelo **Comitê de Ética em Pesquisa da Irmandade da Santa Casa de Misericórdia de São Paulo**, sob o parecer consubstanciado nº **4.675.341**, em conformidade com a **Resolução CNS nº 466/2012**.

Todos os participantes, ou seus responsáveis legais, assinaram o **Termo de Consentimento Livre e Esclarecido (TCLE)** antes da inclusão no estudo. A confidencialidade dos dados foi integralmente preservada.

4. RESULTADOS

Durante o período de dezembro de 2020 a dezembro de 2023, foram avaliados pacientes com diagnóstico confirmado de infecção pelo SARS-CoV-2 e manifestações cerebrovasculares agudas atendidos no Hospital da Santa Casa de Misericórdia de São Paulo.

Os resultados da pesquisa foram consolidados e apresentados sob a forma de três artigos científicos, publicados (ou aceitos para publicação) em periódicos indexados, conforme descrito a seguir.

Artigo 1 – Neurological Manifestations of COVID-19 and the Importance of Magnetic Resonance Imaging.

DOI:10.2174/1871527320666210122093458
Qualis CAPES: A3 (Área: Medicina I)

Resumo:

Este artigo descreve as manifestações neurológicas associadas à infecção pelo SARS-CoV-2, com ênfase no papel da ressonância magnética (RM) na caracterização das lesões do sistema nervoso central. A análise destacou o envolvimento cerebral multifocal, a presença de micro-hemorragias e lesões isquêmicas subcorticais, reforçando o papel da neuroimagem na avaliação diagnóstica precoce. Os resultados sugerem que o SARS-CoV-2 possui potencial neurotrópico relevante, afetando tanto o sistema nervoso central quanto periférico, e que a RM é uma ferramenta fundamental para identificar essas alterações mesmo em estágios iniciais da infecção.

Artigo 2 – Neurological Syndromes Associated with COVID-19: A Multicenter Study in Brazil

BMC Infectious Diseases. 2025; 25:123.
DOI: 10.1186/s12879-025-10504-6
Qualis CAPES: A3 (Área: Medicina I)

Resumo:

Trata-se de um estudo multicêntrico brasileiro que avaliou as manifestações neurológicas de pacientes com COVID-19 atendidos em diferentes centros hospitalares. Entre as complicações descritas, destacaram-se as encefalopatias agudas, acidentes vasculares cerebrais, síndrome de Guillain-Barré e outras neuropatias inflamatórias. O estudo evidenciou alta prevalência de

manifestações neurológicas em pacientes com COVID-19, especialmente em casos graves, e demonstrou correlação entre marcadores inflamatórios elevados, estado pró-trombótico e maior risco de eventos cerebrovasculares.

Artigo 3 – Neurological burden of covid-19: a study of cerebrovascular events in a Brazilian tertiary hospital.

ISSN: 0025-7680 - **Qualis CAPES:** B1 (Área: Medicina I)

Status: Aceito para publicação (pré-impressão)

Resumo:

Este artigo analisou a ocorrência e o perfil clínico-radiológico dos eventos cerebrovasculares em pacientes com COVID-19 no Brasil. A maioria dos casos identificados foi de acidente vascular cerebral isquêmico, seguido por eventos hemorrágicos e raros casos de trombose venosa cerebral. A idade média dos pacientes foi superior à da população geral de infectados, e observou-se maior incidência em homens com comorbidades cardiovasculares prévias. Os resultados indicam que a COVID-19 pode atuar como **fator desencadeante** ou **agravante** de eventos cerebrovasculares, possivelmente mediado por mecanismos de disfunção endotelial, hipercoagulabilidade e inflamação sistêmica. A taxa de mortalidade hospitalar foi maior nos casos com hemorragia intracraniana e nos pacientes submetidos a anticoagulação terapêutica prévia. O estudo destaca ainda a importância de protocolos de **monitoramento clínico e radiológico contínuo** durante e após a infecção, e ressalta a necessidade de **estratégias preventivas** voltadas ao rastreamento precoce de fatores de risco e controle de comorbidades.

Artigo 1 – Neurological Manifestations of COVID-19 and the Importance of Magnetic Resonance Imaging. CNS & Neurological Disorders – Drug Targets, 2021.

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CNS & Neurological Disorders - Drug Targets, 2021, *20*, 390-391

LETTER TO THE EDITOR

Neurological Manifestations of COVID-19 and the Importance of Magnetic Resonance Imaging

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Abstract: A letter to the editor to discuss several uses of brain magnetic resonance imaging (MRI) in the investigation of neurological manifestations of covid-19. Described several situations in which the MRI is needed. Brain MRI is an important diagnostic method in the covid-19 scenario, to investigate possible neurological complications of the disease.

DEAR EDITOR:

In the face of the pandemic due to the new coronavirus, COVID-19, the number of patients with neurological involvement is increasing. Neurotropism has been described as a common feature of coronaviruses. Brain involvement can result from the spread of SARS-CoV-2 through the circulation or the olfactory pathway from the cribriform plaque during an early or later stage of infection. After invading the central nervous system, the virus usually spreads quickly, in a multifocal and generally symmetrical manner, involving the thalamus, brain stem, brain white matter and cerebellum. Some researchers have already detected the SARS-CoV nucleic acid in Cerebrospinal Fluid (CSF) and brain tissue during the autopsy of these patients[1].

The new coronavirus, like SARS-CoV, uses a peak S1 protein that allows the connection between virion and cell membrane, interacting with the host's Angiotensin Converting Enzyme 2 (ACE2) receptor. The binding affinity of this SARS-CoV-2 protein has been shown to be 10 to 20 times higher than that of SARS-CoV [1].

Manifestations in the central nervous system are frequent, ranging from dizziness, headache, ataxia, to severe conditions such as encephalitis, acute toxic encephalopathy, myelitis, stroke, and neurogenic respiratory failure [2, 3]. Many of the changes in the nervous system are typically represented in brain Magnetic Resonance Imaging (MRI).

Headache is a common symptom in patients with Covid-19, occurring in up to 53.3% of cases. The mechanisms that cause headache in Covid-19 patients are not yet fully understood, with the participation of inflammatory mediators being suggested when the headache is the result of systemic viral infection. Headache can be secondary to several mechanisms and conditions, such as encephalitis, necro-hemorrhagic encephalopathy and cerebral vascular disease, including stroke and cerebral venous thrombosis. The differentiation of these conditions is very important and has therapeutic implications. Brain MRI is the preferred imaging test to establish this differentiation, allowing quick and effective action. In some cases of encephalitis and necro-hemorrhagic encephalopathy, MRI was more sensitive than tomography to identify brain lesions. Therefore, MRI is an essential tool to examine the proper management of patients with Covid-19 and headache [3, 4].

It is also known that patients with COVID-19 have a higher risk of thromboembolic events, including stroke, and an increase in cases of occlusion of large cerebral vessels due to this infection has been described [5]. These proximal occlusions can lead, in addition to paralysis and dysphasia, to episodes of altered level of consciousness and thus some patients may have the onset of the condition undefined. A head tomography exam, in this scenario, is not indicated because it does not allow estimation of the time of occurrence of ictus [6]. MRI is mandatory in this situation, as described in the last consensus of the American Academy of Neurology in conjunction with the American Academy of Stroke, because it can estimate the patient's ictus time (by FLAIR/DWI mismatch or perfusion studies), thus providing an adequate acute treatment [7]. With the MRI exam, it is possible to treat stroke patients due to COVID-19, allowing an adequate and precise intervention with significant reduction of sequelae and deaths.

Severe cases may present with a behavioral or conscience disorder and eventually epileptic seizures, as seen, for example, in acute necrotizing encephalitis, have shown

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on MRI great cerebral involvement, confirming the diagnosis and guiding the conduct [8].

Therefore, MRI is essential for a correct and fast diagnosis of the frequent neurological complications in COVID-19. Even cases with initially subtle manifestations can be managed more precisely and with greater safety and possibly with better functional outcomes. Early diagnosis through MRI may even prevent invasive and expensive procedures, contributing to a more effective and quick treatment.

CONCLUSION

Although MRI may have its unique function in diagnosing COVID-19 neurological manifestations, chest CT, High Resolution CT (HRCT) is still the most effective way for the COVID-19 confirmation, since the diagnosis is based on the combination of chest CT and brain MRI could be more precise.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Artigo 2 – Neurological Syndromes Associated with COVID-19: A Multicenter Study in Brazil

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RESEARCH

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Neurological syndromes associated with COVID-19: a multicenter study in Brazil

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Abstract

Background Neurological manifestations associated with COVID-19 remain partially described, mainly in low- and middle-income countries where diagnostic tools are limited. To address this, we assembled medical centers in Brazil with the goal of describing neurological syndromes associated with COVID-19 during the first wave of the pandemic.

Methods From June 1st, 2020 to June 1st, 2021, non-consecutive adult patients with new onset of six neurological syndromes up to 60 days after confirmed COVID-19 were included. Data were compiled from four tertiary centers and compared with general local COVID-19 data, as well as with a previous cohort focused on vascular syndrome.

Results 197 patients were included, presenting with vascular syndromes (81), encephalopathy (68), encephalitis (19), Guillain-Barré syndrome (13), other neuropathies (12), and myelitis (4). The incidence curve of neurocovid mirrored that of COVID-19. Neurological syndromes were present regardless of COVID-19 severity. The median time from COVID-19 to onset of neurological symptoms was 14 days, suggesting a post-infectious immune-mediated mechanism. Patients were 10 times more likely to die (χ^2 (1) = 356.55, $p < 0.01$, OR = 10.89) and 38 times more likely to be hospitalized than other COVID-19 patients (χ^2 (1) = 1167.9, $p < 0.01$, OR = 38.22). Those developing vascular syndromes patients were 3 times more likely to require ICU (χ^2 (1) = 37.12, $p < 0.01$, OR = 3.78) and 4 times more likely to die (χ^2 (1) = 58.808, $p < 0.01$, OR = 4.73) than patients with vascular syndromes due to different etiologies.

Conclusions Our study corroborates the association of neurological syndromes with COVID-19. The incidence correlated with local waves of COVID-19, and patients with neurocovid exhibited a higher susceptibility to adverse outcomes compared to other COVID-19 patients. Among all neurological syndromes, vascular syndromes were the most common, and their severity surpassed that of vascular syndromes not attributed to COVID-19.

Keywords COVID-19, Viral infections, Infection, Post-Infectious Disorders

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Background

Throughout history, viral emergencies have consistently exhibited an intriguing association with concurrent neurological manifestations [1]. It is noteworthy that these neurological sequelae, although not typically the primary syndrome characterizing an epidemic, frequently emerge as a striking and critical facet, demanding specialized medical attention [2].

The COVID-19 pandemic serves as a pertinent contemporary example of this phenomenon. From the earliest reported cases in Wuhan, a significant proportion of infected individuals, estimated to be around 30%, exhibited neurological symptoms [3]. As our understanding of the novel coronavirus, SARS-CoV-2, progressed and global infection rates rose, these neurological presentations transitioned from sporadic symptoms to worrisome syndromes that have yet to be fully characterized [4].

Shifting our attention to the South American epicenter of the SARS-CoV-2 outbreak, Brazil bears a concerning burden with over 37 million confirmed COVID-19 cases and a tragic toll of more than 700,000 fatalities [5]. And while these numbers have been publicized and been the focus of a combination of political and social challenges [6, 7], the potential long-term health issues associated with COVID-19, such as neurological, cardiovascular, and musculoskeletal problems were consistently overlooked.

Recognizing the crucial gap in comprehending and addressing the broader implications of the pandemic, we proactively initiated collaboration with neurology reference centers experienced in neurovirology. This collaboration aimed to rapidly navigate the challenges posed by lockdown situations, with the overarching goal of characterizing and accounting for neurological manifestations associated with COVID-19 during a period of different variants insurgence [8, 9] and lack of vaccination.

In this report, we share our experience with the study of COVID-19-related neurological syndromes from the cohort assembled by the NeurocovBR study group during the early pandemics in Brazil.

Methods

NeurocovBR

In March 2020, following confirmation of the first case of COVID-19 in Brazil [6], the NeurocovBR study group was established. This group was comprised of national neurology reference centers (in public or private practice) with prior experience in neurovirology and was coordinated by the Tropical Medicine Institute of Sao Paulo (IMT USP). IMT USP also conducts bench research in virology and had the additional shared responsibility of developing and validating new assays related to SARS-CoV-2 in Brazil during the pandemic.

NeurocovBR was organized into two distinct layers: a comprehensive clinical-demographic layer and a laboratory layer. Each clinical participating center had the option to contribute solely to the clinical-demographic layer or to engage in both layers, depending on whether their internal protocols and contamination control measures allowed for full participation.

Study design and patient selection

For the clinical-demographic layer, a total of four sites situated in hotspot regions for COVID-19 participated in the study in addition to IMT USP. Three of these sites were located in Sao Paulo State (*Instituto de Infectologia Emilio Ribas, Irmandade Santa Casa de Misericordia de Sao Paulo and Hospital Israelita Albert Einstein*), southeast Brazil, while the fourth site was in Ceara State (*Hospital Geral de Fortaleza*), in the northeastern region of the country. Enrollment started on June 1, 2020, and continued until June 1, 2021. If the patient had the first COVID-19 and neurological symptoms starting before June 1, 2020, enrollment was acceptable if he remained with neurological signs or symptoms (it could be a sequelae) by the study start.

Inclusion criteria required patients to be 18 years of age or older, fulfill WHO criteria for COVID-19 [10], meet the provisional Ellul criteria for SARS-CoV-2 neurologic-associated syndromes [4], and exhibit novel neurological symptoms within 60 days of COVID-19 infection (Table s1).

It was admissible for patients to be referred to the designated study sites by general practitioners, and individuals also had the option to personally request an evaluation. Every patient, whether as an inpatient or an outpatient, underwent an evaluation conducted by a neurologist affiliated with the study group, to ensure the precise classification of the neurological syndrome.

Patients presenting with isolated neurological symptoms, such as anosmia, myalgia, or headache, were excluded from the study if no further neurologic syndrome developed in 60 days. This timeframe was adopted to ensure that syndromes, including those that may develop after mild symptoms, such as Guillain-Barré Syndrome, and persist for up to an additional four weeks, were not overlooked [11]. COVID-19 vaccination was not an exclusion criterion; however, during the study period, it was not available to participants for various reasons, and no patients received the vaccine.

Evaluation

Demographic data were collected from medical records, patient interviews, or interviews with a designated proxy when the patient was unable to provide the information directly. A structured interview was designed specifically

for this study (supplementary material). It included information such as age, gender, comorbidities, the date of onset of the first COVID-19 symptom, the date of the first neurological sign or symptom, COVID-19 signs and symptoms, and parameters for assessing the severity of COVID-19 [12].

For patients with vascular syndrome, the severity of COVID-19 was classified based on symptoms and signs observed the day before the onset of the first neurological symptom. This was necessary because otherwise, a stroke would automatically classify patients as having critical COVID-19, preventing us from demonstrating that individuals with mild, moderate, and severe COVID-19 could also develop COVID-19-associated stroke.

To assess the severity of neurological syndromes, we employed the Modified Rankin Scale (mRS) and the Glasgow Coma Scale (GCS) for all syndromes. For vascular syndrome patients, mRS was scored 24h after acute phase treatment. Furthermore, the Liverpool Outcome Score (LOS) was used for encephalopathy and encephalitis, the NIH Stroke Scale (NIHSS) for vascular syndrome, and the Overall Neuropathy Limitations Scale (ONLS) for conditions such as Guillain-Barré syndrome and other neuropathies.

To account for overall patient outcomes, we collected in-hospital data, which included the need for admission to the intensive care unit (ICU) and/or mechanical ventilation (MV) assistance, as well as the presence of complications such as acute kidney injury (AKI) or coinfections. We also documented the length of in-hospital stay, recorded cases of mortality, and tracked time-to-death.

All patients underwent SARS-CoV-2 testing through one or both of the ELISA IgA (Euroimmun, Lubeck, Germany) in serum samples and/or RT-PCR methods (RealStar RT-PCR kit, Altona Diagnostics, Hamburg, Germany) from oropharyngeal swab (samples during the COVID-19 acute phase). It is worth noting that additional cerebrospinal fluid (CSF) and serum measurements are not covered within the scope of this report.

Data storage

Data were stored in an electronic data capture system specifically designed for this study. Only the local site coordinator and the principal researcher designated by them were granted access to input the data. Subsequently, this data was centrally reviewed by the study coordinators to mitigate any potential inconsistencies.

Syndromic reclassification

After the latest data inclusion, all entries underwent review for a second confirmation of diagnosis. In our study design, we adopted the provisional Ellul criteria [4] to define neurocovid syndromes, which determines meningitis, encephalitis, acute disseminated encephalitis, myelitis, Guillain-Barré syndrome and cerebrovascular disease as primary syndromes. However, distinct and consistent clusters emerged within our sample. To highlight these differences and provide greater clarity to the reader, we reclassified the encountered syndromes into six distinct categories: (i) Vascular syndromes, encompassing confirmed cases of ischemic stroke, hemorrhagic stroke, or cerebral venous thrombosis; (ii) Encephalopathy, characterized as level 3 and 4 of SARS-CoV-2 encephalitis [4]; (iii) Encephalitis, identified as level 1 and 2 of SARS-CoV-2 encephalitis [4]; (iv) Guillain-Barré syndrome, specifically associated with SARS-CoV-2 [4]; (v) Other neuropathies, referring to acute neuropathies related to SARS-CoV-2 [4], (vi) Myelitis, defined as SARS-CoV-2-induced myelitis [4] (supplementary material, Table s1). It is noteworthy to mention that no instances of other syndromes were encountered within our sample.

Comparison data

To compare the NeurocovBR data with general COVID-19 data from the states of Ceara and Sao Paulo, we accessed publicly available information from the Brazilian governmental health authority (Coronavírus Brasil, OpenDATASUS) [5]. For comparing the NeurocovBR vascular syndrome data with data on vascular syndromes predating the COVID-19 pandemic, we relied on detailed local stroke data from a previously published article [13].

Statistical analysis

Continuous data were summarized as the mean and standard deviation or median plus interquartile range (IQR). Categorical data were presented as counts and percentages. Group comparisons were conducted using the chi-square test for categorical data, with Yates' correction applied in cases where expected cell frequencies were less than 5. Non-parametric rank tests were used for continuous data, except when comparing with general vascular data, where we employed a one-sided t-test. In this parametric test, no difference in results was observed when using bootstrapping with 2,000 repetitions on NeurocovBR vascular data to achieve normality assumptions; therefore, we worked with the original sample, assuming the central limit theorem.

We used Cohen's d to determine the size effect when a one-sided t-test was used and odds ratios for chi-square tests. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed, and graphs were created, using the R programming language version 3.3.0+.

Standard Protocol Approvals, Registrations and Patient Consents

This study obtained approval from the ethics committee at the Universidade de São Paulo (CAAE: 31,378,820.1.1001.0068) and the ethics committees of the study sites. Written informed consent was obtained from all patients or their next of kin, and their personal information is protected by ethical procedures. The study adheres to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments, as well as relevant Brazilian regulations.

Results

Patient selection

From an initial cohort of 233 patients, 36 individuals (15.5%) were excluded, resulting in a final analysis cohort of 197 patients (Fig. 1). Among the ten syndromes that were not associated with COVID-19, eight were linked to various causative agents, while two were classified as psychogenic. Within the subset of six patients exhibiting isolated neurological symptoms, four presented with isolated headaches, one experienced a temporary loss of consciousness, and another reported vertigo. Furthermore, among the patients with vascular syndrome, encephalopathy, and encephalitis, three, five, and two patients, respectively exhibited concurrent neuropathy, which was categorized as critical illness polyneuropathy. This comorbidity was attributed to their prolonged in-hospital stay and their clinical conditions, rather than being directly linked to SARS-CoV-2. Additionally, one patient diagnosed with encephalitis also manifested myelitis with minimal clinical manifestations, ultimately receiving a final classification of encephalitis.

NeurocovBR

Among the six primary neurological syndromes, two—vascular syndrome and encephalopathy—accounted for over 75% of the cases, while the remaining four – encephalitis, GBS, other neuropathies, and myelitis – collectively accounted for less than 25%. It is noteworthy that obesity, which is recognized as risk factors for severe COVID-19, was not prevalent in this context [14]. Symptoms such as fever, cough, and dyspnea were commonly reported, with anosmia/hyposmia exceeding 30% only in cases of encephalitis (Table 1, Table s2).

Notably, in cases of GBS (4, 30.4%), vascular syndrome (11, 13.6%), encephalitis (1, 5.3%), and encephalopathy (1, 1.5%), some patients were asymptomatic for COVID-19 infection and were diagnosed through mandatory SARS-CoV-2 in-hospital screening (Table 1). The manifestation of neurological syndromes appeared irrespective of the severity of the associated COVID-19 infection and typically developed approximately two weeks following the initial infection (median 14 days, IQR 7–24). The timeline for the onset of neurological syndromes varied, with vascular syndromes and encephalitis presenting in a shorter period and neuropathies emerging over a longer duration (Table 1).

In-depth assessments of patients' clinical conditions revealed a significant proportion of individuals with moderate or severe scores on outcome scales such as GCS to all syndromes, LOS to encephalopathy and

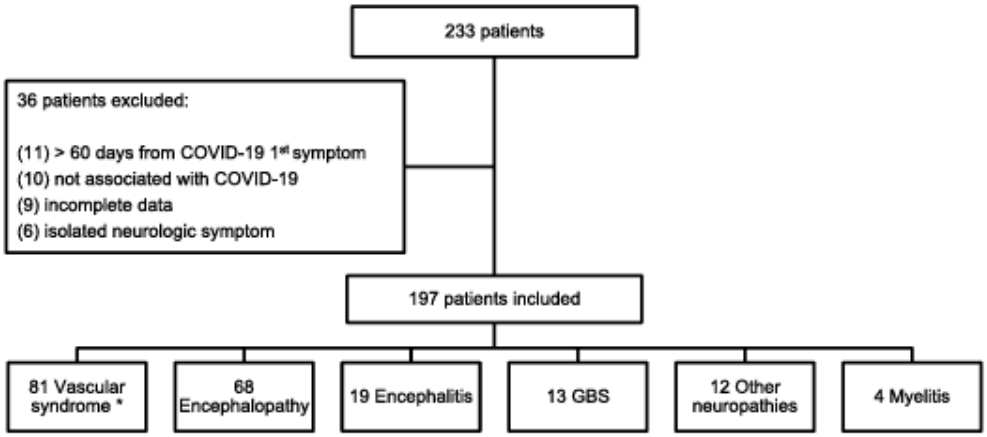

Fig. 1 NeurocovBR patient's flowchart. Legends: * The vascular syndrome includes 52 cases of ischemic stroke, 21 cases of hemorrhagic stroke, and 8 cases of cerebral venous thrombosis. GBS = Guillain-Barré Syndrome

Table 1 Demography of NeurocovBR patients

	All patients	Vascular	Encephalopathy	Encephalitis	GBS	Neuropathies	Myelitis
n, (%)	197 (100)	81 (41.1)	68 (34.5)	19 (9.6)	13 (6.6)	12 (6.1)	4 (2.1)
Age, median, (IQR)	57 (43–67)	62 (50–71)	57 (43.5–65)	55 (41.5–60.5)	45 (43–54)	40 (34.25–53)	40 (26–56.25)
Female, n, (%)	109 (55.3)	46 (56.8)	41 (60.3)	8 (42.1)	8 (61.5)	4 (33.3)	2 (50)
Comorbidities, n, (%)							
HBP	84 (42.6)	45 (51.1)	29 (42.6)	5 (26.3)	3 (23.1)	2 (16.7)	0 (0)
DM	57 (28.9)	28 (31.8)	16 (23.5)	5 (26.3)	2 (15.4)	5 (41.7)	1 (25)
Obesity	30 (15.2)	14 (15.9)	9 (13.2)	0 (0)	2 (15.4)	5 (41.7)	0 (0)
Smoker	27 (13.7)	15 (17)	9 (13.2)	1 (5.3)	2 (15.4)	0 (0)	0 (0)
Autoimmune disease	3 (1.5)	2 (2.3)	1 (5.3)	0 (0)	0 (0)	0 (0)	0 (0)
No comorbidities	47 (23.9)	18 (20.5)	17 (25)	4 (21.1)	5 (38.5)	1 (8.3)	2 (50)
COVID-19 signs and symptoms, n, (%)							
Fever	135 (68.5)	53 (60.2)	50 (73.5)	13 (68.4)	7 (53.8)	9 (75)	3 (75)
Cough	126 (64)	55 (62.5)	48 (70.6)	9 (47.4)	5 (38.5)	8 (66.7)	1 (25)
Sore throat	22 (11.2)	3 (3.4)	15 (22.1)	2 (10.5)	0 (0)	1 (8.3)	1 (25)
Runny nose	26 (13.2)	2 (2.3)	16 (23.5)	4 (21.1)	3 (23.1)	0 (0)	1 (25)
Myalgia	47 (23.9)	12 (13.6)	26 (38.2)	4 (21.1)	3 (23.1)	2 (16.7)	0 (0)
Headache	45 (22.8)	18 (20.5)	20 (29.4)	5 (26.3)	1 (7.7)	1 (8.3)	0 (0)
Asthenia	53 (26.9)	18 (20.5)	20 (19.4)	5 (26.3)	4 (30.8)	5 (41.7)	1 (25)
Dyspnea	85 (43.1)	45 (51.1)	32 (47.1)	1 (5.3)	1 (7.7)	6 (50)	0 (0)
StO2 < 95%	53 (26.9)	33 (37.5)	14 (20.6)	2 (10.5)	1 (7.7)	3 (25)	0 (0)
Anosmia/hyposmia	32 (16.3)	2 (2.3)	21 (3.8)	6 (31.6)	1 (7.7)	2 (16.7)	0 (0)
No COVID symptoms	14 (7.1)	7 (8)	1 (1.5)	1 (5.3)	4 (30.8)	0 (0)	1 (25)
COVID-19 severity, n, (%)*							
Asymptomatic	17 (8.6)	11 (13.6)	1 (1.5)	1 (5.3)	4 (30.8)	0 (0)	0 (0)
Mild	58 (29.4)	15 (18.5)	21 (30.9)	10 (52.6)	6 (46.2)	3 (25)	3 (75)
Moderate	32 (16.2)	12 (14.8)	14 (20.6)	2 (10.5)	2 (15.4)	1 (8.3)	1 (25)
Severe	21 (10.7)	9 (11.1)	9 (13.2)	3 (15.8)	0 (0)	0 (0)	0 (0)
Critical	69 (35)	34 (42)	23 (33.8)	3 (15.8)	1 (7.7)	8 (66.7)	0 (0)
Δt COVID-Neuro, d, median, (IQR)	14 (7–24)	10 (6–14)	18 (12–31)	8 (3–24)	23 (15–24)	24 (16.75–39.5)	18 (11.25–14)

Legends: *GBS* Guillain-Barré Syndrome, *HBP* high blood pressure, *DM* diabetes mellitus. * COVID-19 severity was attributed before the vascular syndrome ictus

encephalitis, NIHSS to vascular syndromes, and ONLS to GBS and other neuropathies upon admission (Table 2, Table s3). Additionally, patients from all syndromes presented with co-infections (vascular syndromes, 67.8%; encephalopathy, 38.2%; encephalitis, 52.6%; GBS, 30.8%; other neuropathies, 66.7%; myelitis, 25%), while acute kidney injury was present in only four syndromes (vascular syndromes, 59.3%; encephalopathy, 32.4%; encephalitis, 31.5%; other neuropathies, 33.3%). The mortality was higher among patients with vascular syndromes (55.6%), followed by encephalitis (15.8%), encephalopathy (11.8%) and other neuropathies (8.3%), while absent for GBS and myelitis (Table 2).

NeurocovBR – vascular syndromes vs. encephalopathy

In a separate analysis comparing detailed data from vascular and encephalopathy syndromes, which were significantly more prevalent (χ^2 (5) = 164.68, p < 0.01), we found that vascular patients were older (U = 2139.5, p = 0.019), with a nearly equal gender distribution (χ^2 (1) = 0.07, p = 0.79) in comparison with encephalopathy, and COVID-19 severity was not a determining factor for these syndromes (χ^2 (4) = 7.24, p = 0.12). Details are provided in Table 3.

The period between the onset of initial COVID-19 symptoms and the first neurological symptoms was found to be shortest in vascular patients versus encephalopathy patients (U = 3476.5, p < 0.01). Additionally, vascular patients exhibited more severe clinical symptoms when compared with encephalopathy patients, as indicated by a significantly higher probability of presenting with mRS ≥ 3 (χ^2 (1) = 29.605, p < 0.01, OR = 8.21) and a GCS < 9 (χ^2 (1) = 16.51, p < 0.01, OR = 7.41).

Six vascular patients (7.4%) and four encephalopathy patients (5.9%) (supplementary material, Table s2) had a previous ischemic stroke. Only two patients from the

Table 2 Clinical characteristics and outcomes of NeurocovBR patients

	All patients	Vascular	Encephalopathy	Encephalitis	GBS	Neuropathies	Myelitis
n, (%)	197 (100)	81 (41.1)	68 (34.5)	19 (9.6)	13 (6.6)	12 (6.1)	4 (2.1)
mRS at admission, n, (%)							
< 3	63 (32)	11 (13.6)	39 (57.4)	5 (26.3)	1 (7.7)	6 (50)	1 (25)
≥ 3	132 (67)	69 (85.2)	28 (41.1)	14 (73.7)	12 (92.3)	6 (50)	3 (75)
unknown	2 (1)	1 (1.2)	1 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)
Specific scales at admission, n, (%)							
GCS 9—12	_	24 (29.6)	4 (6.5)	3(15.8)	_	_	_
GCS < 9	_	30 (37)	5 (7.4)	3(15.8)	_	_	_
LOS 3	_	_	17 (25)	7 (36.8)	_	_	_
LOS < 3	_	_	32 (47)	2 (10.5)	_	_	_
NIHSS 6—15	_	21 (26)	_	_	_	_	_
NIHSS > 15	_	42 (51.9)	_	_	_	_	_
ONLS 5—9	_	_	_	_	5 (38.5)	1 (8.3)	_
ONLS > 9	_	_	_	_	4 (30.8)	3 (25)	_
Hospitalization, n, (%)							
Yes	156 (79.2)	72 (88.9)	46 (67.6)	14 (73.7)	12 (92.3)	10 (83.3)	2 (50)
Needed ICU	137 (60.5)	65 (80.2)	45 (66.2)	11 (57.9)	6 (46.2)	9 (75)	1 (25)
Needed MV	103 (52.3)	55 (67.9)	28 (41.2)	8 (42.1)	4 (30.8)	8 (66.7)	0 (0)
Neurocovid identified during hospitalization	82 (41.6)	42 (51.9)	27 (39.7)	5 (26.3)	1 (7.7)	7 (58.3)	0 (0)
Neurocovid identified after extubating	37 (18.8)	6 (7.4)	20 (29.4)	2 (10.5)	1 (7.7)	8 (66.7)	0 (0)
Δt hospitalization, d, median, (IQR)	22 (11–44)	13 (6.5–22)	24 (11–42)	17.5 (9.25–51)	15 (13–21)	36 (17–48)	11 (10–17)
In-hospital complications, n, (%)							
Co-infections	104 (52.8)	55 (67.9)	26 (38.2)	10 (52.6)	4 (30.8)	8 (66.7)	1 (25)
AKI with dialysis	41 (20.8)	26 (32.1)	12 (17.6)	1 (5.3)	0 (0)	2 (16.7)	0 (0)
AKI without	39 (19.8)	22 (27.2)	10 (14.7)	5 (26.3)	0 (0)	2 (16.7)	0 (0)
Specialist decision treatments, n, (%)							
HCQ	9 (4.6)	2 (2.5)	5 (7.4)	1 (5.3)	0 (0)	1 (8.3)	0 (0)
Anticoagulants	131 (66.5)	62 (81.5)	34 (50)	12 (63.2)	8 (61.5)	7 (58.3)	0 (0)
Corticosteroid therapy	125 (63.5)	53 (65.4)	42 (61.8)	16 (84.2)	3 (23.1)	8 (66.7)	3 (75)
Tocilizumab	2 (1)	0 (0)	1 (1.5)	0 (0)	1 (7.7)	0 (0)	0 (0)
Outcomes							
Death, n, (%)	57 (28.9)	45 (55.6)	8 (11.8)	3 (15.8)	0 (0)	1 (8.3)	0 (0)
Δt COVID-death, d, median (IQR)	24 (17–34)	22 (16.5–29.5)	30 (24.5–64)	92 (72.2–106)	-	43	-_
Δt Neurocovid-death, d, median, (IQR)	15 (7–24)	11.5 (6–21.5)	18.5 (15–40.8)	72.5 (62.8–85.8)	-	18	-

Legends: *GBS* Guillain-Barré Syndrome, *mRS* modified Rankin scale, *GCS* Glasgow coma scale, *LOS* Liverpool outcome score, *NIHSS* NIH stroke scale, *ONLS* overall neuropathy limitations scale, *ICU* intensive care unit, *MV* mechanical ventilation, *AKI* acute kidney injury, *HCQ* hydroxychloroquine

vascular syndrome group had a previous mRS score of 3, while all others had a score 1 or 2, thus not significantly affecting the mRS comparison between groups. In the encephalopathy group, two patients (2.9%) had mild dementia, with a prior mRS score of 2. All patients with a previously altered mRS showed and increment of at least 1 point in the study evaluation.

Vascular patients were also 3.83 times more likely to require hospitalization (χ^2 (1) = 8.8751, $p < 0.01$, OR = 3.83) and 9.38 times more likely to die (χ^2 (1) = 29.05, $p < 0.01$, OR = 9.38) when compared to encephalopathy patients.

Table 3 Characteristics of patients with Vascular Syndromes versus Encephalopathy

	Vascular	Encephalopathy	*p*	*OR*
n	81	68	< 0.01	_
Age, median, (IQR); mean (± SD)	62 (50–71)	57 (43.5–65)	< 0.05	_
Female, n, (%)	46 (56.8)	41 (60.3)	0.79	_
COVID-19 severity, n, (%)				
Asymptomatic	11 (13.6)	1 (1.5)	0.12	_
Mild	15 (18.5)	21 (30.9)		
Moderate	12 (14.8)	14 (20.6)		
Severe	9 (11.1)	9 (13.2)		
Critical	34 (42)	23 (33.8)		
Δt COVID-Neuro, d, median, (IQR)	10 (6–14)	18 (12–31)	< 0.01	_
mRS at admission, n, (%)				
≥ 3	69 (85.2)	28 (41.1)	< 0.01	8.21
Specific scales at admission, n, (%)				
GCS < 9	30 (37)	5 (7.4)	< 0.01	7.41
Hospitalization due to COVID-19, n, (%)				
Yes	72 (88.9)	46 (67.6)	< 0.01	3.83
Needed ICU	65 (80.2)	45 (66.2)	0.07	2.07
Needed MV	55 (67.9)	28 (41.2)	< 0.01	3.02
Neurocovid identified during hospitalization	42 (51.9)	27 (39.7)	0.18	_
Neurocovid identified after extubating	6 (7.4)	20 (29.4)	< 0.01	0.19
Δt hospitalization, d, median, (IQR)	13 (6.5–22)	24 (11–42)	< 0.05	
In-hospital complications, n, (%)				
Co-infections	55 (67.9)	26 (38.2)	< 0.01	2.46
AKI with dialysis	26 (32.1)	12 (17.6)	0.06	2.20
AKI without	22 (27.2)	10 (14.7)	0.10	_
Outcomes				
Death, n, (%)	45 (55.6)	8 (11.8)	< 0.01	9.38
Δt COVID-death, d, (IQR); mean (± SD)	22 (16.5—29.5)	30 (24.5—64)	< 0.05	_
Δt Neurocovid-death, d, median, (IQR)	11.5 (6—21.5)	18.5 (15—40.8)	0.07	_

Legends: *mRS* modified Rankin scale, *GCS* Glasgow coma scale, *ICU* intensive care unit, *MV* mechanical ventilation, *AKI* acute kidney injury

Comparative analysis

NeurocovBR vs COVID-19

The incidence histogram of neurologic syndromes mirrored the incidence histogram of confirmed COVID-19 cases (Fig. 2). NeurocovBR patients were generally older compared to the general Brazilian COVID-19 population (54.7 ± 15.9 vs. 43.2 ± 15.9 years, $p < 0.01$). Furthermore, NeurocovBR patients were 38 times more likely to require hospitalization (χ^2 (1) = 1167.9, $p < 0.01$, OR = 38.22), and the presence of a neurological syndrome was associated with an increased likelihood of mortality (χ^2 (1) = 356.55, $p < 0.01$, OR = 10.89). Refer to Table 4 for details.

Hospitalized NeurocovBR vs Hospitalized COVID-19

When focusing solely on hospitalized patients (Table 4), we observed that the mean age was similar between the two groups, with a slightly increased chance of being female (χ^2 (1) = 8.75, $p < 0.01$, OR 1.62) in NeurocovBR. The odds of death were also slightly higher for NeurocovBR patients (χ^2 (1) = 12.55, $p < 0.01$, OR 1.83).

Vascular NeurocovBR vs Vascular predating COVID-19

In a separate analysis comparing NeurocovBR vascular data with Brazilian vascular data from before the COVID-19 pandemic (Table 5), we observed that NeurocovBR patients were younger (t(80) = −4.70, $p < 0.01$, Cohen's d = 0.52). Notably, hypertension (HBP), diabetes mellitus (DM), and smoking were not identified as risk factors among our patients. Despite the absence of these well-established risk factors, NeurocovBR vascular patients were 3.78 times more likely to require ICU care (χ^2 (1) = 37.12, $p < 0.01$, OR = 3.78), 6.14 times more likely to acquire co-infections during hospitalization (χ^2 (1) = 75.95, $p < 0.01$, OR = 6.14), and 4.73 times more likely to die (χ^2 (1) = 58.808, $p < 0.01$, OR = 4.73) (Table 5)

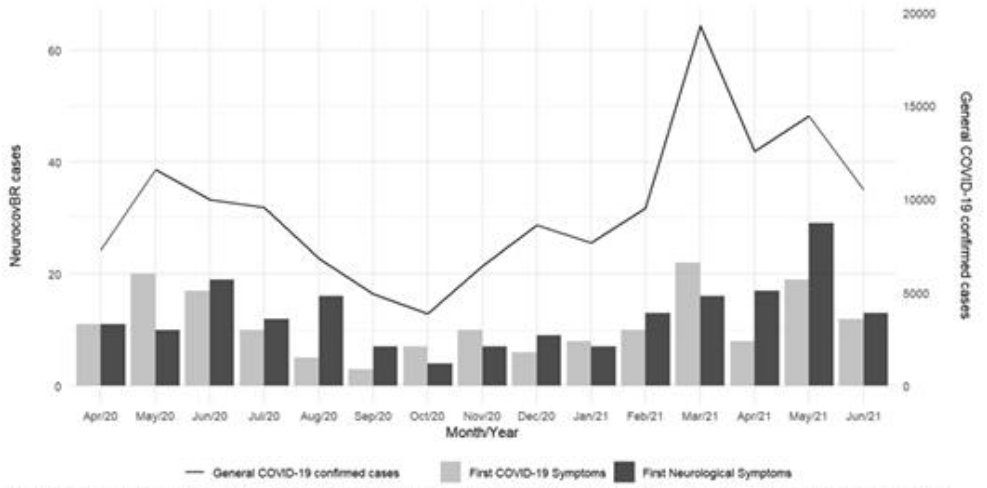

Fig. 2 Incidence of general COVID-19 confirmed cases* and incidence of COVID-19 and neurological symptoms in NeurocovBR. Legends: *Data from hospitalized COVID-19 patients

Table 4 Demography and outcomes comparisons between COVID-19 and NeurocovBR patients

	COVID-19	NeurocovBR	*p*	*OR*	COVID-19	NeurocovBR	*p*	*OR*
	all cases				**hospitalized patients**			
n	4,428,129	197			400,901	156		
Age, y, mean (± SD)	43.2 (± 15.9)	54.7 (± 15.9)	< 0.01		58 (± 16.6)	56 (± 15.6)	0.26	
Female, n, (%)	2,368,087 (53.4)	109 (55.3)	0.84	0.96	175,171 (43.7)	87 (55.8)	< 0.01	1.62
Hospitalizations, n, (%)	400,901 (9)	156 (79.2)	< 0.01	38.22	400,901 (100)	156 (100)		
Death, n, (%)	159,552 (3.6)	57 (28.9)	< 0.01	10.89	109,021 (30.3)	52 (33.3)	< 0.01	1.83

Legends: *OR* odds ratio, *SD* standard deviation

when compared with vascular patients negative for COVID-19.

Discussion

Our study corroborates the association of neurologic syndromes with COVID-19 in the early pandemics. Their incidence correlated with local waves of COVID-19 infection. Although their occurrence remained lower than that of respiratory tract infections, patients with neurocovid exhibited a higher susceptibility to adverse outcomes, as did hospitalized COVID-19 patients. Among all neurological syndromes, vascular syndromes were particularly prominent, and they were more severe than comparable vascular syndromes attributed to other well-known risk factors.

As in previous viral epidemics, like HIV, ZIKV, and CHIKV, the initial associated neurologic syndromes tended to manifest in a small subset of patients and mirror fluctuations in the incidence of the primary syndrome [15–21]. We observed here, similar to previous epidemics, an average two-week interval between the onset of infection and the emergence of neurologic symptoms. This is consistent with a disease mechanism likely associated with an inflammatory process [22]. The precise mechanism(s) for viral neuropathogenesis remains to be determined. In vivo viruses may circumvent anti-viral defense barriers, enter the bloodstream and by axonal transport reach the CNS and activate innate immune responses [23].

Considering that SARS-CoV-2 is transmitted primarily through respiratory droplets [24], a CNS invasion through the olfactory sensory nerves was the first hypothesis. This was influenced by the high incidence of anosmia and MRI studies demonstrating olfactory bulb and adjacent cortical alterations [25–27]. A deeper investigation into the olfactory bulb parenchyma, however,

Table 5 General stroke versus NeurocovBR stroke

	General Stroke [11]	NeurocovBR Stroke	*p*	*OR*
n, (%)	2407 (100)	81 (100)		
Age, mean (± SD)	67.6 (± 14.4)	59.5 (± 15.5)	< 0.01	_
Female, n (%)	1248 (51.8)	46 (56.8)	0.46	_
Comorbidities, n (%)				
HBP	2118 (88)	45 (51.1)	< 0.01	0.17
DM	1126 (46.8)	28 (31.8)	< 0.05	0.60
Smoker	736 (30.6)	15 (17)	< 0.05	0.51
Hospitalization, n, (%)				
Needed ICU	597 (24.8)	46 (56.8)	< 0.01	3.78
Δt hospitalization, d, mean (± SD)	15.4 (± 20.1)	18.7 (± 23)	0.20	_
In-hospital complications, n, (%)				
Co-infections	424 (17.6)	55 (67.9)	< 0.01	6.14
Outcomes				
Death, n, (%)	503 (20.9)	45 (55.6)	< 0.01	4.73

Legends: *OR* odds ratio, *HBP* high blood pressure, *DM* diabetes mellitus, *ICU* intensive care unit, *d* days

failed to identify SARS-CoV-2 RNA vestiges [28]. Surprisingly, analysis of the adjacent leptomeninges suggested not a classic neurotropism for the olfactory bulb, but possibly the CSF as a carrier for viruses present in the bloodstream or from a scaping of sustentacular cells of the olfactory mucosa, SARS-CoV-2 target cells [28].

In our population, encephalitis patients presented with the highest frequency of anosmia/hyposmia (31.6%). This led us to suggest an association between a high viral load near the olfactory bulb and viral encephalitis. This might also be a pathway for the initiation of other associated neurological syndromes, but it is not likely to be the predominant mechanism in all cases [22].

Evaluating the vascular cases, we observed a higher proportion of patients with recognized risk factors for stroke, such as HBP (51%), DM (31.8%), obesity (15.9%) and smoking (17%) [29, 30]. However, comparing those with non-COVID stroke patients and evaluating the majority of patients with NIHSS > 15 (therefore with large vessel stroke), we realized that SARS-CoV-2 probably exerted a substantial influence on the pathogenesis of these cases.

The median timeframe of 10 days between COVID-19 and vascular syndromes also suggests an underlying state of increasing immune system activation, initially associated with vascular wall inflammation. This hypothesis gains support from a previous study [31] that compared human autopsy specimens to rhesus macaques infected with SARS-CoV-2. Their study revealed a likely evolutionary cascade of inflammatory activation during a 14-day period, where the infection triggered the up-regulation of the inflammatory and complement pathways. This resulted in the initial intense recruitment of innate immune system components, leading to significant endotelitis [31].

This phenomenon would certainly justify the occurrence of small vessel vasculitis. But, it remains unclear, however, if it is enough to address the high proportion of large vessel strokes [32–34]. In thrombectomy reports, large vessels appeared normal, while pulmonary emboli and deep venous thrombosis were prevalent in many patients [32]. This underscores the consideration of paradoxical embolism as a significant possibility [32] and indicates that vasculitis is present and contributes to COVID-19 stroke, but probably through an indirect pathway.

Our general epidemiological findings on vascular syndromes align with those of large cohorts from the Americas, Europe, and Asia [35–40]. Similar to our study, these cohorts reported younger patients, a higher proportion of ischemic strokes (predominantly large-vessel strokes), and increased mortality rates with more co-infections when compared to stroke cases predating COVID-19. Unlike our study, which focuses on all neurological syndromes, those studies were specifically designed to examine vascular syndromes. As a result, they had the statistical power and appropriate methodology to investigate both traditional stroke risk factors and those associated with neuro-COVID. However, apart from atrial fibrillation, these factors do not appear to be the sole determinants of vascular syndromes in neurocovid, reinforcing the hypothesis that an underlying mechanism related to SARS-CoV-2, possibly inflammatory, is also involved.

Another consideration in favour of indirect inflammatory COVID-19 damage to the CNS is the large proportion of patients with encephalopathy. Patients referred to different studies as having brain fog, curiously, rarely present MRI alteration or CSF pleocytosis. However, their subacute cognitive impairment is evident [41]. In a previous report [42], we discussed the occurrence of such symptoms in several infectious and autoimmune diseases. Specifically, there is a possible influence of microglial monitoring [43], with aberrant synaptic pruning in inflammatory states such as in COVID-19, accompanied by massive complement recruitment. [43–45].

Surprisingly, neurologic syndromes occurred in our cohort regardless of COVID-19 severity. Nevertheless, it became evident in our study that neurocovid places a considerable burden on the healthcare system, increasing the demand for hospital beds and medical support. This is manifested by the considerably higher odds ratios for hospitalizations and death. Patients were

often hospitalized for more than 20 days, potentially in ICU settings. Furthermore, it is worth noting that surviving patients with high specific severity scores (mRS, GCS, LOS, NIHSS, ONLS) required an extended period of rehabilitation and faced a heightened risk of post-discharge mortality due to secondary complications [46–50].

A recurring challenge in large neurovirology cohorts, and thus a limitation, is the difficulty in gathering a sufficient number of subjects that meet appropriate criteria for statistical comparisons. Our cohort was no exception and faced the additional issue of non-consecutive inclusions due to asynchronous lockdown periods, shortage of personal protective equipment limiting neurologist assessments, and other pandemic restrictions. These conditions limited, for instance, our capability to perform subgroup analysis to statistically distinguish primary neurological effects of SARS-CoV-2 from complications secondary to systemic conditions, such as AKI, present in 40.6% of our sample.

To mitigate these limitations, however, we implemented rigorous inclusion criteria based on an experienced neurological evaluation, classified patients into strict syndromic categories, and included neurology centers from different states with different economic backgrounds, yet all allocated in the country's COVID-19 epicenters. We believe these measures approximate our findings from the actual numbers of neurological manifestations of COVID-19 in Brazil.

Conclusion

In conclusion, our findings illustrate the seriousness of COVID-19-associated neurologic syndromes, shedding light on how they intensify the burden on the healthcare system and may result in potential chronic, long-term consequences. The resemblance of certain data to that of previous viral epidemics underscores the need for establishing ongoing neurovigilance centers with the capacity for rapid national deployment. This will substantially aid in the formulation of timely recommendations to reduce mortality and disability.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

A.M.B.M., C.M.R. and A.C.P.O. contributed with study concept and design; A.M.B.M., A.B.F.G., F.M.M.C., F.T.M.O., L.S.A.S., F.E.D., J.V.L.M., M.V.F., J.E.V. R.M.N.M., J.S., V.R.P., R.M.M., C.M.R. and A.C.P.O. contributed to data acquisition; analysis and interpretation of data; all authors contributed with critical revision of the manuscript from important intellectual content.

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Availability of data and materials

All data available regarding the patients reported in this study will be available to any qualified researcher upon pertinent request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study obtained approval from the ethics committee at the Universidade de São Paulo (CAAE: 31378820.1.1001.0068) and the ethics committees of the study sites. Written informed consent was obtained from all patients or their next of kin, and their personal information is protected by ethical procedures. The study adheres to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments, as well as relevant Brazilian regulations.

Consent for publication

Not applicable.

Competing interests

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Original article

NEUROLOGICAL BURDEN OF COVID-19: A STUDY OF CEREBROVASCULAR EVENTS IN A BRAZILIAN TERTIARY HOSPITAL

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Abstract

Introduction: Neurological complications, particularly cerebrovascular diseases, have emerged as a significant concern in patients with coronavirus disease (COVID-19). Understanding these characteristics is essential for improving the clinical management and outcomes.

Materials and methods: This observational study analyzed data from patients hospitalized at Hospital da Irmandade da Santa Casa de Misericórdia de São Paulo between 2020 and 2021. We included patients aged ≥18 years with a confirmed SARS-CoV-2 infection and a diagnosis of cerebrovascular disease within 60 days of symptom onset. Clinical, demographic, and outcome data were collected and analyzed.

Results: Among the 1998 patients with confirmed COVID-19, 550 (27.5%) presented with neurological symptoms. Fifty patients were diagnosed with cerebrovascular disease: 27 (54%) had ischemic stroke, 20 (40%) had hemorrhagic stroke, and three (6%) had cerebral venous thrombosis. Patients with neurological symptoms had significantly higher mortality rates and longer hospital stays than those without neurological symptoms.

Conclusion: This study highlights the severity and clinical impact of cerebrovascular events in COVID-19 patients. These findings reinforce the need for early neurological evaluation, and underscore the importance of accessible and cost-effective strategies for surveillance, prevention, and timely intervention in high-risk populations.

Key words: COVID-19, cerebrovascular disease, stroke, SARS-CoV-2, cerebral venous thrombosis, neurological complications

Resumen

Carga neurológica en COVID-19: estudio de eventos cerebrovasculares en un hospital terciario brasileño

Introducción: Las complicaciones neurológicas, en particular las enfermedades cerebrovasculares, han surgido como una preocupación importante en pacientes con enfermedad por coronavirus (COVID-19). Comprender estas características es esencial para mejorar el manejo clínico y los resultados.

Materiales y métodos: Este estudio observacional analizó datos de pacientes hospitalizados en el Hospital da Irmandade da Santa Casa de Misericórdia de São Paulo entre 2020 y 2021. Incluimos pacientes ≥18 años con infección confirmada por SARS-CoV-2 y un diagnóstico de enfermedad cerebrovascular dentro de los 60 días posteriores al inicio de los síntomas. Se recopilaron y analizaron datos clínicos, demográficos y de resultados.

Resultados: Entre los 1998 pacientes con COVID-19 confirmada, 550 (27.5%) presentaron síntomas neurológicos. Cincuenta pacientes fueron diagnosticados con enfermedad cerebrovascular: 27 (54%) presentaron accidente cerebrovascular isquémico, 20 (40%) accidente cerebrovascular hemorrágico y tres (6%) trombosis venosa cerebral. Los pacientes con síntomas neurológicos tuvieron tasas de mortalidad significativamente más altas y estancias hospitalarias más prolongadas que aquellos sin síntomas neurológicos.

Conclusion: Este estudio destaca la gravedad y el impacto clínico de los eventos cerebrovasculares en pacientes con COVID-19. Estos hallazgos refuerzan la necesidad

de una evaluación neurológica temprana y subrayan la importancia de estrategias accesibles y rentables para la vigilancia, la prevención y la intervención oportuna en poblaciones de alto riesgo.

Palabras clave: COVID-19, enfermedad cerebrovascular, ACV, SARS-CoV-2, trombosis cerebral venosa, complicaciones neurológicas

KEY POINTS
Current knowledge

- The clinical impact of COVID-19 is still being observed. Regarding neurological aspects, evidence about the occurrence of cerebrovascular events is scarce.

Contribution of the article to current knowledge

- This research contributes by highlighting the clinical severity of these complications in Brazil, reinforcing the need for early diagnosis, prevention, and management strategies to reduce mortality and sequelae.

The relationship between infectious agents, particularly viral ones, and neurological manifestations with vascular involvement in the central nervous system has consistently been the subject of clinical and epidemiological studies and analyses[1].

Studies gained momentum mainly after December 2019, when in the city of Wuhan, China, the emergence of a new, highly pathogenic virus from the Coronaviridae family, called SARS-CoV-2, responsible for the COVID19 pandemic, was observed[2].

Neurotropism is a common feature of coronaviruses. Brain involvement may result from the dissemination of SARS-CoV-2 through systemic circulation or via the olfactory pathway through the cribriform plate during the early or late phase of infection. Given the epidemiological, health, morbidity, and mortality relevance of influenza-like syndromes with neurological complications, especially those caused by SARS-CoV-2, and the possible relationship with the occurrence of cerebrovascular disease, new studies are necessary to evaluate the presence of neurological signs and symptoms in patients with COVID-19. The studies were conducted to prepare neurologists and non-neurologists for the rapid detection and treatment of potentially fatal and disabling conditions[3-5].

Regarding cerebrovascular diseases associated with COVID-19, several studies initially attempted to establish, describe, or better study the relationship between the events and infectious agents. In May 2020, Ghannam et al. reported that cerebrovascular incidents accounted for 48.8% of all neurological events in patients with COVID-19; of these, 87.5% had ischemic strokes, 5% had cerebral venous thromboses, 5% had intraparenchymal hemorrhages, and 2.5% had subarachnoid hemorrhages[6].

In this study, we will share the experience of a tertiary neurological reference center for cerebrovascular diseases that was part of the NeurocovBR study group during the first wave of COVID-19 cases, highlighting the study of neurological manifestations in patients with COVID19 and cerebrovascular diseases in the service.

Materials and methods

Local of the study

In March 2020, following the confirmation of the first case of COVID-19 in Brazil, the NeurocovBR study group was established[7,8].

The data presented in this work refer to cases evaluated only at the Hospital da Irmandade da Santa Casa de Misericordia de São Paulo and aimed to study the cases of patients with COVID-19 and cerebrovascular diseases.

Inclusion criteria required patients to be 18 years of age or older, fulfill the World Health Organization criteria for COVID-19[9], meet the provisional Ellul criteria for SARS-CoV-2 neurological-associated syndromes[10], and exhibit novel neurological symptoms within 60 days of COVID-19 infection.

Data assessment

Demographic information was obtained from medical records, patient interviews, or, when necessary, interviews with a designated proxy if the patient was unable to provide details directly. The severity of COVID-19 was determined based on the symptoms and clinical signs observed on the day preceding the onset of initial neurological symptoms. To assess overall patient outcomes, we gathered in-hospital data, including the need for intensive care unit (ICU) admission and/or mechanical ven-

tilation (MV) support as well as the occurrence of complications. Additionally, we documented the duration of hospitalization, recorded mortality cases, and monitored the time to death. All patients underwent SARS-CoV-2 testing using one or both of the following methods: ELISA for IgA in serum samples and/or RT-PCR from oropharyngeal swabs. Vascular syndromes included confirmed cases of ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis.

Statistical analysis

Continuous data were expressed as the mean with standard deviation or as the median accompanied by the interquartile range (IQR). Categorical data are reported as frequencies and percentages.

Standard protocol approvals, registrations and patient consents

This study was approved by the ethics committee of the University of São Paulo (CAAE: 31378820.1.1001.0068) and ethics committees of the study sites. Written informed consent was obtained from all the patients or their next of kin, and their personal information was protected by ethical procedures. The study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments as well as relevant Brazilian regulations.

Results

Patient selection

Patients with positive test results for the Sars-CoV-2 virus (1998 patients) were included. Of these patients, 550 were admitted to the hospital because of neurological symptoms and 1448 without neurological symptoms. Neurological manifestations were monitored in the hospital environment through in-person evaluations by a neurology team. The inclusion of patients within the group with cerebrovascular diseases (50 patients; 27 with ischemic stroke, 20 with hemorrhagic stroke and 3 with cerebral venous thrombosis) occurred through anamnesis, physical examination, and complementary tests that confirmed the presence of cerebrovascular disease.

Analysis of the length of hospital stay and the outcome of patients hospitalized with confirmed COVID-19 (hospital discharge versus death), in relation to the cases that presented neurological manifestations upon admission and those who were admitted to the hospital environment without neurological manifestations, showed that the length of hospital stay was longer among patients who died in relation to those who were discharged from hospital and that this difference was statistically significant among all patients classified with COVID-19 and in the subgroup of patients with neurological symptoms upon admission (Table 1).

Through these results, we can also observe the long hospitalization time of these patients from the first wave of covid19, observe the high mortality rate, and how admission with neurological symptoms was a determinant of greater severity (Fig. 1).

Analyzing the most frequent diagnoses during the syndromic approach upon hospital admission of patients, it can be seen that most patients were screened for neurological symptoms and respiratory symptoms, with most receiving a final diagnosis of neurological disease (cerebrovascular disease) and/or COVID-19. A more detailed analysis revealed that most patients with neurological symptoms were only diagnosed with COVID-19 through screening that was carried out during the pandemic, as these were not the predominant symptoms at admission (Table 2).

Table 1 | Analysis of length of hospital stay and outcome (hospital discharge versus death) in patients with COVID-19, in relation to cases that presented neurological manifestations, and those patients admitted to the hospital without neurological manifestations. São Paulo-SP, 2020-2021

Variable	Total n=1998	Discharge n=1231	Death n=767	p- value
Time in hospitalization (months)	11.3±14.3	25.8±6.3	61.2±24.1	≤0.001
Neurological (n=550)	10.6±21.9	9.3±18.6	14.8±30.1	≤0.001
Non- neurological (n=1448)	11.6±9.9	11.6±9.9	11.7±10.0	0.755

Figure 1 |Estimated survival time, according to clinical diagnosis of COVID19 and neurological or non-neurological symptoms during hospital admission. São Paulo-SP, 2020-2021. (p ≤0.001 - Log Rank Test)

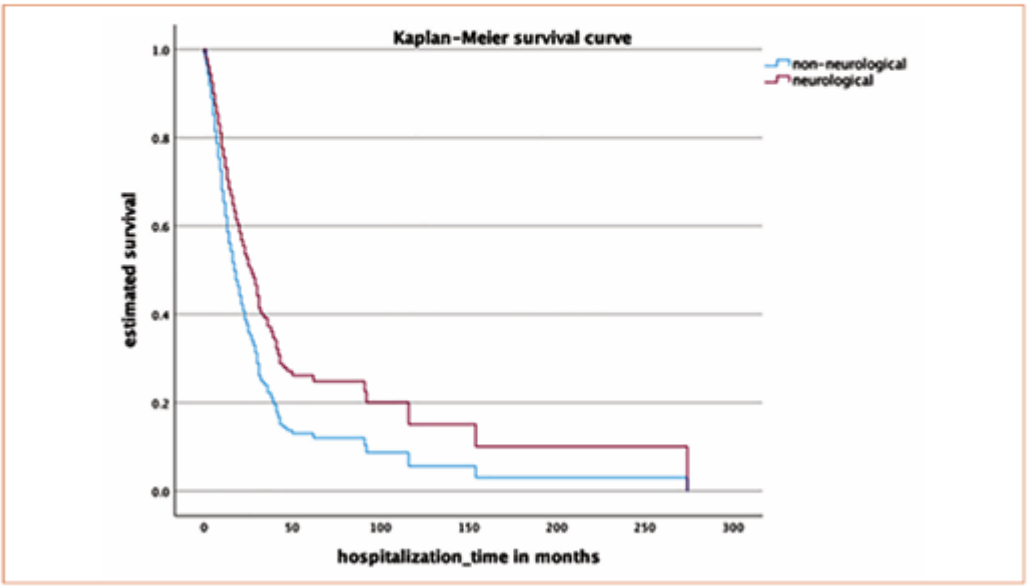

Table 2 | Prevalence of the most frequent syndromes according to the international coding of diseases, in patients with neurological symptoms and without neurological symptoms on admission, hospitalized, with confirmed diagnosis of COVID-19, São Paulo-SP, 2020-2021

Syndromic diagnoses in patients with COVID-19	Non-neurological n=1448 (%)	Neurological n=552 (%)
Vertebrobasilar syndrome	----	49 (8.9)
Carotid syndrome	1 (0.1)	20 (3.6)
Transient ischemic stroke	----	43 (7.8)
Subarachnoid hemorrhage	1 (0.1)	19 (3.4)
Cerebral infarction	-----	34 (6.2)
Viral pneumonia	437 (30.2)	----
Adult respiratory distress syndrome	60 (4.1)	----
Acute respiratory failure	42 (2.9)	----

By assessing the prevalence of the main causes of death according to the international coding of the most frequent diseases in patients with and without neurological symptoms who were hospitalized and diagnosed with COVID-19, it can be seen that those who were admitted with neurological symptoms died due to neurological disease and not necessarily from the COVID-19 infection (Table 3).

Similarly, drawing a parallel, it is evident that patients with non-neurological symptoms and COVID-19 died mostly due to metabolic conditions, sepsis, and respiratory complications (i.e., not due to neurological causes) (Table 4).

Discussion

In this study, 1498 patients with COVID-19 were studied, of whom 552 presented with neu-

Table 3 | Prevalence of causes of death according to the international coding of most frequent diseases, in patients with neurological symptoms and without neurological symptoms, hospitalized and diagnosed with COVID-19, São Paulo-SP, 2020-2021

Most frequent deaths in patients with COVID-19	Non-neurological n=1448 (%)	Neurological n=552 (%)
Total deaths	809 (55.9)	425(77.0)
Septicemia	27 (1.9)	4 (0.7)
COVID-19	304 (21.0)	-------
Hyperkalemia	10 (0.7)	------
Subarachnoid hemorrhage	1 (0.1)	19 (3.4)
Cerebrovascular disease	1 (0.1)	27 (4.9)
Respiratory failure	21 (1.5)	7 (1.3)
Circulatory shock	48 (3.3)	4 (0.7)
Severe acute respiratory syndrome	23 (1.6)	-------

Table 4 |Prevalence of comorbidities, initial symptoms and most frequent hospitalization indicators in patients with cerebrovascular disease hospitalized with COVID-19, comparison between patients with ischemic stroke and patients with hemorrhagic stroke. São Paulo-SP, 2020-2021

Variables Comorbidities Symptoms Hospitalization indicators	Total n=47 (%)	Stroke ischemic n=27 (57.4%)	Stroke hemorrhagic n=20 (42.6%)	p- value
SAH	**26 (55.3)**	18 (66.7)	8 (40.0)	0.069
DM	**17 (36.2)**	13 (48.1)	4 (20.0)	0.067
Alcoholism	**2 (4.3)**	1 (3.7)	1 (5.0)	0.828
Obesity	**11 (23.4)**	7 (25.9)	4 (20.0)	0.737
Active neoplasia	**5 (10.6)**	5 (18.5)	-----	0.063
Smoking	**10 (21.3)**	7 (25.9)	3 (15.0)	0.481
Previous stroke	**5 (10.6)**	5 (18.5)	-----	0.063
Fever	**35 (74.5)**	20 (74.1)	15 (75.0)	0.943
Cough	**40 (85.0)**	25 (92.6)	15 (75.0)	0.119
Myalgia	**8 (17.0)**	5 (18.5)	3 (15.0)	0.751
Headache	**12 (25.5)**	6 (22.2)	6 (30.0)	0.545
Diarrhea	**3 (6.4)**	2 (7.4)	1 (5.0)	0.739
Anosmia	**1 (2.1)**	1 (3.7)	-----	0.384
Hospitalization due to COVID	**42 (89.4%)**	26 (96.3%)	16 (80.0%)	0.148
COVID ICU	**41 (87.2%)**	25 (92.6%)	16 (80.0%)	0.379
VM by COVID	**38 (80.9%)**	22 (84.6%)	16 (80.0%)	0.898
Days of hospitalization (mean ± SD)	**13.7±9.7**	13.5±10.0	13.7±6.9	0.510
COVID-19 classification				
Asymptomatic	**1 (2.1%)**	-----	1 (5.0%)	
Severe	**9 (19.2%)**	6 (22.2%)	3 (15.0%)	
Critical	**30 (63.8%)**	17 (63.0%)	13 (65.0%)	
Moderate	**5 (10.6%)**	3 (11.1%)	2 (10.0%)	
Mild	**2 (4.3%)**	1 (3.7%)	1 (5.0%)	

SAH: systemic arterial hypertension; DM: diabetes mellitus; ICU: intensive care unit; VM: mechanical ventilation

rological symptoms during hospitalization that were suspected to have neurological syndromes (sequelae of previous events, recrudescence of signs and/or symptoms, or acute conditions). The general objective of interconsultations is to distinguish between old conditions that have worsened due to the infectious condition or to identify new events that may require urgent, emergency, or specific outpatient procedures. We observed that approximately 2.3% of patients presented with neurological syndromes compatible with recent cerebrovascular disease (acute/subacute). Of the patients with confirmed cases of recent cerebrovascular disease, 27 were affected by ischemic stroke, 20 by hemorrhagic stroke (1 patient with both findings), and 3 by cerebral venous thrombosis. These data are like those of previous studies whose evaluation period is practically concomitant with that carried out by our group (first and second waves of COVID-19 cases before mass vaccination)[11–14].

When evaluating international records of cases of cerebrovascular disease in hospitalized patients with SARS-CoV-2 infection, we found that the overall risk of stroke varied considerably from places with a rate of 0.5%[15], others with 0.9% of patients hospitalized with COVID-19[16], and some with rates as high as 2%. This difference in incidence rates may be related to the profile of the hospital structures studied, given the difference in the severity of patients hospitalized with COVID-19 infection (higher in tertiary and quaternary services in the care lines) prevalence of cardiovascular risk factors in the population studied (higher in outpatient referral services for clinical specialties) ability to accurately determine and diagnose all strokes (at a time when medical services were overloaded) and differences in the availability of institutional complementary examinations during the pandemic period under study.

In the present study, 27.5% of patients hospitalized for COVID-19 presented neurological manifestations, notably 50 cases of acute cerebrovascular disease (54% ischemic, 40% hemorrhagic, and 6% cerebral venous thrombosis). Mao et al. (2020)[11], in their Wuhan cohort, identified neurological manifestations in 36.4% of patients, with cerebrovascular events being among the most serious findings, especially in patients with severe disease and pre-existing risk factors. The comparison suggests a consistent pattern across different scenarios, reinforcing that the clinical severity and systemic inflammatory profile of COVID-19 are associated with significant neurological complications. However, the relatively high proportion of hemorrhagic stroke in our series may indicate regional differences related to comorbidities, anticoagulation use during hospitalization, and the severity of cases treated at a tertiary referral hospital.

When compared with data from Yaghi et al. (2020)[16], who analyzed hospitalized patients in New York and found a stroke rate of 0.9% among those infected with SARS-CoV-2, our findings reveal a higher incidence (2.5%). These same authors highlighted that ischemic events were predominant and were associated with high levels of inflammatory and prothrombotic markers, suggesting a central role of the systemic inflammatory response in the pathophysiology. In contrast, in the present study, there was a more balanced distribution between ischemic and hemorrhagic events, which may reflect both differences in demographic profile and prevalence of hypertension and diabetes, as well as challenges in clinical management in the context of hospital overload. This comparison highlights that, although thrombotic mechanisms are consistent globally, clinical presentations and proportions of stroke subtypes may vary according to local and healthcare system characteristics.

The patients evaluated in the study at our center mostly presented with COVID-19 and cerebrovascular disease associated with severe inflammation and infection, and therefore, were in a hypercoagulable state. Significantly increased inflammation may be one of the reasons for abnormal coagulation function in the early phase and may also be one of the reasons for the onset and predisposition to cerebrovascular disease[17]. In general, the mechanism underlying cerebrovascular disease caused by COVID-19 remains unclear. Currently, most opinions still focus on the hypercoagulable state caused by systemic inflammation[18,19].

In recent years, evidence has shown that several acute and chronic cardiovascular conditions can occur after COVID-19 infection, including acute pulmonary embolism, deep vein

thrombosis, heart failure, arterial hypertension, atrial fibrillation and diabetes. All these conditions, especially if they remain undiagnosed and untreated, may represent concomitant risk factors for the onset of ischemic stroke. However, it is not yet possible to determine whether the onset of these new cardiovascular diseases represents a direct consequence of COVID-19, or whether the virus may merely act as a triggering factor in a clinical condition.

The data obtained are useful to alert the population of the risks and thus minimize the possibility of cerebrovascular disease events during hospitalization, in the convalescence and recovery phase of the infectious process, and after hospital discharge in COVID-19 survivors. Additional studies are needed to determine the potential benefits of anticoagulant therapy (as well as doses and duration of use) in reducing the risk of ischemic stroke[20].

Compared with reports of ischemic events, fewer cases of hemorrhagic stroke were observed in patients with COVID-19, as in our case series[21]. Based on a cohort of 755 COVID-19-positive patients (out of a total of 3824) in whom neuroimaging studies were performed during hospitalization, Dogra et al. estimated that the prevalence of intracranial hemorrhage (ICH) was 4.4% (n = 37), representing almost 11% of all cerebrovascular diseases in the investigated group. Almost 80% of ICH cases occur in male patients. The mean age of the COVID-19 patients with acute cerebrovascular disease was higher than that of individuals not affected by the infection. Fifteen percent of ICH cases were parenchymal hemorrhages with mass effects and brain herniation, with the mortality rate reaching 100%[22].

Punctate hemorrhages accounted for 25% of intracranial hemorrhages, while small-to-moderate hemorrhages were observed in 60% of the patients. It is noteworthy that 67% of the investigated individuals received therapeutic anticoagulation and 9% received prophylactic anticoagulation before the onset of intracranial hemorrhage. Given these data, it seems that the use of anticoagulation, whether prophylactic or full, should always be associated with a good overall clinical evaluation so that the risks and benefits of this medical intervention can be weighed[22].

In a systematic review, Maury et al. analyzed data on COVID-19-related intracranial hemorrhage from nine cohort studies from Belgium, China, France, Italy, the United Kingdom, and the United States. The estimated prevalence of ICH ranged from 0.2% in the French cohort, which included 46 centers, to 0.8% in a study of three centers in Italy[23,24]. data were closer to the values found in our case series.

Regarding cerebrovascular complications due to Sars-CoV-2 infection, the relationship between cerebral venous thrombosis (CVT) and COVID-19 is noteworthy because in infected individuals, the incidence of CVT is estimated at 42.8 per million[25].

The incidence was even higher among hospitalized COVID-19 patients (231 per million). For better understanding and comparison, the incidence of CVT in the pre-COVID era was estimated at 13.9–20.2 per million[26–29].

We had three cases in our case series, which within the context of more than a thousand patients infected by a virus with neurotropism and in serious conditions, we can conclude that it is within numbers close to pre-pandemic values.

For comparative analysis purposes, we can use the largest published series of cases of CVT associated with COVID-19 in 2024, Scutelnic et al.[30] published data collected in 21 hospitals in 13 countries, with 70 patients, showing that, although not significant, the mortality rate in patients with CVT and COVID-19 was higher than in controls (7% vs. 3%). These results may have clinical significance, indicating that COVID-19 contributes to the sequelae of CVT. In this study, most patients with CVT due to COVID-19 (87%) were asymptomatic, mild, or moderate. In addition, the initial characteristics were quite similar in the COVID-CVT and control groups, probably explaining the similar results in functional outcomes of surviving patients. The published data show important analyses regarding signs and symptoms, assessment of disability scales, and functional outcomes; however, few differences in relation to the results were observed in the pre-pandemic era[30].

Limitations include the fact that this is an observational study and is not multicenter, which limits external validity. Furthermore, data collection occurred during the first outbreak of the

pandemic, a period marked by overburdened health services and restricted access to additional testing, which may have led to underreporting or delayed diagnosis of cerebrovascular events. Another important aspect was the lack of post-discharge follow-up, making it impossible to assess the functional progress and possible late sequelae of patients.

In conclusion, the absolute number of cerebrovascular disease cases has considerably increased. The contribution of several risk factors has also changed in recent years, and we must remember the possibility of an association between cerebrovascular disease and infectious agents. In this study, we can observe the severity of cases associated with COVID-19 and thus provide information that may help in understanding the importance of effective, accessible, and economical measures to improve surveillance and prevention of cerebrovascular diseases, especially in relation to the control of modifiable risk factors, such as systemic arterial hypertension (SAH), changes in lifestyle (smoking), and environmental factors (exposure to infectious agents). Thus, we must remember that access to intensive care and early rehabilitation can modify the outcomes and sequelae presented, as well as make clarifies how they are essential factors in the lines of care, especially in the public health environment, where they need to be implemented urgently to reduce the disabling sequelae resulting from stroke.

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Conflict of interest: None to declare

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5. CONSIDERAÇÕES FINAIS

Nos últimos anos, evidências têm demonstrado que diversas condições cardiovasculares agudas e crônicas podem ocorrer após a infecção por COVID-19, incluindo embolia pulmonar aguda, trombose venosa profunda, insuficiência cardíaca, hipertensão arterial sistêmica, fibrilação atrial e diabetes mellitus (1–4). Todas essas condições, especialmente quando não diagnosticadas ou tratadas adequadamente, podem representar fatores de risco concomitantes para o desenvolvimento de acidente vascular cerebral isquêmico (5,6).

Ainda não é possível determinar com precisão se o surgimento dessas novas doenças cardiovasculares representa uma consequência direta da infecção pelo SARS-CoV-2 ou se o vírus atua como um fator desencadeante em indivíduos predispostos (7,8). Entretanto, a crescente incidência de eventos cerebrovasculares observada após a pandemia reforça a necessidade de vigilância clínica e acompanhamento prolongado dos pacientes acometidos pela infecção (9,10).

Os dados obtidos neste estudo contribuem para alertar a comunidade médica e a população sobre os riscos de eventos cerebrovasculares durante a hospitalização, na fase de convalescença e no período pós-alta em sobreviventes da COVID-19 (11–13). Além disso, reforçam a importância de estratégias preventivas e terapêuticas específicas para esse grupo de pacientes. Estudos adicionais ainda são necessários para avaliar os benefícios potenciais da terapia anticoagulante, assim como suas doses ideais e duração de uso, na redução do risco de acidente vascular cerebral isquêmico (14,15).

Em comparação com os relatos de eventos isquêmicos, observou-se menor número de casos de acidente vascular cerebral hemorrágico entre os pacientes com COVID-19, corroborando achados de outras séries clínicas (16–19). Em uma coorte de 755 pacientes com infecção confirmada, a prevalência de hemorragia intracraniana foi de 4,4%, representando aproximadamente 11% de todas as doenças cerebrovasculares no grupo estudado (20). A maioria dos casos ocorreu em homens e esteve associada a altas taxas de mortalidade, sobretudo nas hemorragias parenquimatosas extensas e com efeito de massa (21,22).

Em relação à trombose venosa cerebral, a associação com a infecção por SARS-CoV-2 mostrou-se relevante. Em indivíduos infectados, a incidência estimada foi de 42,8 por milhão, valor superior ao observado na era pré-pandêmica, que variava entre 13,9 e

20,2 por milhão (23–26). No presente estudo, foram identificados três casos de trombose venosa cerebral, achado compatível com dados internacionais e que reforça a hipótese de que a infecção viral possa atuar como fator precipitante em pacientes predispostos (27,28).

Os achados aqui apresentados sugerem que o uso de anticoagulação, seja em dose profilática ou terapêutica plena, deve sempre ser ponderado em conjunto com uma avaliação clínica criteriosa, de modo a equilibrar riscos e benefícios. A ocorrência de eventos hemorrágicos em pacientes sob anticoagulação reforça a importância do monitoramento cuidadoso e da individualização da conduta terapêutica (29,30).

Entre as limitações do estudo, destacam-se o caráter observacional e unicêntrico, o que restringe a validade externa, e o fato de a coleta de dados ter ocorrido durante a primeira fase da pandemia, período marcado por sobrecarga dos serviços de saúde e acesso limitado a exames complementares. A ausência de acompanhamento pós-alta hospitalar também impossibilitou a avaliação de sequelas tardias e da recuperação funcional a longo prazo (31,32).

Em conclusão, observou-se aumento considerável no número absoluto de casos de doença cerebrovascular durante a pandemia de COVID-19, com alteração do perfil de risco e da gravidade dos pacientes acometidos (33,34). A infecção pelo SARS-CoV-2 mostrou-se associada a mecanismos vasculares complexos, envolvendo inflamação sistêmica, disfunção endotelial e estado pró-trombótico (35,36).

Os resultados reforçam a importância da adoção de medidas eficazes, acessíveis e sustentáveis voltadas à **prevenção e vigilância das doenças cerebrovasculares**, com especial atenção ao controle rigoroso dos fatores de risco modificáveis, como hipertensão arterial sistêmica, diabetes mellitus, tabagismo e dislipidemia (37–39).

Além disso, o acesso oportuno à **terapia intensiva e à reabilitação precoce** deve ser considerado um componente essencial na linha de cuidado do paciente com acidente vascular cerebral, sobretudo no contexto da saúde pública, onde tais medidas podem reduzir significativamente a mortalidade e as sequelas incapacitantes associadas ao AVC (40).

6. REFERÊNCIAS BIBLIOGRÁFICAS

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7. ANEXOS

ANEXO 1: APROVAÇÃO PELO COMITÊ DE ÉTICA EM PESQUISA

SANTA CASA DE MISERICÓRDIA DE SÃO

PlataForma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: MANIFESTAÇÕES NEUROLÓGICAS AGUDAS ASSOCIADAS AO VÍRUS SARS-CoV-

Pesquisador: FRANCISCO TOMAZ MENESES DE OLIVEIRA

Área Temática:

Versão: 2

CAAE: 31378820.1.2007.5479

Instituição Proponente: IRMANDADE DA SANTA CASA DE MISERICORDIA DE SAO PAULO

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.434.289

Apresentação do Projeto:

Trata-se de um estudo observacional prospectivo, que avaliará as características epidemiológicas, clínicas,laboratoriais, eletrofisiológicas e radiológicas de pacientes com diagnóstico de encefalite, mielite e/ou polineuropatia periférica aguda durante período de epidemia de SARS-Cov-2. O centro proponente do estudo será o Instituto de Medicina Tropical da Faculdade de Medicina da Universidade de São Paulo e os centros participantes: Instituto de Infectologia Emílio Ribas, Hospital Israelita Albert Einstein, Hospital Geral de Fortaleza, Hospital Sírio Libanês Brasília, Hospital Universitário de Brasília e Hospital Santa Casa de São Paulo.

Objetivo da Pesquisa:

Objetivo Primário:

Caracterizar o perfil epidemiológico, clínico, laboratorial, eletrofisiológico e radiológico de pacientes acometidos por mielite, encefalite, AVC e/ou polineuropatia periférica aguda em vigência de epidemia associada ao vírus SARS-Cov-2.

Objetivo Secundário:

1. Descrever as características epidemiológicas dos sujeitos, identificando características próprias ao acometimento por SARS-CoV-2;

2. Descrever as características clínicas de fase aguda e desfecho clínico após 6 meses dos sujeitos;

3. Descrever as características de exames complementares laboratoriais, eletrofisiológicos e radiológicos apresentados pelos sujeitos, identificando características próprias ao acometimento

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por SARS-CoV4. Caracterizar e confirmar o diagnóstico de SARS-Cov-2 (molecular e sorológico) no sistema nervoso central e
periférico através do liquor e/ou sangue dos sujeitos;5. Avaliar e comparar a persistência de SARS-CoV-2 no momento do diagnóstico neurológico e 90 dias após em liquor e soro dos pacientes;6. Avaliar e comparar a mensuração de biomarcadores de degeneração neuronal, citocinas e quimiocinas pró e anti-inflamatórias no momento do diagnóstico neurológico e 90 dias após em liquor e soro dos pacientes;
7. Identificar possíveis fatores prognósticos de pacientes com manifestações neurológicas associadas a infecção por SARS-CoV-2.

Avaliação dos Riscos e Benefícios:

Riscos:

Acidentalmente dados poderão ser expostos ou perdidos em caso de furto ou roubo de material de pesquisa.

Benefícios:

1.O conhecimento sobre os sintomas e sinais das síndromes avaliadas na vigência da SARS-CoV-2, ajudando na melhoria do atendimento de mais pessoas que a desenvolvam no futuro;

2.O conhecimento sobre possíveis fatores de risco para o surgimento das síndromes avaliadas na vigência da SARS-CoV-2;

3.Contribuição para o planejamento em saúde pública de síndromes neurológicas na vigência da SARS-CoV -2.

Comentários e Considerações sobre a Pesquisa:

Foi solicitado esclarecimento referente a frase descrita no TCLE e TALE: "IREMOS PEDIR PARA VOCÊ A DOAÇÃO DE SANGUE E DE LIQUOR (LIQUIDO ESPINHAL), visto que a coleta destes materiais já foi feita em função da doença que o paciente manifesta.

O Pesquisador afirmou que estes procedimentos fazem parte de conduta realizada em função da doença. Então não se faz necessária a descrição no TCLE e TALE a coleta de sangue e liquor.

Considerações sobre os Termos de apresentação obrigatória:

Apresenta folha de rosto, TCLE e TALE, descrição dos centros participantes do estudo e orçamento detalhado.

Conclusões ou Pendências e Lista de Inadequações:

O pesquisador realizou alterações no TCLE e TALE atendendo a solicitação do CEP.

A frase:"IREMOS PEDIR PARA VOCÊ A DOAÇÃO DE SANGUE E DE LIQUOR (LIQUIDO ESPINHAL) foi alterada para:
"A coleta destes materiais já foi feita como parte do tratamento e diagnóstico habitual da doença que o (a) senhor (a) manifesta e será repetida após 3 meses, por indicação do seu médico (a), para a realização de alguns exames, portando você não será submetido (a) a estes exames novamente somente para fins deste estudo.

Estas alterações também foram realizadas no TALE conforme descrito abaixo:

"A coleta destes materiais já foi feita como parte do tratamento e diagnóstico habitual da doença que seu (a) filho (a) manifesta e será repetida após 3 meses, por indicação do seu médico (a), para a realização de alguns exames, portando ele (a) não será submetido (a) a estes exames novamente somente para fins deste estudo".

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1601108.pdf	24/11/2020 08:35:42		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	NC_TCLE_ASSENTIMENTO_SC.pdf	24/11/2020 08:35:12	Rosa Maria Nascimento Marcusso	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	NC_TCLE_ASSENTIMENTO_SC.docx	24/11/2020 08:34:54	Rosa Maria Nascimento Marcusso	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	NC_TCLE_PAIS_SC.pdf	24/11/2020 08:34:28	Rosa Maria Nascimento Marcusso	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	NC_TCLE_PAIS_SC.docx	24/11/2020 08:33:48	Rosa Maria Nascimento Marcusso	Aceito
TCLE / Termos de Assentimento / Justificativa de	NC_TCLE_SC.pdf	24/11/2020 08:33:35	Rosa Maria Nascimento Marcusso	Aceito

SANTA CASA DE MISERICÓRDIA DE SÃO

Ausência	NC_TCLE_SC.pdf	24/11/2020 08:33:35	Rosa Maria Nascimento Marcusso	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	NC_TCLE_SC.docx	24/11/2020 08:33:20	Rosa Maria Nascimento Marcusso	Aceito
Declaração de Instituição e Infraestrutura	Of_ACPC_02992020.pdf	22/10/2020 10:28:36	HAMANDA SILVA OLIVEIRA	Aceito
Outros	Manifestacoes_SantaCasa.pdf	22/09/2020 20:55:14	Rosa Maria Nascimento Marcusso	Aceito
Folha de Rosto	Folha_Rosto_SC.pdf	24/08/2020 06:53:49	Rosa Maria Nascimento Marcusso	Aceito
Projeto Detalhado / Brochura Investigador	NC_Projeto_submissao_cep_plataforma_brasil_SC.docx	31/07/2020 11:55:15	Rosa Maria Nascimento Marcusso	Aceito
Outros	NC_emenda_02.pdf	07/07/2020 10:31:44	Aline de Moura Brasil Matos	Aceito
Outros	NC_emenda_01.doc	11/05/2020 12:32:06	Aline de Moura Brasil Matos	Aceito
Outros	NC_declaracao_custos.docx	04/05/2020 14:14:56	Aline de Moura Brasil Matos	Aceito
Outros	NC_centros_participantes.docx	04/05/2020 10:48:53	Aline de Moura Brasil Matos	Aceito
Outros	Apendice_1_Instrumento.pdf	26/04/2020 22:35:16	Aline de Moura Brasil Matos	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 02 de Dezembro de 2020

Assinado por:
Vera Lúcia dos Santos Alves
(Coordenador(a))

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ANEXO 2: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Caro Participante:

Gostaríamos de te convidar para participar voluntariamente da pesquisa intitulada "**PERFIL DE PACIENTES COM COVID19 E DOENÇA CEREBROVASCULAR EM UM CENTRO DE REFERÊNCIA DE NEUROLOGIA EM SÃO PAULO, BRASIL**", que se refere a um projeto de pesquisa coordenado pelo Dr Francisco Tomaz Meneses de Oliveira, médico da neurologia da Irmandade da Santa Casa de Misericórdia de São Paulo, que possui como orientador o Prof. Dr Rubens José Gagliardi.

Este estudo tem como objetivo estudar a prevalência de complicações cerebrovasculares nos pacientes com COVID-19 (doença causada pelo novo coronavírus – Sars-Cov2 atendidos na Santa Casa de Misericórdia de São Paulo.

Na sua participação, você permitirá que sejam colhidos os dados contidos em seu prontuário através de protocolo de pesquisa previamente estabelecido, além de informações que você mesmo fornecerá com o preenchimento de um questionário que avaliará a presença de comorbidades, sintomas de síndrome gripal e sinais e/ou sintomas neurológicos.

Esses dados serão anexados ao de outros pacientes por meio de tabelas e, após isso, serão submetidos à avaliação estatística e descritos em forma de artigos científicos. Em caso de necessidade de gravações e filmagens, após a transcrição destas para os bancos de dados, elas serão desgravadas e deletadas dos aparelhos eletrônicos que realizaram as gravações. Em nenhum momento você será identificado.

Os resultados da pesquisa serão publicados e, ainda assim, a sua identidade será preservada. Você não terá nenhum gasto e ganho financeiro por participar na pesquisa.

Este trabalho apresenta o risco de quebra da confidencialidade, porém a proteção da confidencialidade será assegurada pelo armazenamento correto dos dados, não havendo vinculação dos protocolos de pesquisa ao nome do sujeito pesquisado. Durante todo o trabalho, o sigilo do paciente será preservado.

Existe o risco de devolução ou comunicação inapropriada de resultados dos estudos, este será minimizado treinando os pesquisadores para que eles tenham domínio de todas as etapas da pesquisa. Os benefícios serão acrescentar novos conhecimentos e dados ao perfil dos pacientes com COVID19 e doenças cerebrovasculares.

Você é livre para deixar de participar da pesquisa a qualquer momento sem nenhum prejuízo ou coação. Uma via original deste Termo de Consentimento Livre e Esclarecido ficará com você. Seu nome não será utilizado em qualquer fase da pesquisa, o que garante seu

anonimato, bem como a divulgação dos resultados será feita de forma a não identificar os voluntários.

Não será cobrado nada, não haverá gastos e não estão previstos ressarcimentos ou indenizações, pois o estudo envolve somente entrevista e nenhum procedimento ou intervenção será realizado no(a) senhor(a) ou outra razão.

Gostaríamos de esclarecer que sua participação é voluntária e que poderá se recusar a participar ou retirar o seu consentimento, ou ainda descontinuar sua participação se assim o preferir, sem penalização alguma ou sem prejuízo ao seu cuidado.

Caso aceite participar voluntariamente do estudo, o(a) senhor(a) ficará com uma cópia deste Termo de Consentimento Livre e Esclarecido.

Qualquer dúvida a respeito da pesquisa, você poderá entrar em contato com Dr Francisco Tomaz Meneses de Oliveira no telefone (11) 2176-7000 ou através do endereço Rua Dr. Cesário Mota Junior, 112, Vila Buarque, São Paulo/SP, CEP 01.221-010. Poderá também entrar em contato com o Comitê de Ética em Pesquisa – Hospital Santa Casa de São Paulo: Rua Santa Isabel, 305, 4° andar, Vila Buarque, São Paulo/SP, CEP 01.221-010. Contato: (11) 2176-7689.

Desde já, agradecemos sua atenção e participação e colocamo-nos à disposição para maiores informações.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim.

Eu discuti com Dr Francisco Tomaz Meneses de Oliveira ou pessoa por ele delegado sobre a minha decisão em participar nesse estudo.

Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar do estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste serviço.

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Assinatura do paciente/representante legal. Data_____/_____/_____

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Assinatura da testemunha. Data_____/_____/_____

Para casos de voluntários, analfabetos, semianalfabetos ou portadores de deficiência auditiva ou visual.

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

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Assinatura do responsável pelo estudo. Data_____/_____/_____