

UNIVERSIDADE SÃO FRANCISCO
Programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde

LAÍS SILVA NASCIMENTO

**CARACTERÍSTICAS CLÍNICAS DE PACIENTES COM
DOENÇA DE CROHN HOSPITALIZADOS POR INFECÇÕES
AGUDAS GRAVES DURANTE A
PANDEMIA DE COVID-19**

Bragança Paulista
2024

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Tese apresentada ao Programa de Pós-Graduação *Stricto Sensu* em Ciências da Saúde da Universidade São Francisco, para obtenção do Título de Doutor em Ciências da Saúde.

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RESUMO

A síndrome respiratória aguda grave causada pelo coronavírus (SARS-CoV-2) foi responsável por uma das maiores pandemias do século 21, gerando um cenário de preocupação com os cuidados de saúde no Brasil e no mundo. Pacientes com DII apresentam um risco potencialmente maior de complicações desta doença infecciosa devido ao uso de tratamentos imunossupressores e/ou biológicos e devido às crises desta doença crônica. Objetivos: Avaliar as características demográficas e clínicas de pacientes hospitalizados por covid-19 e com doença de Crohn no Brasil em um período de dois anos de pandemia de covid-19. Métodos: No presente estudo, realizamos uma análise epidemiológica utilizando os dados disponíveis no OpenDataSUS. Foi realizada uma análise para avaliar dois tópicos: comparar os dados demográficos, sintomas clínicos, comorbidades e informações de internação de acordo com os grupos de SRAG. Resultados: Os estados de São Paulo, Paraná e Minas Gerais foram responsáveis por 50% dos casos notificados de COVID-19. O grupo racial mais afetado foi composto por indivíduos que se autodeclararam mestiços. As comorbidades comuns incluíam doenças cardíacas, diabetes mellitus e obesidade. A faixa etária mais afetada foi de 25 a 60 anos, principalmente entre pacientes hospitalizados com DC e COVID-19 que acabaram sucumbindo à doença. Uma análise multivariada foi conduzida para identificar os seguintes fatores de risco significativos para morte: (a) a presença de distúrbio neurológico (OR = 6,716; IC 95% = 1,954–23,078), (b) a necessidade de tratamento intensivo (OR = 3,348; IC 95% = 1,770–6,335) e (c) a necessidade de ventilação mecânica invasiva (OR = 59,017; IC 95% = 19,796–175,944). Conclusão: Não houve prevalência discernível baseada em gênero entre pacientes hospitalizados com DC e COVID-19; no entanto, indivíduos de raça mista foram afetados desproporcionalmente. A faixa etária de 25 a 60 anos surgiu como o grupo demográfico mais vulnerável, com altos riscos de hospitalização e mortalidade.

Palavras-chave: COVID-19. Doença de Crohn. Hospitalização. Brasil.

ABSTRACT

Severe Acute Respiratory Syndrome caused by the coronavirus (SARS-CoV-2) was responsible for one of the largest pandemics of the 21st century, creating a global healthcare crisis and raising significant concerns regarding healthcare systems in Brazil and worldwide. Patients with Inflammatory Bowel Disease (IBD) are at potentially increased risk for complications from this infectious disease due to the use of immunosuppressive and/or biologic treatments, as well as exacerbations of their chronic condition. Objective: The aim of this study was to assess the demographic and clinical characteristics of hospitalized patients with Crohn's disease and COVID-19 in Brazil during a two-year period of the COVID-19 pandemic. Methods: In this study, we conducted an epidemiological analysis using data from OpenDataSUS. The analysis focused on two main aspects: comparing demographic data, clinical symptoms, comorbidities, and hospitalization information according to the SARS groups. Results: The states of São Paulo, Paraná, and Minas Gerais accounted for 50% of the reported COVID-19 cases. The racial group most affected was individuals who self-identified as mixed-race. Common comorbidities included cardiovascular diseases, diabetes mellitus, and obesity. The age group most affected was between 25 and 60 years, particularly among patients hospitalized with both Crohn's disease and COVID-19, who ultimately succumbed to the disease. A multivariate analysis was performed to identify the following risk factors for death: (a) presence of neurological disorders (OR = 6.716; 95% CI = 1.954–23.078), (b) need for intensive care treatment (OR = 3.348; 95% CI = 1.770–6.335), and (c) requirement for invasive mechanical ventilation (OR = 59.017; 95% CI = 19.796–175.944). Conclusion: No discernible gender-based prevalence was found among hospitalized patients with Crohn's disease and COVID-19; however, racial disparities were observed, with individuals of mixed-race being disproportionately affected. The age group of 25 to 60 years emerged as the most vulnerable demographic, with significantly elevated risks of hospitalization and mortality.

Keywords: *Covid-19. Crohn Disease. Hospitalization. Brazil.*

LISTA DE SÍMBOLOS E ABREVIações

DII – Doença inflamatória intestinal

DC – Doença de Crohn

ECA2 – Enzima conversora de angiotensina II

Pabs – Anticorpo contra tecido pancreático exócrino

RCU – Retocolite Ulcerativa

RNA – Ácido desoxirribonucleico

SARS-COV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

TMPRSS2 – Protease serina transmembrana 2

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1. INTRODUÇÃO

1.1. Covid-19

A covid-19 é uma infecção respiratória aguda grave, causada pelo novo coronavírus que mais tarde foi denominado de *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2), potencialmente grave e de elevada transmissibilidade. Responsável por uma das maiores pandemias do século 21, gerando um cenário de preocupação com os cuidados de saúde do Brasil e do mundo (ZOU et al., 2019; OMS, 2020). O SARS-CoV-2 é um betacoronavírus descoberto em amostras de lavado broncoalveolar obtidas de pacientes com pneumonia de etiologia desconhecida na cidade de Wuhan, província de Hubei, China, em dezembro de 2019 (ZHU et al.,2020; BRASIL 2020).

O SARS-CoV-2 é um vírus de cadeia simples de RNA, envolta por uma bicamada lipídica. Através das mucosas nasal, oral e ocular o vírus entra no organismo humano e liga a sua proteína de superfície espiculada, proteína Spike (S), ao receptor, a enzima conversora da angiotensina II (ECA2), da célula hospedeira, receptor prevalentemente expresso nos pulmões, coração, rins, tecido adiposo, esôfago, estômago, bexiga, íleo e cólon (WAN et al., 2020; XIAO et al., 2020; ZOU et al., 2020).

A transmissão ocorre, principalmente, por meio do contato com gotículas respiratórias. Por isso, medidas de saúde pública destinadas à prevenção e ao controle da infecção, como adesão ao distanciamento social, isolamento de casos e contatos, bem como o diagnóstico oportuno, são estratégias que devem ser adotadas em conjunto para mitigar a transmissão do vírus (CUMMINGS, et.,2020).

Os principais sintomas da covid-19 são: tosse, dispneia, mialgias, dor de garganta, febre e outras manifestações clínicas, como alterações gastrointestinais. Entretanto, as manifestações variam de casos assintomáticos e infecções leves das vias aéreas superiores até casos graves e fatais com pneumonia e insuficiência respiratória aguda grave (LAKE, 2020).

Além dos sintomas respiratórios, em média de 15% dos pacientes com covid-19 também apresentaram sintomas gastrointestinais, como náuseas, vômitos, diarreia, emagrecimento e perda de apetite (MAO et al., 2020). Sintomas encontrados em pacientes que desenvolveram a forma grave de covid-19, podem estar associados a alta capacidade do vírus infiltrar e proliferar para o trato gastrointestinal e sobre expressão da protease serina transmembrana 2 (TMPRSS2) nos enterócitos, que apresentam um importante papel na entrada de vírus para as células

humanas (WAN et al., 2020). Enzimas que encontramos em indivíduos com Doença Inflamatória intestinal (DII), o que pode aumentar a vulnerabilidade a infecção por covid-19 (GARG et al., 2020).

Fatores sociais, idade avançada e presença de comorbidades (imunossupressão, diabetes mellitus, doenças cardíacas e hipertensão arterial sistêmica) podem favorecer a evolução da forma grave da doença (RUBIN et al., 2020; SANCHE et al., 2020).

A confirmação do primeiro caso oficial da doença no Brasil ocorreu em 26 de fevereiro de 2020, com mais de 210 milhões de habitantes, o Brasil possui a sexta maior população mundial, assim como uma das mais diversas em termos sociodemográficos e que se encontra heterogeneamente distribuída no quinto maior território mundial, depois da Rússia, Canadá, Estados Unidos e China. Em conjunto com outros fatores, essa situação levou o País a apresentar um perfil muito particular no que se refere à distribuição de covid-19, figurando, em muitos momentos, no topo da lista de países com o maior número de casos e óbitos associados à doença (BRASIL, 2020).

No Brasil foram registrados mais de 30 milhões de casos positivos para covid-19, dentre as regiões brasileiras, a sudeste foi a mais afetada com uma média de 15 mil casos da doença. O Brasil foi responsável por mais de 690 mil casos de óbito por covid-19 (BRASIL, 2024).

A covid-19 é mais do que apenas uma síndrome respiratória, os últimos estudos concluem que altos níveis de substâncias químicas endógenas são produzidas em resposta à inflamação causada, podendo causar alterações e distúrbios nos tecidos alvo, ultrapassando barreiras de proteção e atingindo de forma sistêmica o organismo (CHAN et al., 2020). O quadro clínico grave é caracterizado por distúrbio inflamatório de citocinas, com alterações hematológicas e de coagulação que podem levar a danos teciduais e morte (ESLER, 2020).

Uma proporção substancial dos casos de covid-19 evolui para a síndrome do desconforto respiratória aguda grave secundária a lesão pulmonar crítica. A hiperinflamação após a infecção por SARS-CoV-2 é reconhecida como um mecanismo fundamental que contribui para o desenvolvimento de insuficiência respiratória progressiva, síndrome de disfunção de múltiplos órgãos e mortalidade (NETO; CORREA, 2020).

Porém o período de distanciamento social e as incertezas em relação ao cenário pandêmico causaram piora nos aspectos físicos, comportamentais e psicológicos da população. Além disso, observou-se o agravamento de doenças crônicas preexistentes, doenças cardiopulmonares, comorbidades metabólicas, doenças autoimunes e pacientes submetidos a qualquer tratamento

que possa comprometer sua imunidade (por exemplo, quimioterapia, radioterapia ou corticoterapia), possivelmente pela dificuldade de acesso aos serviços públicos de saúde (WILLIAMS et al., 2020). Como consequência, tais pacientes com apresentam maior risco de morte (CANABARRO et al., 2020).

1.2. Doença inflamatória intestinal

As DII são condições autoimunes que causam uma ativação crônica do sistema imunológico intestinal, caracterizadas por períodos alternados de atividade e remissão. Os principais tipos de DII: a Retocolite Ulcerativa (RU) e a Doença de Crohn (DC). A distinção entre eles é baseada na distribuição da doença e nos achados histopatológicos. A DC é uma afecção que pode acometer qualquer parte do trato gastrointestinal, sendo o íleo terminal e o cólon as áreas mais comumente afetadas. Apresenta sintomas recorrentes e remitentes, o que pode causar danos intestinais e incapacidade ao longo do tempo (SULZ et al., 2020, CUSHING; HIGGINS, 2021, STENCZEL et al., 2021).

A DII afeta mais de cinco milhões de pessoas em todo o mundo e, no Brasil, tem sido observado um aumento no número de novos casos nos últimos anos. (ANANTHAKRISHNAN, 2015). No Brasil a prevalência é de 100 casos para cada 100 mil habitantes (BRASIL, 2024). Acredita-se que sejam estimulados por um sistema imunológico desregulado, gerando uma agressão nas paredes intestinais e atingindo as camadas e mucosas causando lesões (PAI; GEBOES, 2018).

As DII são doenças inflamatórias crônicas debilitantes do trato gastrointestinal, com pico de início na adolescência e na idade adulta jovem, caracterizadas também como doenças inflamatórias crônicas complexas com múltiplos fatores, como sofrimento psicológico, disfunção autonômica, disbiose do microbioma intestinal e modulações imunológicas associadas à atividade da doença. A incidência de DII tem mostrado uma tendência crescente nas últimas décadas. Isto foi inicialmente observado em países ocidentais e agora está sendo cada vez mais observado em países como Japão, China e Índia. As DII são reconhecidas como um sério problema de saúde pública mundial, com um peso econômico e financeiro crescente (TAVAKOLI et al., 2021; BRUNER et al., 2023).

A DC é uma doença inflamatória intestinal crônica remitente, é influenciada pela predisposição genética e está significativamente associada a fatores de estilo de vida. Isso inclui

o consumo de alimentos processados e ultraprocessados, o aumento da exposição a poluentes ambientais, o uso de álcool e de drogas. A DC é ainda mais exacerbada pela urbanização e industrialização, que perturbam a homeostase intestinal e provocam respostas imunitárias que resultam em inflamação intestinal crônica. Esta condição impacta profundamente a qualidade de vida dos indivíduos afetados (GUAN, 2019; QUARESMA; KAPLAN; KOTZE, 2019).

A causa exata da DC não foi definida, porém a desregulação imune, disbiose microbiana e gatilhos ambientais em indivíduos com predisposição genética são achados clínicos nesse grupo de pacientes. Esses fatores em conjunto levam ao rompimento da mucosa intestinal. A inflamação pode ser observada com áreas saudáveis alternando com áreas acometidas, criando um padrão de "pedra de calçada". A classificação de Montreal é usada para orientar o fenótipo da doença, levando em consideração a idade no diagnóstico, a localização e o comportamento da doença em cada paciente (SULZ et al., 2020, PETAGNA, 2020, STENCZEL et al., 2021, SHAH; ITZKOWITZ, 2022)

A fisiopatogênese da DC, baseia-se na inflamação tecidual. Essa inflamação está ligada a uma resposta imunológica exacerbada aos antígenos bacterianos do lúmen intestinal, instigando diversos tipos de células imunes, como linfócitos TCD4 e TCD8, linfócitos B, monócitos CD14 e células natural killers. (PETAGNA, 2020, CUSHING; HIGGINS, 2021).

Os sintomas mais comuns da DII incluem diarreia, sangramento retal, náuseas e vômitos intermitentes e dor ou sensibilidade abdominal. Os sintomas são decorrentes de danos intestinais decorrentes da resposta inflamatória exagerada. As complicações dessas doenças imunomediadas incluem anemia, desnutrição, obstrução intestinal, fístula, infecção e aumento do risco de câncer de cólon. Também podem ocorrer manifestações extraintestinais, como problemas articulares (artralgia, artrite e espondilite anquilosante), erupções cutâneas e problemas de pele (eritema nodoso, psoríase), doença hepática crônica (colangite esclerosante primária) e problemas oculares (como uveíte). A qualidade de vida dos pacientes com DII pode ser substancialmente afetada por estas manifestações extraintestinais (HELLER et al., 2005; KAMADA; ROGLER, 2016; FLYNN; EISENSTEIN, 2019; TAVAKOLI et al., 2021; ROGLER et al., 2021).

As manifestações extraintestinais são comuns tanto na RCU quanto na DC, envolvendo mais comumente o sistema musculoesquelético (por exemplo, artrite periférica e axial, entesite), pele (por exemplo, pioderma gangrenoso, eritema nodosum, síndrome de Sweet e estomatite aftosa), trato hepatobiliar (colangite esclerosante primária) e olhos (episclerite, uveíte anterior e irrite). No entanto, quase todos os órgãos podem ser afetados. Estas manifestações orgânicas

podem não ser clinicamente óbvias nem fáceis de detectar. Por exemplo, uma pancreatite aguda ou crônica associada à DII (e não a medicamentos para a DII, como a azatioprina) é rara. No entanto, insuficiência exócrina assintomática, anomalias do ducto pancreático e hiperamilasemia são observadas em até 18% dos pacientes com DII e anticorpos contra tecido pancreático exócrino (PAbs) podem ser encontrados em até 29% dos pacientes com DC (VAVRICKA et al., 2015; VEGH et al., 2016; GARBER; REGUEIRO, 2019; ROGLER et al., 2021).

O diagnóstico da DC é feito pela combinação de critérios clínicos, histológicos, bioquímicos, endoscópicos e de imagem, porém não há um padrão-ouro definido. As células inflamatórias desempenham um papel crucial na manutenção da atividade da doença, e muitas das abordagens terapêuticas visam inibir a cascata de citocinas inflamatórias e pró-inflamatórias. O tratamento tem abordagem multidisciplinar, visando sempre em aspectos clínicos, como foco principal na cicatrização da mucosa e a redução dos sintomas, quanto cirúrgicos, para tratar complicações. Embora não exista uma cura definitiva para a DC, o diagnóstico e tratamento precoces são essenciais para reduzir os impactos na qualidade de vida do paciente (MICHAEL CHRISTIAN SULZ et al., 2020, PETAGNA et al., 2020, POPA; PREDA; DUMITRASCU, 2020).

O tratamento da DC tem como objetivo suprimir a atividade desregulada do sistema imune com o objetivo de controlar a doença e alcançar a remissão. São utilizados, corticosteroides, imunossupressores, terapias biológicas e modificadores do sistema imunológico. Os corticosteroides são utilizados inicialmente em doses mais altas para induzir a remissão da doença. (VEAUTHIER; HORNECKER, 2018, CUSHING; HIGGINS, 2021, VASUDEVAN et al., 2021).

O metotrexato e as tiopurinas, são imunomoduladores que atuam na fase de manutenção do tratamento, possuindo um início de ação mais lento, porém com o importante efeito de auxiliar na redução das doses de corticosteroides, além disso a combinação de azatioprina com agentes anti-fator de necrose tumoral (TNF) mostrou-se eficaz no manejo da DC moderada a grave, apresentando taxas importantes de remissão da doença com menor uso de corticosteroides. (VEAUTHIER; HORNECKER, 2018, SLEIMAN et al., 2020, CUSHING; HIGGINS, 2021, VASUDEVAN et al., 2021).

No tratamento da DC, o uso de terapias imunomoduladoras visa controlar a resposta imunológica, mas muitos desses tratamentos estão associados ao aumento de riscos de infecções, tornando o indivíduo potencialmente suscetível a desenvolver a forma grave da covid-19, uma vez que o sistema imunológico sistema está totalmente comprometido (SINGH et al., 2021).

O tratamento tem início com o uso de medicamentos, e em alguns casos a indicação cirúrgica é considerada quando outras abordagens não são suficientes. Atualmente, aproximadamente 3 em cada 4 pacientes com DC passarão por uma cirurgia ao longo de suas vidas, a evolução da DC pode levar a complicações, e cerca de 29% dos pacientes já apresentam uma complicação no momento do diagnóstico, o que aumenta a necessidade de cirurgias, hospitalizações e a morbidade geral. (VEAUTHIER; HORNECKER, 2018, MARIA et al., 2021)

Não há cura para a DII, mas o tratamento convencional da DC tem como objetivo suprimir a alta atividade do sistema imune para controlar a doença e alcançar a remissão dos sintomas. (VEAUTHIER; HORNECKER, 2018, CUSHING; HIGGINS, 2021, VASUDEVAN et al., 2021).

Durante o curso da pandemia, especulou-se que os pacientes com DII apresentam um risco potencialmente maior de complicações desta doença infecciosa devido ao uso de tratamentos imunossupressores e/ou biológicos e devido às crises desta doença crônica, que muitas vezes requerem tratamento urgente, cuidados e às vezes hospitalização, resultando numa grande mudança no acesso aos cuidados de saúde entre os pacientes com DII, incluindo a diminuição das visitas presenciais padrão e o atraso no uso de produtos biológicos, predispondo esses pacientes crônicos a potenciais danos, em comparação com a população em geral (LAGO et al., 2021; ZHANG et al., 2021).

Além disso, a pandemia gerou apreensão significativa em relação ao manejo terapêutico de pacientes com DII. Investigações recentes sugerem que os pacientes com DII podem apresentar apresentações mais graves de covid-19 devido a um estado imunológico desregulado e à utilização de medicamentos imunossupressores (CUMMINGS et al., 2020) Como citado anteriormente, a pandemia além de dificultar o diagnóstico precoce, também interferiu no acesso ao tratamento de pacientes com doenças prévias, como indivíduos com Doença de Crohn (DC), que são imunossuprimidos devido a doença e aos medicamentos utilizados (RUBIN et al., 2020) e frequentemente apresentam exacerbações quando o tratamento não é realizado de forma correta (PAPACOSTA et al., 2017; LOPES, 2017).

Desde o início da pandemia de Covid-19, um número crescente de estudos tem se concentrado no rápido diagnóstico, no desenvolvimento e na reorientação de novas terapias, porém não se sabe ao certo quais os efeitos a longo prazo podem ser gerados no organismo de uma pessoa que foi infectada. No entanto, descobriu-se que a covid-19 é mais do que apenas uma síndrome respiratória, os estudos demonstram que altos níveis de substâncias químicas endógenas produzidas em resposta à inflamação causada por esse vírus são capazes de

ultrapassar as barreiras de proteção da imunidade tecidual inata, atingindo o nível sistêmico por meio da transmissão hematogênica (JIN et al., 2020).

Apesar da significância clínica dessa intersecção, estudos elucidando o perfil epidemiológico de indivíduos com DC concomitante e covid-19 são escassos. Portanto, a presente investigação se esforça para avaliar as características demográficas e clínicas de pacientes hospitalizados com covid-19 e DC concomitante no Brasil ao longo de um período de 2 anos em meio à pandemia de covid-19.

2. OBJETIVOS

2.1 Objetivo Geral

Avaliar as características demográficas e clínicas de pacientes hospitalizados por covid-19 e com DC no Brasil em um período de dois anos de pandemia de covid-19.

2.2 Objetivos Específicos

Identificar as principais comorbidades na população com DC e covid-19.

Identificar os sinais e sintomas mais prevalentes em pacientes com covid-19 e DC.

3. CAPÍTULO 1: Artigo publicado

Perfil epidemiológico de pacientes hospitalizados com doença de Crohn devido à infecção respiratória aguda grave durante a pandemia de COVID-19: um relato de 2 anos do Brasil



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Epidemiological profile of patients hospitalized with Crohn's disease due to severe acute respiratory infection during the COVID-19 pandemic: a 2-year report from Brazil

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Background and aims: The novel coronavirus-induced severe acute respiratory syndrome (COVID-19) led to one of the most significant global pandemics of the 21st century, causing substantial challenges for healthcare systems worldwide, including those in Brazil. This study aimed to investigate the demographic and clinical profiles of hospitalized patients in Brazil who had both COVID-19 and Crohn's disease (CD) over a 2-year period.

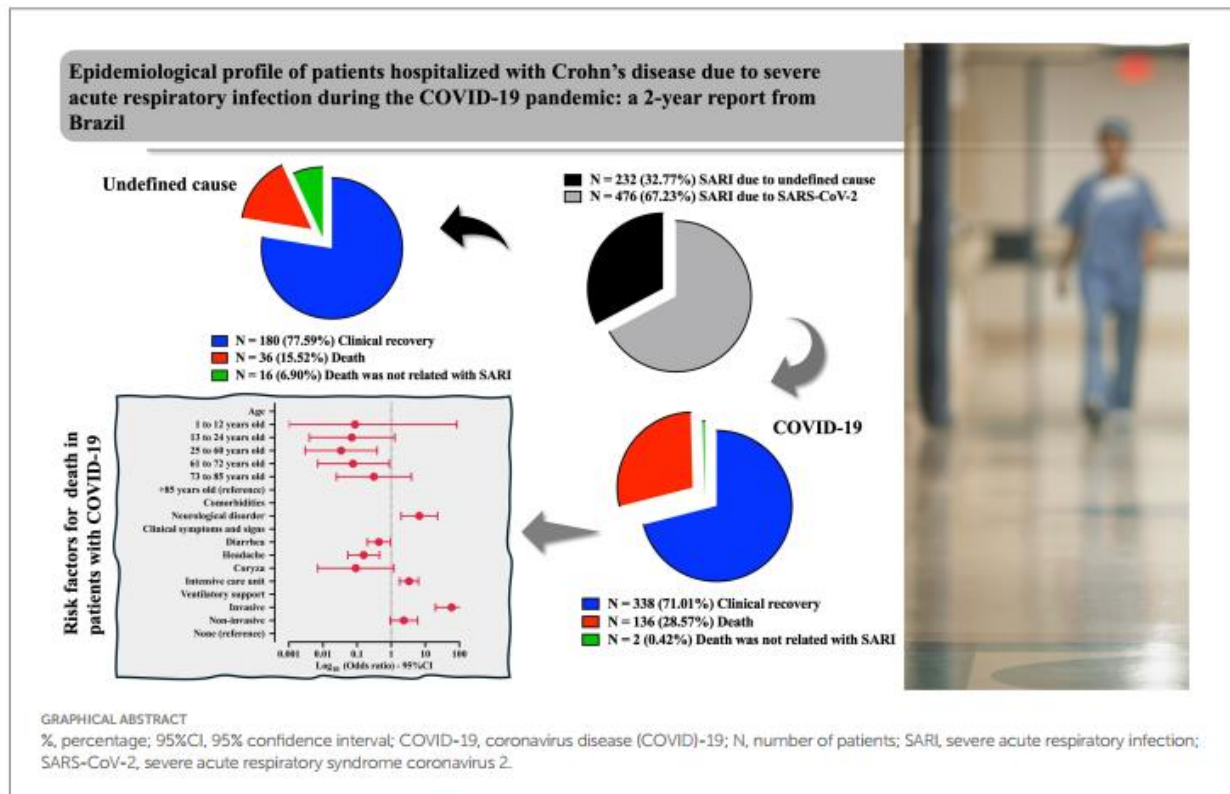
Methods: An epidemiological analysis was conducted using data from Open-Data-SUS. The study focused on describing the demographic characteristics, clinical manifestations, comorbidities, and hospitalization details of patients afflicted with severe acute respiratory syndrome due to COVID-19 and CD, with the aim of predicting mortality risk.

Results: The states of São Paulo, Paraná, and Minas Gerais accounted for 50% of the reported COVID-19 cases. The most affected racial group consisted of individuals who self-declared as mixed race. Common comorbidities included heart disease, diabetes mellitus, and obesity. The age group most affected was 25 to 60 years old, particularly among hospitalized patients with both CD and COVID-19 who ultimately succumbed to the illness. A multivariable analysis was conducted to identify the following significant risk factors for death: (a) the presence of neurological disorder (OR = 6.716; 95% CI = 1.954–23.078), (b) the need for intensive care (OR = 3.348; 95% CI = 1.770–6.335), and (c) the need for invasive mechanical ventilation (OR = 59.017; 95% CI = 19.796–175.944).

Conclusion: There was no discernible gender-based prevalence among hospitalized patients with CD and COVID-19; however, individuals of mixed race were disproportionately affected. The 25 to 60 age group emerged as the most vulnerable demographic group, with high risks of hospitalization and mortality. Moreover, the study highlights the potential for COVID-19 to induce systemic pathologies that may result in long-term degenerative effects and sequelae.

KEYWORDS

COVID-19, Crohn's disease, epidemiology, hospitalization, SARS-CoV-2



1 Introduction

The severe acute respiratory syndrome caused by the new coronavirus (SARS-CoV-2, severe acute respiratory syndrome coronavirus 2) was responsible for one of the biggest pandemics of the 21st century, raising concerns about health care in Brazil and globally (1, 2). The SARS-CoV-2 infection can cause various clinical manifestations, such as fever, dyspnea, myalgias, and gastrointestinal problems, which may progress to death, which is associated mainly with pulmonary complications (3). The severe clinical condition is characterized by an inflammatory disorder of cytokines with hematological and coagulation changes that can lead to tissue damage and death (4). The mortality rate can be considered high and is associated with social factors, older age, and the presence of comorbidities (for example, immunosuppression, diabetes mellitus, heart disease, and systemic arterial hypertension) (5).

Since the beginning of the COVID-19 pandemic, the number of studies addressing developing and redirecting new therapies has been growing rapidly. SARS-CoV-2 causes more than just respiratory symptoms; recent studies have concluded that high levels of endogenous chemicals are produced in response to the inflammation caused by this condition, which can lead to alterations and disturbances in target tissues, surpassing protective barriers and affecting the organism systemically (6).

Patients with cardiopulmonary diseases or metabolic comorbidities, autoimmune diseases, or those undergoing any treatment that may compromise their immunity (such as chemotherapy, radiotherapy, or corticosteroid therapy) are at a higher risk of death (7). Inflammatory bowel disease affects more than five million people worldwide, and in Brazil, an increase in the number of new cases has been observed in recent years. The incidence of

inflammatory bowel disease is 13.30 new cases per 100,000 inhabitants annually (8). Crohn's disease (CD) and ulcerative colitis are two major forms of inflammatory bowel disease, both of which are idiopathic, chronic, and autoimmune in origin (9), with a tendency to relapse over time (10). These conditions are thought to be triggered by a dysregulated immune response, resulting in inflammation that damages the intestinal walls, affecting multiple layers and mucous membranes, and causing lesions (11).

In CD, a defect in the intestinal barrier is primarily observed, leading to increased permeability to antigens, which triggers an exaggerated immune response and chronic inflammation. However, the alteration of the intestinal mucosal barrier alone is insufficient for disease development. Genetic, socioenvironmental, microbiological, and immunological factors also play critical roles as risk factors in the onset and progression of the disease (12).

Inflammatory bowel diseases also exhibit extraintestinal manifestations, which are often more problematic than intestinal ones and may or may not correlate with clinical activity. Pulmonary involvement is infrequent, usually asymptomatic or related to changes in respiratory function tests, but bronchiectasis and pneumonia are more common in ulcerative colitis. It is important to note that many respiratory manifestations of inflammatory bowel diseases are related to the immunosuppressive and immunobiological drugs used (13, 14). Therapeutic interventions for CD often include immunomodulatory agents to regulate the aberrant immune response. However, these treatments inherently increase the risk of infections, potentially predisposing individuals to severe COVID-19 manifestations due to compromised immune function (15).

The COVID-19 pandemic has had widespread and multifaceted impacts on global health, which continues to be the subject of ongoing research. Restrictions on movement and contact reduced adherence to

treatment, and the introduction of new vaccines have all contributed to heightened levels of stress (16–18). Psychological stress and adverse psychosocial conditions are known to exacerbate intestinal inflammatory (19), potentially increasing relapse rates in patients with inflammatory bowel diseases, even those with quiescent disease. Consequently, these factors can accelerate the progression of inflammatory bowel diseases (20, 21). Notably, stress is a well-documented factor that substantially contributes to the exacerbation of CD (22, 23). During the COVID-19 pandemic, heightened stress levels have been reported in the general population, potentially affecting the trajectory of disease activity (24, 25).

Despite the clinical significance of this intersection, studies elucidating the epidemiological profile of individuals with concurrent CD and COVID-19 are scarce. Hence, the present investigation endeavors to assess the demographic and clinical characteristics of patients hospitalized with COVID-19 and concomitant CD in Brazil over 2-years period amid the COVID-19 pandemic.

2 Methods

An epidemiological analysis was carried out using the data available at Open-Data-SUS.¹ The Brazilian Ministry of Health compiled the data based on severe acute respiratory infection (SARI) surveillance data through the Information System Platform for Epidemiological Surveillance of Influenza (SIVEP-flu, acronym for *Sistema de Informação de Vigilância Epidemiológica da Gripe*). The SIVEP-flu dataset has been used since 2009, and it was mainly implemented due to the H1N1 virus pandemic (swine flu). It is also responsible for centralizing the SARI reports for the Brazilian Ministry of Health (26). Several previous studies also used this dataset, mainly for the COVID-19 pandemic (27–39).

The analysis was performed to evaluate two topics, namely, (i) to compare the demographic data, clinical symptoms, comorbidities, and hospitalization information according to the SARI groups [patients with COVID-19 versus hospitalized patients due to an undefined cause (possible COVID-19 underdiagnosis)]; and (ii) to identify the risk of death due to SARS-CoV-2 infection using the patients features (bivariate and multivariable analysis) regarding demographic data, clinical symptoms, comorbidities, and hospitalization information. The CD was self-reported by patients for inclusion in the database; in addition, the comorbidity was confirmed, when possible, from the information derived from clinical data or diagnoses certified by the Brazilian healthcare system because several patients were imputed from the Brazilian Unified Health System or from the institutions where the patients performed their follow-up.

The following workflow was applied in the study:

- a) Race classification: Although the meaning of race and ethnicity might overlap, the Merriam-Webster dictionary defines race as “a group sharing outward physical characteristics and some commonalities of culture and history”, whereas ethnicity is defined as “markers acquired from the group with which one shares cultural, traditional, and familial bonds” (38). Thus, from now on, the term race will be used and not ethnicity since it is most suitable for our variable. Moreover, the Brazilian Institute of Geography and Statistics classifies Brazilian citizens into five official races as follows: White people, Black people, individuals with multiracial backgrounds (mixed individuals), Asian individuals, and Indigenous peoples (31, 40). The race was self-declared, and the individuals should identify themselves by selecting only one category. In addition, the patients were grouped according to age using the age periods of human life, as reported by Dyussenbaye (41). In this context, the individuals were grouped as follows: (infancy period) <1 year of age, (childhood period) 1 to 12 years old, (period of youth) 13 to 24 years old, (maturity stage) 25 to 60 years old, (presenile period) 61 to 72 years old, (senile period) 73 to 85 years old, and (elderly period) +85 years old.
- b) Data acquisition: The authors obtained the .csv file from the Open-Data-SUS platform (see text footnote 1). The authors downloaded the file and opened it using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Macintosh, Version 27.0, IBM Inc., Armonk, NY, United States). Subsequently, the data collection process was conducted from 29 December 2019 to 20 March 2022. The inclusion criteria included individuals who tested positive for SARS-CoV-2 via real-time polymerase chain reaction (RT-PCR) or had an undefined agent causing SARI, and who had CD as a comorbidity. Other diseases that affected the inflammatory digestive tract were not included, as their classification could not be obtained from the dataset.
- c) Dataset adjustments and data description: The dataset provided the following information: (i) demographic profile, including gender (male and female), age (<1-year-old, 1 to 12 years old, 13 to 24 years old, 25 to 60 years old, 61 to 72 years old, 73 to 85 years old, and +85 years old), and place of residence (urban, rural, and peri-urban); (ii) data for virus infection such as residing in a place with a flu outbreak, presence of hospital-acquired infection (nosocomial), and antiviral drug use to treat the influenza virus infection; (iii) presence of comorbidities [comorbidities (at least one comorbidity), heart disease, hematologic disorder, Down syndrome, hepatic disorder, asthma, diabetes mellitus, neurological disorder, systemic arterial hypertension, chronic respiratory disorders, immunosuppressive disorder, renal disease, obesity, and other comorbidities (excluding the previous ones)]; (iv) clinical symptoms related to SARI (fever, cough, sore throat, dyspnea, respiratory discomfort, oxygen saturation below 95%, diarrhea, vomit, abdominal pain, fatigue, anosmia, ageusia, myalgia, and other symptoms); (v) need for intensive care unit (ICU) treatment and need for mechanical ventilation support (invasive mechanical ventilation, non-invasive mechanical ventilation, and absence of mechanical ventilation); and (vi) outcomes (hospital discharge or death). For accuracy, the authors revised the epidemiological data from the individuals with SARI obtained in the dataset. The authors also coded the categorical data using numbers to perform the attribute of missing data and descriptive and inferential statistical analyses. The authors saved the SPSS dataset as a .xls file to perform the missing data imputation.

¹ <https://opendatasus.saude.gov.br/>

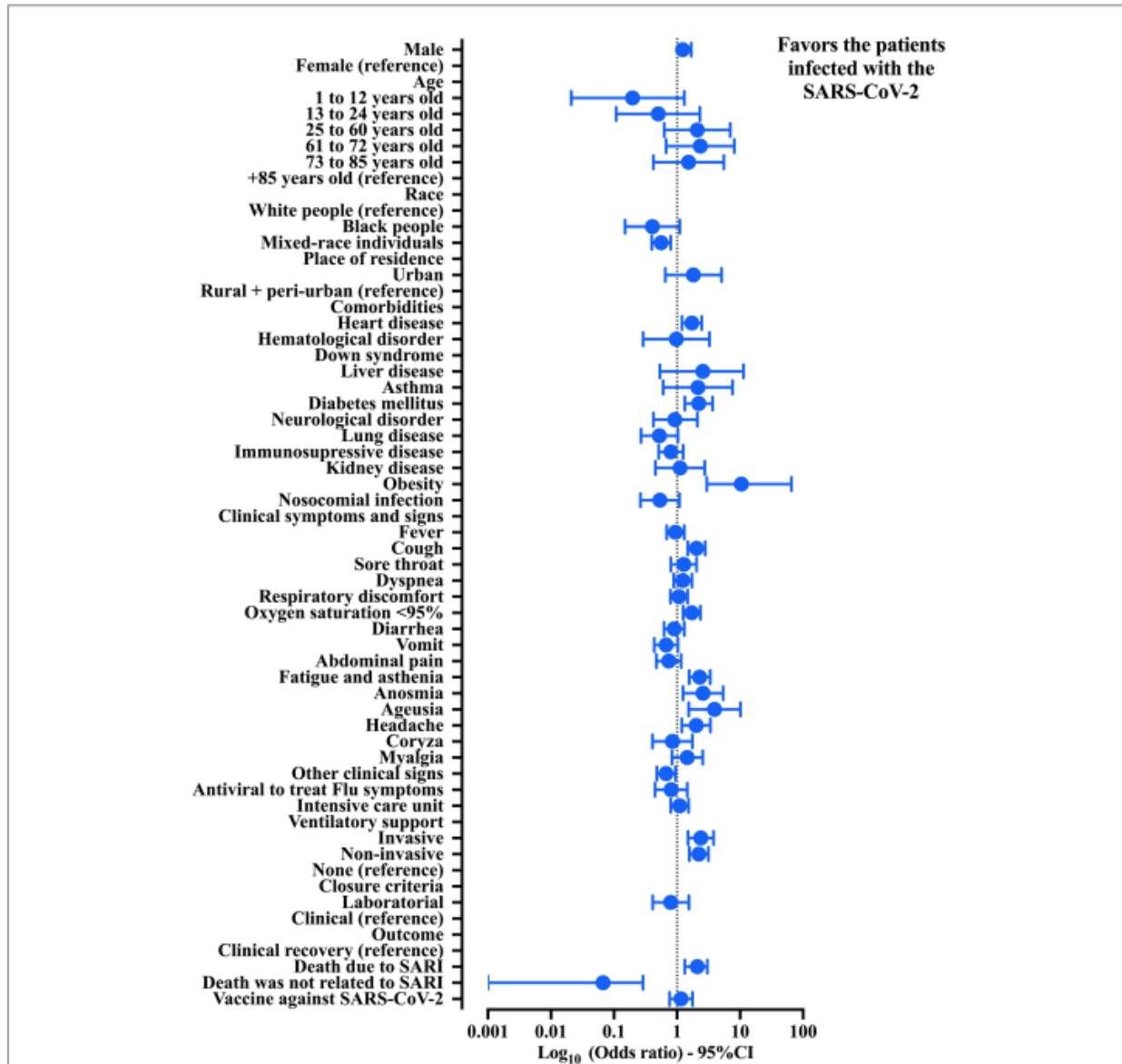
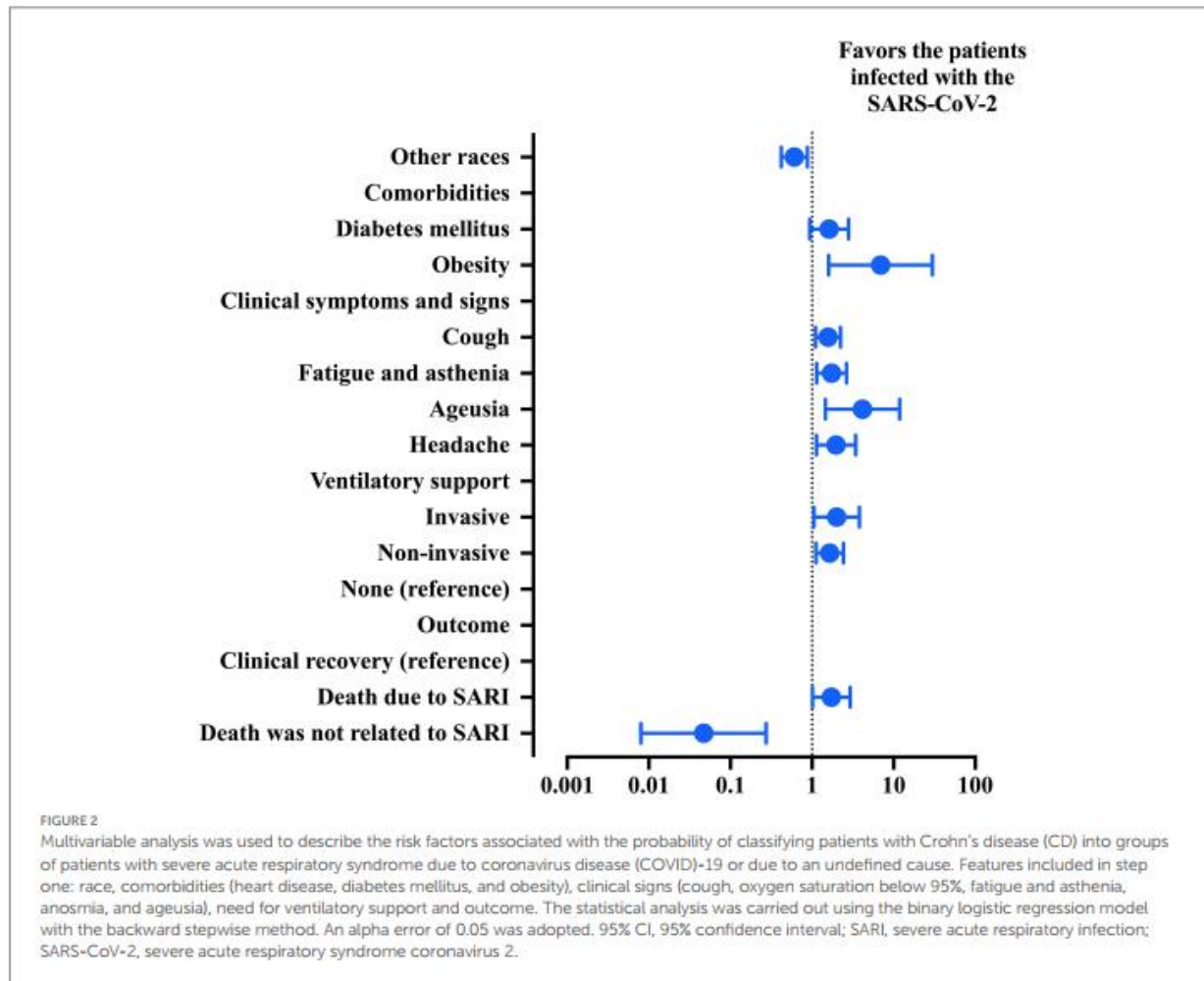


FIGURE 1
 Association between the patients hospitalized with Crohn's disease (CD) and severe acute respiratory infection (SARI) grouped by etiological agents regarding the demographic and clinical features. Crude data were obtained from the Open-Data SUS (<https://opendatasus.saude.gov.br/>). The data collection process was conducted from 29 December 2019 to 20 March 2022. 95% CI, 95% confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2. The statistical analysis was done using the chi-square test and Fisher exact test. It was not possible to calculate the odds ratio and the 95% CI for Down syndrome because none of patients was classified in the group of SARI due to an undefined cause.

d) Missing data analysis: The inclusion of missing data for some features was performed for the following reasons: (i) the dataset had more than 5% missing data, (ii) the dataset did not have missing data only for the dependent variable, and (iii) the authors assumed that the variables were missing completely at random. Additionally, four characteristics were excluded for having over 40.0% missingness, which included imaging exams [X-ray (75.1%) and high-resolution computed tomography (53.2%) of the chest], educational level (59.6%), residence in a place with previous flu outbreak (66.3%), and vaccination against influenza virus (60.6%). The

missing data was imputed using the XLSTAT Statistical Software for Excel (Addinsoft Inc., Paris, Île-de-France, France). For the qualitative (categorical data) analysis, missing data was estimated using the NIPALS (Nonlinear Iterative Partial Least Squares) algorithm. The XLSTAT Statistical Software generated a new Excel dataset (.xls) used to perform the inferential statistical analyses in the SPSS software.

e) Descriptive analysis: Descriptive analyses were carried out using the number of individuals (*N*) and the percentage (%) for categorical data. For the inferential statistical analyses,



whenever possible, the odds ratio (OR) and 95% confidence interval (95% CI) were also presented (see below).

- f) Bivariate analysis: The authors performed the bivariate statistical analysis using the SPSS software and OpenEpi software (OpenEpi: Open-Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, 2013/04/06). The chi-square test and Fisher Exact test were used to evaluate the frequency of death according to the epidemiological data among the individuals with positive SARS-CoV-2 infection. The OR and 95% CI were calculated to estimate the association of each marker with the presence of death. The OR was calculated using the OpenEpi software for 2×2 tables, including the value for each patient's characteristics. The authors summarized the results in tables and figures. The figures were built using GraphPad Prism version 10.2.3 for Mac (<http://www.graphpad.com>, GraphPad Software, San Diego, CA, United States). The same protocol was applied to compare the differences between patients grouped regarding the SARI classification, such as patients with SARS-CoV-2 or an undefined etiological agent.
- g) Multivariable analysis: Multivariable analysis was performed using the binary logistic regression model with the backward stepwise method. Markers with a p -value of ≤ 0.05 in the bivariate analysis

were included in the regression model. The response variable was the health outcome (hospital discharge or death) or the groups for the SARI classification. The authors did not use the data for symptoms (other) and the patients' features with a p -value of >0.05 in the bivariate analysis. The logistic regression model presented (i) B coefficient [including the SE (standard error)], which for the constant was called intercept; (ii) the Wald chi-square test and its significance; (iii) degrees of freedom (df) for the Wald chi-square test; and (iv) $\text{Exp}(B)$, which represents the exponentiation of the B coefficient (OR) including its 95% CI. Before conducting the statistical analysis, the authors tested the markers for multicollinearity, using cut-offs of <0.1 for tolerance and >10 for variance inflation factor.

This study did not require approval from the ethics committee, as the data were publicly available and did not contain personal information about the individuals, thereby being exempt from ethical review.

Despite the clinical significance of this intersection, studies elucidating the epidemiological profile of individuals with concurrent CD and COVID-19 are scarce. Hence, the present investigation endeavors to assess the demographic and clinical characteristics of patients hospitalized with COVID-19 and concomitant CD in Brazil over 2-years period amid the COVID-19 pandemic.

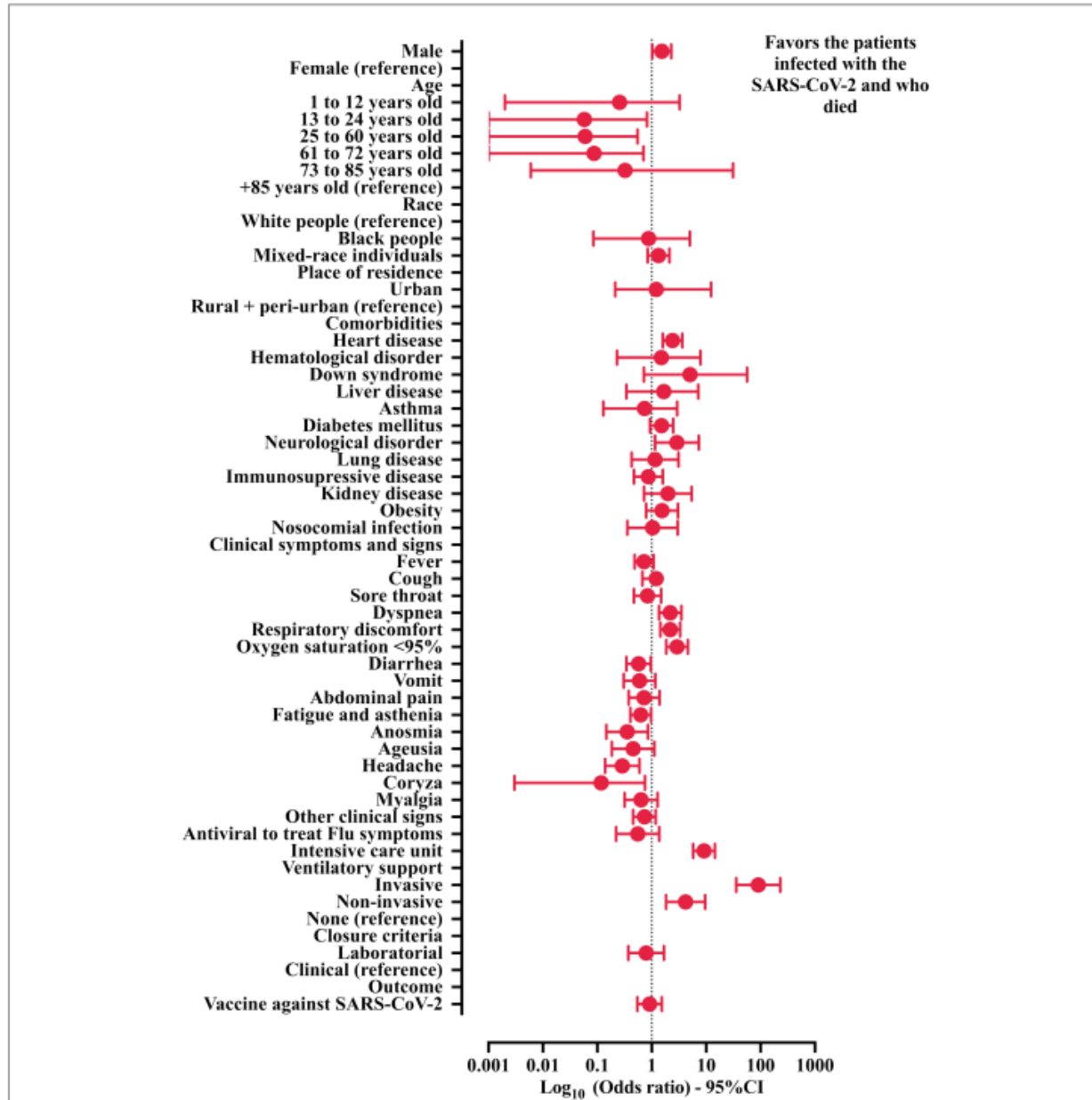


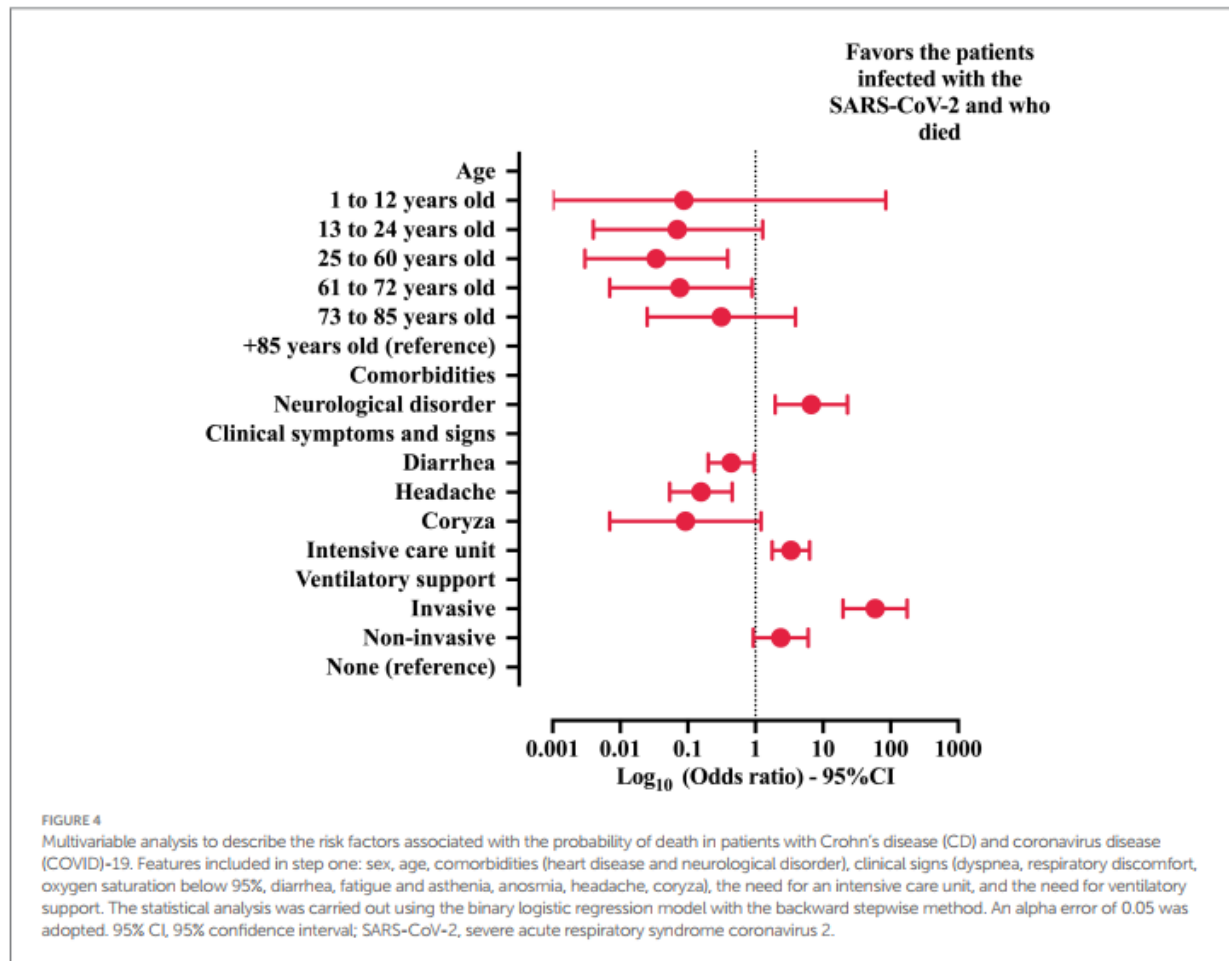
FIGURE 3
 Association between demographic and clinical features and death in the patients hospitalized with Crohn's disease (CD) and severe acute respiratory infection (SARI) due to SARS-CoV-2. Crude data was obtained from the Open-Data SUS (<https://opendatasus.saude.gov.br/>). The data collection process was conducted from 29 December 2019 to 20 March 2022. 95% CI, 95% confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2. The statistical analysis was done using the chi-square test and Fisher exact test.

3 Results

3.1 Epidemiological information

Table 1 shows the places of notification, residence, and hospitalization of hospitalized patients with CD and SARI in Brazil during the COVID-19 pandemic. The cases were computed in 23 states plus the Federal District; therefore, states such as Acre, Amapá, and Tocantins, all located in the northern region, were not described during the study because these states did not have any cases of CD

imputed in the Open-Data-SUS. In our data, a low divergence between the state and federal districts was observed in relation to where the patients were notified, lived, and were hospitalized. Only three states accounted for over 50% of all reported cases for both SARI due to an undefined etiological agent [São Paulo (83, 35.8%), Paraná (37, 15.9%), and Minas Gerais (33, 14.2%)] and SARS-CoV-2 infection [São Paulo (174, 36.6%), Minas Gerais (63, 13.2%), and Rio Grande do Sul (48, 10.1%)]. As described before, the same profile was found for the place of residence [SARI due to an undefined etiological agent—São Paulo (82, 35.3%), Paraná (36, 15.5%), and Minas Gerais



(33, 14.2%), as well as SARS-CoV-2 infection—São Paulo (171, 35.9%), Minas Gerais (64, 13.4%), and Rio Grande do Sul (48, 10.1%)] and place of hospitalization [SARI due to an undefined etiological agent—São Paulo (83, 35.8%), Paraná (37, 15.9%), and Minas Gerais (33, 14.2%), as well as SARS-CoV-2 infection—São Paulo (174, 36.6%), Minas Gerais (63, 13.2%), and Rio Grande do Sul (48, 10.1%)].

3.2 Bivariate and multivariable analysis to determine the predictors for SARS-CoV-2 infection among those with CD and SARI

The association of hospitalized patients with CD and SARI according to the SARS-CoV-2 infection diagnosis is shown below (Table 2 and Figure 1). Our data revealed a low prevalence of female sex (50.4%) and a higher incidence of patients in adult age (25 to 60 years old) (59.6%). Sex and age were not associated with grouping according to the SARS-CoV-2 infection diagnosis. White people presented the highest prevalence (70.8%), and when the White people were compared with the mixed individuals, a low risk of SARS-CoV-2 infection was described (OR=0.562; 95% CI=0.397–0.796). Moreover, the majority of the patients lived in urban areas (97.9%) without association with the probability of classification to a positive SARS-CoV-2 diagnosis.

The most prevalent comorbidities were heart disease (30.2%), diabetes mellitus (15.1%), immunosuppressive disease (13.7%), obesity (5.9%), and lung disease (5.1%). However, only three were associated with a higher probability of being classified as a positive case for SARS-CoV-2 infection as follows: (a) heart disease (OR=1.726, 95% CI=1.204–2.476), (b) diabetes mellitus (OR=2.216, 95% CI=1.226–3.673), and (c) obesity (OR=10.530, 95% CI=2.979–65.300) (Table 2 and Figure 1).

The nosocomial infection occurred only in 32 (4.5%) of the cases. The main clinical symptoms and signs were respiratory and involved the presence of dyspnea (67.4%), cough (60.7%), fever (59.5%), oxygen saturation below 95% (56.8%), and respiratory discomfort (53.4%). Among them, only two were associated with the SARS-CoV-2 infection, namely cough (OR=2.044; 95% CI=1.484–2.815) and oxygen saturation below 95% (OR=1.715; 95% CI=1.249–2.354). In addition, other clinical symptoms and signs with a low prevalence were more common among those classified as patients with SARS-CoV-2, which included fatigue and asthenia (28.5%—OR=2.291; 95% CI=1.559–3.364), headache (13.6%—OR=2.014; 95% CI=1.197–3.387), anosmia (7.6%—OR=2.587; 95% CI=1.242–5.388), and ageusia (6.1%—OR=3.939; 95% CI=1.529–10.140). Finally, the presence of other clinical symptoms and signs (28.1%) was more frequent in patients without a confirmatory test for SARS-CoV-2 infection (OR=0.673; 95% CI=0.478–0.947) (Table 2 and Figure 1).

TABLE 1 Description of the places of notification, residence, and hospitalization of the patients hospitalized with Crohn's disease (CD) and with severe acute respiratory infection (SARI) in Brazil during the coronavirus disease (COVID)-19 pandemic.

States and Federal District	Place of notification		Place of residence		Place of hospitalization	
	SARI due to an undefined cause	SARS-CoV-2	SARI due to an undefined cause	SARS-CoV-2	SARI due to an undefined cause	SARS-CoV-2
Alagoas	1 (0.4%)	4 (0.8%)	2 (0.9%)	4 (0.8%)	1 (0.4%)	4 (0.8%)
Amazonas	0 (0.0%)	3 (0.6%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	3 (0.6%)
Bahia	11 (4.7%)	13 (2.7%)	11 (4.7%)	13 (2.7%)	11 (4.7%)	13 (2.7%)
Ceará	6 (2.6%)	12 (2.5%)	6 (2.6%)	12 (2.5%)	6 (2.6%)	12 (2.5%)
Federal District	1 (0.4%)	11 (2.3%)	1 (0.4%)	11 (2.3%)	1 (0.4%)	11 (2.3%)
Espírito Santo	1 (0.4%)	1 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	1 (0.2%)
Goiás	3 (1.3%)	15 (3.2%)	3 (1.3%)	15 (3.2%)	3 (1.3%)	15 (3.2%)
Maranhão	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0.0%)
Minas Gerais	33 (14.2%)	63 (13.2%)	33 (14.2%)	64 (13.4%)	33 (14.2%)	63 (13.2%)
Mato Grosso do Sul	4 (1.7%)	8 (1.7%)	4 (1.7%)	8 (1.7%)	4 (1.7%)	8 (1.7%)
Mato Grosso	2 (0.9%)	4 (0.8%)	2 (0.9%)	5 (1.1%)	2 (0.9%)	4 (0.8%)
Pará	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Paraíba	3 (1.3%)	2 (0.4%)	3 (1.3%)	2 (0.4%)	3 (1.3%)	2 (0.4%)
Pernambuco	2 (0.9%)	5 (1.1%)	2 (0.9%)	5 (1.1%)	2 (0.9%)	5 (1.1%)
Piauí	1 (0.4%)	5 (1.1%)	1 (0.4%)	4 (0.8%)	1 (0.4%)	5 (1.1%)
Paraná	37 (15.9%)	40 (8.4%)	36 (15.5%)	40 (8.4%)	37 (15.9%)	40 (8.4%)
Rio de Janeiro	11 (4.7%)	31 (6.5%)	11 (4.7%)	31 (6.5%)	11 (4.7%)	31 (6.5%)
Rio Grande do Norte	2 (0.9%)	6 (1.3%)	2 (0.9%)	6 (1.3%)	2 (0.9%)	6 (1.3%)
Rondônia	2 (0.9%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	2 (0.9%)	0 (0.0%)
Roraima	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Rio Grande do Sul	18 (7.8%)	48 (10.1%)	18 (7.8%)	48 (10.1%)	18 (7.8%)	48 (10.1%)
Santa Catarina	9 (3.9%)	28 (5.9%)	10 (4.3%)	29 (6.1%)	9 (3.9%)	28 (5.9%)
Sergipe	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.4%)
São Paulo	83 (35.8%)	174 (36.6%)	82 (35.3%)	171 (35.9%)	83 (35.8%)	174 (36.6%)

The data were described using the number (N) and the percentage (%) of individuals. Crude data were obtained from the Open-Data SUS (<https://opendatasus.saude.gov.br/>). The data collection process was conducted from 29 December 2019 to 20 March 2022. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The use of antiviral drugs to treat flu symptoms and the need for ICUs occurred respectively in 51 (7.2%) and 267 (37.7%) cases without association with the SARS-CoV-2 diagnosis. Most of the patients needed invasive (18.8%) or non-invasive (47.3%) ventilatory support. Both mechanical ventilatory modes were more frequent in patients infected with the SARS-CoV-2 [(invasive ventilatory support) OR=2.382; 95% CI=1.496–3.794; (non-invasive ventilatory support) OR=2.227; 95% CI=1.568–3.161]. In our study population, 172 (24.3%) patients died due to SARI progression, and 18 (2.5%) died, but this outcome was unrelated to SARI. Death due to SARI was more common in patients with COVID-19 diagnosis (OR=2.012; 95% CI=1.336–3.30), while death unrelated to SARI occurred predominantly in patients with SARI due to other causes rather than SARS-CoV-2 infection (OR=0.067; 95% CI=0.001–0.289). Only 126 (17.8%) of the patients were vaccinated against COVID-19, and the vaccination was not associated with the group's classification (Table 2 and Figure 1).

A multivariable analysis was conducted (Table 3 and Figure 2) to describe the risk factors associated with the likelihood of classifying patients with CD into the groups of patients with SARI. In brief, the predictors of SARS-CoV-2 infection were (a) obesity (OR=6.922; 95% CI=1.605–29.849), (b) cough (OR=1.574; 95% CI=1.107–2.238), (c)

fatigue and asthenia (OR=1.731; 95% CI=1.137–2.637), (d) ageusia (OR=4.156; 95% CI=1.459–11.839), (e) headache (OR=1.973; 95% CI=1.133–3.436), (f) need for ventilatory support [invasive (OR=2.005; 95% CI=1.059–3.796) and non-invasive (OR=1.647; 95% CI=1.117–2.431) ventilatory support], and (g) death due to SARI (OR=1.724; 95% CI=1.014–2.931). However, two factors were protective against the COVID-19 diagnosis, namely, (a) race (OR=0.606; 95% CI=0.419–0.878; other than whites' people) and (b) death unrelated to SARI (OR=0.047; 95% CI=0.008–0.273).

3.3 Bivariate and multivariable analyses to determine the predictors of death among patients infected with SARS-CoV-2

The association of hospitalized patients with CD infected with SARS-CoV-2 according to the outcomes is demonstrated (Table 4 and Figure 3). In our data, the male sex was identified as an independent marker for a higher probability of death (58.8% versus 41.2%—OR=1.534; 95% CI=1.025–2.294). Furthermore, using patients aged +85 years (3.7% versus 0.3%), the following age categories were

TABLE 2 Association between the patients hospitalized with Crohn's disease (CD) and severe acute respiratory infection (SARI) grouped by etiological agents regarding the demographic and clinical features.

Marker	Data	SARI due to an undefined cause	SARS-CoV-2 (reference)	Total	p	Odds ratio	95% CI
Sex	Male	107 (46.1%)	244 (51.3%)	351 (49.6%)	0.199	1.229	0.971 to 1.683
	Female	125 (53.9%)	232 (48.7%)	357 (50.4%)		1	Reference
Age	1 to 12 years old	14 (6.0%)	3 (0.6%)	17 (2.4%)	0.105	0.197	0.021 to 1.304
	13 to 24 years old	33 (14.2%)	20 (4.2%)	53 (7.5%)	0.303	0.505	0.108 to 2.302
	25 to 60 years old	120 (51.7%)	302 (63.4%)	422 (59.6%)	0.219	2.097	0.628 to 7.001
	61 to 72 years old	36 (15.5%)	101 (21.2%)	137 (19.4%)	0.311	2.338	0.672 to 8.130
	73 to 85 years old	24 (10.3%)	44 (9.2%)	68 (9.6%)	0.517	1.528	0.421 to 5.532
	+85 years old	5 (2.2%)	6 (1.3%)	11 (1.6%)		1	Reference
Race	White people	145 (62.5%)	356 (74.8%)	501 (70.8%)		1	Reference
	Black people	8 (3.4%)	8 (1.7%)	16 (2.3%)	0.069	0.407	0.150 to 1.106
	Asian	0 (0.0%)	3 (0.6%)	3 (0.4%)		NA	NA
	Mixed-race individuals	79 (34.1%)	109 (22.9%)	188 (26.6%)	0.001	0.562	0.397 to 0.796
Place of residence	Urban	225 (97.0%)	468 (98.3%)	693 (97.9%)	0.271	1.820	0.652 to 5.081
	Rural + peri-urban	7 (3.0%)	8 (1.7%)	15 (2.1%)		1	Reference
Comorbidities							
Heart disease	Yes	53 (22.8%)	161 (33.8%)	214 (30.2%)	0.003	1.726	1.204 to 2.476
	No	179 (77.2%)	315 (66.2%)	494 (69.8%)		1	Reference
Hematological disorder	Yes	4 (1.7%)	8 (1.7%)	12 (1.7%)	1.000	0.974	0.290 to 3.269
	No	228 (98.3%)	468 (98.3%)	696 (98.3%)		1	Reference
Down syndrome	Yes	0 (0.0%)	6 (1.3%)	6 (0.8%)	0.185	NA	NA
	No	232 (100.0%)	470 (98.7%)	702 (99.2%)		NA	NA
Liver disease	Yes	2 (0.9%)	10 (2.1%)	12 (1.7%)	0.355	2.468	0.536 to 11.350
	No	230 (99.1%)	466 (97.9%)	696 (98.3%)		1	Reference
Asthma	Yes	3 (1.3%)	13 (2.7%)	16 (2.3%)	0.289	2.143	0.605 to 7.596
	No	229 (98.7%)	463 (97.3%)	692 (97.7%)		1	Reference
Diabetes mellitus	Yes	21 (9.1%)	86 (18.1%)	107 (15.1%)	0.002	2.216	1.336 to 3.673
	No	211 (90.9%)	390 (81.9%)	601 (84.9%)		1	Reference
Neurological disorder	Yes	10 (4.3%)	19 (4.0%)	29 (4.1%)	0.842	0.923	0.422 to 2.108
	No	222 (95.7%)	457 (96.0%)	679 (95.9%)		1	Reference
Lung disease	Yes	17 (7.3%)	19 (4.0%)	36 (5.1%)	0.068	0.526	0.268 to 1.032
	No	215 (92.7%)	457 (96.0%)	672 (94.9%)		1	Reference
Immunosuppressive disease	Yes	36 (15.5%)	61 (12.8%)	97 (13.7%)	0.352	0.800	0.513 to 1.249
	No	196 (84.5%)	415 (87.2%)	611 (86.3%)		1	Reference
Kidney disease	Yes	7 (3.0%)	16 (3.4%)	23 (3.2%)	0.808	1.118	0.454 to 2.756
	No	225 (97.0%)	460 (96.6%)	685 (96.8%)		1	Reference
Obesity	Yes	2 (0.9%)	40 (8.4%)	42 (5.9%)	<0.001	10.530	2.979 to 65.300
	No	230 (99.1%)	436 (91.6%)	666 (94.1%)		1	Reference
Nosocomial infection	Yes	15 (6.5%)	17 (3.6%)	32 (4.5%)	0.082	0.536	0.263 to 1.093
	No	217 (93.5%)	459 (96.4%)	676 (95.5%)		1	Reference
Clinical symptoms and signs							
Fever	Yes	140 (60.3%)	281 (59.0%)	421 (59.5%)	0.739	0.947	0.688 to 1.304
	No	92 (39.7%)	195 (41.0%)	287 (40.5%)		1	Reference

(Continued)

TABLE 2 (Continued)

Marker	Data	SARI due to an undefined cause	SARS-CoV-2 (reference)	Total	<i>p</i>	Odds ratio	95% CI
Cough	Yes	114 (49.1%)	316 (66.4%)	430 (60.7%)	<0.001	2.044	1.484 to 2.815
	No	118 (50.9%)	160 (33.6%)	278 (39.3%)		1	Reference
Sore throat	Yes	28 (12.1%)	71 (14.9%)	99 (14.0%)	0.305	1.277	0.799 to 2.041
	No	204 (87.9%)	405 (85.1%)	609 (86.0%)		1	Reference
Dyspnea	Yes	149 (64.2%)	328 (68.9%)	477 (67.4%)	0.212	1.235	0.886 to 1.719
	No	83 (35.8%)	148 (31.1%)	231 (32.6%)		1	Reference
Respiratory discomfort	Yes	121 (52.2%)	257 (54.0%)	378 (53.4%)	0.646	1.077	0.786 to 1.474
	No	111 (47.8%)	219 (46.0%)	330 (46.6%)		1	Reference
Oxygen saturation	<95%	111 (47.8%)	291 (61.1%)	402 (56.8%)	<0.001	1.715	1.249 to 2.354
	≥95%	121 (52.2%)	185 (38.9%)	306 (43.2%)		1	Reference
Diarrhea	Yes	57 (24.6%)	108 (22.7%)	165 (23.3%)	0.579	0.901	0.624 to 1.302
	No	175 (75.4%)	368 (77.3%)	543 (76.7%)		1	Reference
Vomit	Yes	41 (17.7%)	60 (12.6%)	101 (14.3%)	0.070	0.672	0.436 to 1.035
	No	191 (82.3%)	416 (87.4%)	607 (85.7%)		1	Reference
Abdominal pain	Yes	36 (15.5%)	57 (12.0%)	93 (13.1%)	0.190	0.741	0.472 to 1.162
	No	196 (84.5%)	419 (88.8%)	615 (86.9%)		1	Reference
Fatigue and asthenia	Yes	42 (18.1%)	160 (33.6%)	202 (28.5%)	<0.001	2.291	1.559 to 3.364
	No	190 (81.9%)	316 (66.4%)	506 (71.5%)		1	Reference
Anosmia	Yes	9 (3.9%)	45 (9.5%)	54 (7.6%)	0.009	2.587	1.242 to 5.388
	No	223 (96.1%)	431 (90.5%)	654 (92.4%)		1	Reference
Ageusia	Yes	5 (2.2%)	38 (8.0%)	43 (6.1%)	0.002	3.939	1.529 to 10.140
	No	227 (97.8%)	438 (92.0%)	665 (93.9%)		1	Reference
Headache	Yes	20 (8.6%)	76 (16.0%)	96 (13.6%)	0.007	2.014	1.197 to 3.387
	No	212 (91.4%)	400 (84.0%)	612 (86.4%)		1	Reference
Coryza	Yes	12 (5.2%)	21 (4.4%)	33 (4.7%)	0.652	0.846	0.409 to 1.751
	No	220 (94.8%)	455 (95.6%)	675 (95.3%)		1	Reference
Myalgia	Yes	18 (7.8%)	52 (10.9%)	70 (9.9%)	0.185	1.458	0.832 to 2.554
	No	214 (92.2%)	424 (89.1%)	638 (90.1%)		1	Reference
Other clinical signs	Yes	78 (33.6%)	121 (25.4%)	199 (28.1%)	0.023	0.673	0.478 to 0.947
	No	154 (66.4%)	355 (74.6%)	509 (71.9%)		1	Reference
Antiviral to treat flu symptoms	Yes	19 (8.2%)	32 (6.7%)	51 (7.2%)	0.479	0.808	0.448 to 1.459
	No	213 (91.8%)	444 (93.3%)	657 (92.8%)		1	Reference
Intensive care unit	Yes	84 (36.2%)	183 (38.4%)	267 (37.7%)	0.564	1.100	0.795 to 1.523
	No	148 (63.8%)	293 (61.6%)	441 (62.3%)		1	Reference
Ventilatory support	Invasive	34 (14.7%)	99 (20.8%)	133 (18.8%)	<0.001	2.382	1.496 to 3.794
	Non-invasive	90 (38.8%)	245 (51.5%)	335 (47.3%)	<0.001	2.227	1.568 to 3.161
	None	108 (46.6%)	132 (27.7%)	240 (33.9%)		1	Reference
Closing criteria	Laboratorial	219 (94.4%)	443 (93.1%)	662 (93.5%)	0.501	0.797	0.411 to 1.545
	Clinical	13 (5.6%)	33 (6.8%)	46 (6.5%)		1	Reference
Outcome	Clinical recovery	180 (77.6%)	338 (71.0%)	518 (73.2%)		1	Reference
	Death due to SARI	36 (15.5%)	136 (28.6%)	172 (24.3%)	<0.001	2.012	1.336 to 3.030
	Death was not related to SARI	16 (6.9%)	2 (0.4%)	18 (2.5%)	<0.001	0.067	0.001 to 0.289

(Continued)

TABLE 2 (Continued)

Marker	Data	SARI due to an undefined cause	SARS-CoV-2 (reference)	Total	<i>p</i>	Odds ratio	95% CI
Vaccine against SARS-CoV-2	Yes	38 (16.4%)	88 (18.5%)	126 (17.8%)	0.491	1.158	0.763 to 1.758
	No	194 (83.6%)	388 (81.5%)	582 (82.2%)		1	Reference

The data were described using the number (*N*) and the percentage (%) of individuals. Crude data were obtained from the Open-Data SUS (<https://opendatasus.saude.gov.br/>). Data collection comprised the period from 29 December 2019 to 20 March 2022. 95% CI, 95% confidence interval; NA, not applicable; *p*, *p*-value; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2. The statistical analysis was conducted using the chi-square test and Fisher exact test. An alpha error of 0.05 was adopted. The significant *p*-values were presented using the bold type.

TABLE 3 Multivariable analysis used to describe the risk factors associated with the probability of classifying patients with Crohn's disease (CD) into groups of patients with severe acute respiratory syndrome due to the coronavirus disease (COVID)-19 or due to an undefined cause.

Markers ^a	<i>B</i>	SE	Wald	df	<i>p</i>	Odds ratio	95% CI	
							Lower	Upper
Race (other than whites' people)	-0.500	0.189	7.017	1	0.008	0.606	0.419	0.878
Diabetes mellitus	0.482	0.279	2.993	1	0.084	1.619	0.938	2.796
Obesity	1.935	0.746	6.733	1	0.009	6.922	1.605	29.849
Cough	0.454	0.180	6.384	1	0.012	1.574	1.107	2.238
Fatigue and asthenia	0.549	0.215	6.533	1	0.011	1.731	1.137	2.637
Ageusia	1.424	0.534	7.111	1	0.008	4.156	1.459	11.839
Headache	0.680	0.283	5.764	1	0.016	1.973	1.133	3.436
Ventilatory support								
Invasive	0.696	0.326	4.561	1	0.033	2.005	1.059	3.796
Non-invasive	0.499	0.198	6.329	1	0.012	1.647	1.117	2.431
None			7.965	2	0.019			
Outcome								
Death due to SARI	0.545	0.271	4.048	1	0.044	1.724	1.014	2.931
Death was not related to SARI	-3.063	0.899	11.593	1	<0.001	0.047	0.008	0.273
Clinical recovery			18.092	2	<0.001			
Constant	2.124	0.538	15.585	1	<0.001	8.365		

^aThe features included in step one: race, comorbidities (heart disease, diabetes mellitus, and obesity), clinical signs (cough, oxygen saturation below 95%, fatigue and asthenia, anosmia, and ageusia), need for ventilatory support and outcome.

The statistical analysis was carried out using the binary logistic regression model with the backward stepwise method. An alpha error of 0.05 was adopted. The significant *p*-values were presented using the bold type. 95% CI, 95% confidence interval; *B*, beta coefficient; df, degrees of freedom; *p*, *p*-values; SARI, severe acute respiratory infection; SE, standard error.

considered as protective groups—13 to 24 years old (2.9% versus 4.7%—OR=0.058; 95% CI=0.001–0.710), 25 to 60 years old (50.7% versus 68.6%—OR=0.060; 95% CI=0.001–0.550), and 61 to 72 years old (22.1% versus 21.0%—OR=0.087; 95% CI=0.001–0.820). In addition, neither race nor place of residence was associated with the probability of death (Table 4 and Figure 3).

Among comorbidities, only two were associated with a higher probability of death: neurological disorder (OR=2.901; 95% CI=1.152–7.306) and heart disease (OR=2.412; 95% CI=1.598–3.639). In addition, among the clinical symptoms and signs, three were associated with a higher probability of death [(oxygen saturation below 95%) OR=2.922; 95% CI=1.848–4.622, (dyspnea) OR=2.194; 95% CI=1.362–3.544, and (respiratory discomfort) OR=2.192; 95% CI=1.444–3.329], while five symptoms were associated with a lower probability of death [(coryza) OR=0.118; 95% CI=0.003–0.753, (headache) OR=0.287; 95% CI=0.139–0.593, (anosmia) OR=0.354; 95% CI=0.146–0.856, (diarrhea) OR=0.574; 95% CI=0.342–0.965],

and (fatigue and asthenia) OR=0.629; 95% CI=0.405–0.978. The presence of nosocomial infection and the use of antiviral drugs to treat the flu symptoms were not associated with the probability of death (Table 4 and Figure 3).

The need for ICU treatment (OR=9.156; 95% CI=5.789–14.480) and invasive (OR=90.79; 95% CI=35.79–230.3) or non-invasive (OR=4.205; 95% CI=1.843–9.596) mechanical ventilation were associated with a higher probability of death. Curiously, the vaccines against COVID-19 did not influence the outcomes (Table 4 and Figure 3).

A multivariable analysis was conducted to describe the risk factors associated with the likelihood of classifying patients with CD into the groups with a higher probability of death (Table 5 and Figure 4). In brief, the predictors of death were (a) the presence of neurological disorder (OR=6.716; 95% CI=1.954–23.078), (b) the need for ICU (OR=3.348; 95% CI=1.770–6.335), and (c) the need for invasive mechanical ventilatory support (OR=59.017; 95%

TABLE 4 Association between demographic and clinical features and death in the patients hospitalized with Crohn's disease (CD) and severe acute respiratory infection (SARI) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Marker	Data	Hospital discharge	Death due to SARI ^a	Total	<i>p</i>	Odds ratio	95% CI
Sex	Male	163 (48.2%)	80 (58.8%)	243 (51.3%)	0.037	1.534	1.025 to 2.294
	Female	175 (51.8%)	56 (41.2%)	231 (48.7%)		1	Reference
Age	1 to 12 years old	1 (0.3%)	1 (0.7%)	2 (0.4%)	0.929	0.258	0.002 to 31.28
	13 to 24 years old	16 (4.7%)	4 (2.9%)	20 (4.2%)	0.019	0.058	0.001 to 0.710
	25 to 60 years old	232 (68.6%)	69 (50.7%)	301 (63.5%)	0.007	0.060	0.001 to 0.550
	61 to 72 years old	71 (21.0%)	30 (22.1%)	101 (21.3%)	0.028	0.087	0.001 to 0.820
	73 to 85 years old	17 (5.0%)	27 (19.9%)	44 (9.3%)	0.570	0.324	0.006 to 3.267
	+85 years old	1 (0.3%)	5 (3.7%)	6 (1.3%)		1	Reference
Race	White people	258 (76.3%)	98 (72.1%)	356 (75.1%)		1	Reference
	Black people	6 (1.8%)	2 (1.5%)	8 (1.7%)	1.000	0.878	0.085 to 5.016
	Asian	3 (0.9%)	0 (0.0%)	3 (0.6%)		NA	NA
	Mixed-race individuals	71 (21.0%)	36 (26.5%)	107 (22.6%)	0.222	1.335	0.840 to 2.122
Place of residence	Urban	332 (98.2%)	134 (98.5%)	466 (98.3%)	1	1.210	0.213 to 12.410
	Rural + peri-urban	6 (1.8%)	2 (1.5%)	8 (1.7%)		1	Reference
Comorbidities							
Heart disease	Yes	95 (28.1%)	66 (48.5%)	161 (34.0%)	<0.001	2.412	1.598 to 3.639
	No	243 (71.9%)	70 (51.5%)	313 (66.0%)		1	Reference
Hematological disorder	Yes	5 (1.5%)	3 (2.2%)	8 (1.7%)	0.695	1.501	0.230 to 7.838
	No	333 (98.5%)	133 (97.8%)	466 (98.3%)		1	Reference
Down syndrome	Yes	2 (0.6%)	4 (2.9%)	6 (1.3%)	0.059	5.071	0.717 to 56.680
	No	336 (99.4%)	132 (97.1%)	468 (98.7%)		1	Reference
Liver disorder	Yes	6 (1.8%)	4 (2.9%)	10 (2.1%)	0.483	1.675	0.342 to 7.192
	No	332 (98.2%)	132 (97.1%)	464 (97.9%)		1	Reference
Asthma	Yes	10 (3.0%)	3 (2.2%)	13 (2.7%)	0.766	0.740	0.129 to 2.935
	No	328 (97.0%)	133 (97.8%)	461 (97.3%)		1	Reference
Diabetes mellitus	Yes	55 (16.3%)	31 (22.8%)	86 (18.1%)	0.096	1.519	0.927 to 2.489
	No	283 (83.7%)	105 (77.2%)	388 (81.9%)		1	Reference
Neurological disorder	Yes	9 (2.7%)	10 (7.4%)	19 (4.0%)	0.019	2.901	1.152 to 7.306
	No	329 (97.3%)	126 (92.6%)	455 (96.0%)		1	Reference
Lung disease	Yes	13 (3.8%)	6 (4.4%)	19 (4.0%)	0.776	1.154	0.429 to 3.100
	No	325 (96.2%)	130 (95.6%)	455 (96.0%)		1	Reference
Immunosuppressive disorder	Yes	45 (13.3%)	16 (11.8%)	61 (12.9%)	0.649	0.868	0.472 to 1.596
	No	293 (86.7%)	120 (88.2%)	413 (87.1%)		1	Reference
Kidney disorder	Yes	9 (2.7%)	7 (5.1%)	16 (3.4%)	0.176	1.984	0.724 to 5.438
	No	329 (97.3%)	129 (94.9%)	458 (96.6%)		1	Reference
Obesity	Yes	25 (7.4%)	15 (11.0%)	40 (8.4%)	0.198	1.552	0.791 to 3.044
	No	313 (92.6%)	121 (89.0%)	434 (91.6%)		1	Reference
Nosocomial infection	Yes	12 (3.6%)	5 (3.7%)	17 (3.6%)	0.947	1.037	0.358 to 3.001
	No	326 (96.4%)	131 (96.3%)	457 (96.4%)		1	Reference
Clinical symptoms and signs							
Fever	Yes	208 (61.5%)	73 (53.7%)	281 (59.3%)	0.115	0.724	0.485 to 1.083
	No	130 (38.5%)	63 (46.3%)	193 (40.7%)		1	Reference

(Continued)

TABLE 4 (Continued)

Marker	Data	Hospital discharge	Death due to SARI*	Total	<i>p</i>	Odds ratio	95% CI
Cough	Yes	224 (66.3%)	91 (66.9%)	315 (66.5%)	0.894	1.029	0.675 to 1.570
	No	114 (33.7%)	45 (33.1%)	159 (33.5%)		1	Reference
Sore throat	Yes	52 (15.4%)	18 (13.2%)	70 (14.8%)	0.551	0.839	0.471 to 1.494
	No	286 (84.6%)	118 (86.8%)	404 (85.2%)		1	Reference
Dyspnea	Yes	219 (64.8%)	109 (80.1%)	328 (69.2%)	0.001	2.194	1.362 to 3.534
	No	119 (35.2%)	27 (19.9%)	146 (30.8%)		1	Reference
Respiratory discomfort	Yes	165 (48.8%)	92 (67.6%)	257 (54.2%)	<0.001	2.192	1.444 to 3.329
	No	173 (51.2%)	44 (32.4%)	217 (45.8%)		1	Reference
Oxygen saturation	<95%	185 (54.7%)	106 (77.9%)	291 (61.4%)	<0.001	2.922	1.848 to 4.622
	≥95%	153 (45.3%)	30 (22.1%)	183 (38.6%)		1	Reference
Diarrhea	Yes	85 (25.1%)	22 (16.2%)	107 (22.6%)	0.035	0.574	0.342 to 0.965
	No	253 (74.9%)	114 (83.8%)	367 (77.4%)		1	Reference
Vomit	Yes	47 (13.9%)	12 (8.8%)	59 (12.4%)	0.166	0.599	0.307 to 1.168
	No	291 (86.1%)	124 (91.2%)	415 (87.6%)		1	Reference
Abdominal pain	Yes	43 (12.7%)	13 (9.6%)	56 (11.8%)	0.335	0.725	0.377 to 1.396
	No	295 (87.3%)	123 (90.4%)	418 (88.2%)		1	Reference
Fatigue and asthenia	Yes	123 (36.4%)	36 (26.5%)	159 (33.5%)	0.039	0.629	0.405 to 0.978
	No	215 (63.6%)	100 (73.5%)	315 (66.5%)		1	Reference
Anosmia	Yes	39 (11.5%)	6 (4.4%)	45 (9.5%)	0.017	0.354	0.146 to 0.856
	No	299 (88.5%)	130 (95.6%)	429 (90.5%)		1	Reference
Ageusia	Yes	31 (9.2%)	6 (4.4%)	37 (7.8%)	0.081	0.457	0.186 to 1.122
	No	307 (90.8%)	130 (95.6%)	437 (92.2%)		1	Reference
Headache	Yes	67 (19.8%)	9 (6.6%)	76 (16.0%)	<0.001	0.287	0.139 to 0.593
	No	271 (80.2%)	127 (93.4%)	398 (84.0%)		1	Reference
Coryza	Yes	20 (5.9%)	1 (0.7%)	21 (4.4%)	0.012	0.118	0.003 to 0.753
	No	318 (94.1%)	135 (99.3%)	453 (95.6%)		1	Reference
Myalgia	Yes	41 (12.1%)	11 (8.1%)	52 (11.0%)	0.203	0.638	0.317 to 1.281
	No	297 (87.9%)	125 (91.9%)	422 (89.0%)		1	Reference
Other clinical signs	Yes	91 (26.9%)	29 (21.3%)	120 (25.3%)	0.205	0.736	0.457 to 1.184
	No	247 (73.1%)	107 (78.7%)	354 (74.7%)		1	Reference
Antiviral to treat flu signs	Yes	26 (7.7%)	6 (4.4%)	32 (6.8%)	0.198	0.554	0.223 to 1.377
	No	312 (92.3%)	130 (95.6%)	442 (93.2%)		1	Reference
Intensive care unit	Yes	81 (24.0%)	101 (74.3%)	182 (38.4%)	<0.001	9.156	5.789 to 14.480
	No	257 (76.0%)	35 (25.7%)	292 (61.6%)		1	Reference
Ventilatory support	Invasive	16 (4.7%)	82 (60.3%)	98 (20.7%)	<0.001	90.79	35.79 to 230.3
	Non-invasive	198 (58.6%)	47 (34.6%)	245 (51.7%)	<0.001	4.205	1.843 to 9.596
	None	124 (36.7%)	7 (5.1%)	131 (27.6%)		1	Reference
Closing criteria	Laboratorial	316 (93.5%)	125 (91.9%)	441 (93.0%)	0.552	0.791	0.373 to 1.679
	Clinical	22 (6.5%)	11 (8.1%)	33 (7.0%)		1	Reference
Vaccine against SARS-CoV-2 infection	Yes	64 (18.9%)	24 (17.6%)	88 (18.6%)	0.744	0.917	0.547 to 1.540
	No	274 (81.1%)	112 (82.4%)	386 (81.4%)		1	Reference

*Two patients that died were excluded due to other causes different from the SARS-CoV-2 infection.

The data were described using the number (*N*) and the percentage (%) of individuals. Crude data were obtained from the Open-Data SUS (<https://opendatasus.saude.gov.br/>). The data collection process was conducted from 29 December 2019 to 20 March 2022. 95% CI, 95% confidence interval; *p*, *p*-value. NA, not applicable. The statistical analysis was done using the chi-square test and Fisher exact test. An alpha error of 0.05 was adopted. The significant *p*-values were presented using the bold type.

TABLE 5 Multivariable analysis to describe the risk factors associated with the probability of death in hospitalized patients with Crohn's disease (CD) and severe acute respiratory infection (SARI) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Markers ^a	B	SE	Wald	df	p	Odds ratio	95% CI	
							Lower	Upper
Age								
1 to 12 years old	-2.438	3.510	0.482	1	0.487	0.087	<0.001	84.851
13 to 24 years old	-2.653	1.480	3.216	1	0.073	0.070	0.004	1.280
25 to 60 years old	-3.375	1.241	7.398	1	0.007	0.034	0.003	0.389
61 to 72 years old	-2.576	1.255	4.214	1	0.040	0.076	0.007	0.890
73 to 85 years old	-1.165	1.292	0.813	1	0.367	0.312	0.025	3.923
+85 years old (reference)			27.135	5	<0.001			
Neurological disorder	1.904	0.630	9.145	1	0.002	6.716	1.954	23.078
Diarrhea	-0.827	0.400	4.273	1	0.039	0.437	0.200	0.958
Headache	-1.854	0.542	11.694	1	<0.001	0.157	0.054	0.453
Coryza	-2.390	1.321	3.273	1	0.070	0.092	0.007	1.221
Intensive care unit	1.208	0.325	13.800	1	<0.001	3.348	1.770	6.335
Ventilatory support								
Invasive	4.078	0.557	53.535	1	<0.001	59.017	19.796	175.944
Non-invasive	0.860	0.476	3.263	1	0.071	2.363	0.929	6.009
None (reference)			75.919	2	<0.001			
Constant	0.117	1.250	0.009	1	0.925	1.124		

^aFeatures included in step one: sex, age, comorbidities (heart disease and neurological disorder), clinical signs (dyspnea, respiratory discomfort, oxygen saturation below 95%, diarrhea, fatigue and asthenia, anosmia, headache, coryza), the need for the intensive care unit and the need for ventilatory support.

The statistical analysis was carried out using the binary logistic regression model with the backward stepwise method. An alpha error of 0.05 was adopted. The significant *p*-values were presented using the bold type. 95% CI, 95% confidence interval; B, beta coefficient; df, degrees of freedom; *p*, *p*-values; SE, standard error.

CI = 19.796–175.944). In contrast, the following markers were protective against death: (a) age [(25 to 60 years old) OR = 0.034; 95% CI = 0.003–0.389, and (61 to 72 years old) OR = 0.076; 95% CI = 0.007–0.890], (b) diarrhea (OR = 0.437; 95% CI = 0.200–0.958), and (c) headache (OR = 0.157; 95% CI = 0.054–0.453).

3.4 Association between the probability of death in hospitalized patients with CD and control individuals from other studies previously published

The study conducted a comparative analysis of case fatality rates between patients with CD and control cohorts from literature, all using the Open-Data-SUS database. The comparison focused on hospitalized patients with severe acute respiratory syndrome due to SARS-CoV-2 infection (Table 6). In 2020, patients with CD had a mortality rate of 28.7% (136/475), while control patients had a mortality rate of 33.9% (214,027/630,000), with a statistically significant *p*-value of 0.017 and an OR of 0.786 (95% CI = 0.644–0.959), indicating a lower risk of death for patients with CD. Similarly, in 2021, patients with CD maintained the same mortality rate (28.7%), whereas the control group had a mortality rate of 33.3% (390,192/1,170,000), with a *p*-value of 0.023 and an OR of 0.795 (95% CI = 0.651–0.970), again reflecting a reduced mortality risk for patients with CD. In 2022, the mortality rate for patients with CD remained at 28.7%, while the control group had a mortality rate of 29.3% (65,711/224,000). The *p*-value of 0.757 indicated no significant

difference (OR = 0.969, 95% CI = 0.794–1.183). However, in 2023, patients with CD still had a mortality rate of 28.7%, while the control group had a reduced mortality rate of 24.4% (3,444/14,100), with a significant *p*-value of 0.032 and an OR of 1.248 (95% CI = 1.109–1.528), suggesting a higher mortality risk for patients with CD in that year. Over the entire period, patients with CD exhibited a cumulative mortality rate of 28.7%, compared to 33.2% in controls (673,374/2,025,000), with a *p*-value of 0.039 and an OR of 0.811 (95% CI = 0.665–0.989), suggesting an overall lower mortality risk for patients with CD across the pandemic, particularly in 2020 and 2021. The study underscores the temporal variability in mortality risk for patients with CD and emphasizes the importance of ongoing surveillance for this vulnerable population.

4 Discussion

The onset of the COVID-19 pandemic in March 2020 triggered a global surge in transmission and contamination, culminating in a significant toll of fatalities and overwhelming pressure on healthcare infrastructure. This resulted in a high number of deaths and an intense strain on the healthcare system. Hospitals were reorganized due to the increased need for beds, especially for patients requiring intensive care (1).

Since the onset of the COVID-19 pandemic, numerous studies have focused on accelerated diagnostic methods and the exploration and repurposing of therapeutic approaches. However, the potential long-term effects on individuals who have contracted the virus remain

TABLE 6 Association between the probability of death in hospitalized patients with Crohn's disease (CD) and control individuals from other studies previously published.

Comparative study	Groups	Patients with CD [N (%)]	Other studies [N (%)]	p-value	OR	95% CI
Sansone et al., 2022 ^a	Death	136 (28.7%)	574,887 (34.8%)	<0.001	0.754	0.618–0.921
	Hospital discharge	338 (71.3%)	1,077,870 (65.2%)			
Sansone et al., 2022 ^b	Death	136 (28.7%)	73,723 (26.3%)	0.234	1.129	0.925–1.378
	Hospital discharge	338 (71.3%)	206,810 (73.7%)			
Boscheiro et al., 2022 ^c	Death	136 (28.7%)	25,571 (14.0%)	<0.001	2.468	2.022–3.13
	Hospital discharge	338 (71.3%)	156,871 (86.0%)			
Palamim et al., 2023 ^d —2020	Death	136 (28.7%)	214,027 (33.9%)	0.017	0.786	0.644–0.959
	Hospital discharge	338 (71.3%)	417,893 (66.1%)			
Palamim et al., 2023 ^d —2021	Death	136 (28.7%)	390,192 (33.3%)	0.023	0.795	0.651–0.970
	Hospital discharge	338 (71.3%)	770,806 (66.7%)			
Palamim et al., 2023 ^d —2022	Death	136 (28.7%)	65,711 (29.3%)	0.757	0.969	0.794–1.183
	Hospital discharge	338 (71.3%)	158,253 (70.7%)			
Palamim et al., 2023 ^d —2023	Death	136 (28.7%)	3,444 (24.4%)	0.032	1.248	1.109–1.528
	Hospital discharge	338 (71.3%)	10,682 (75.6%)			
Palamim et al., 2023 ^d —Total	Death	136 (28.7%)	673,374 (33.2%)	0.039	0.811	0.665–0.989
	Hospital discharge	338 (71.3%)	1,357,634 (66.8%)			

All the patients were hospitalized in Brazil due to the presence of severe acute respiratory syndrome caused by the coronavirus disease (COVID)-19. The data were described using the number (N) and percentage (%) of individuals. The significant p-values were presented using the bold type.

^aThe study comprised only the first year of the COVID-19 pandemic when the highest number of deaths (case fatality rates) were observed in Brazil due to the inefficiency of the Brazilian government in dealing with the impact of the COVID-19 pandemic, mainly in the Brazilian Health System (62).

^bThe study also comprised only the first year of the COVID-19 pandemic when the highest number of deaths (case fatality rates) were observed in Brazil due to the inefficiency of the Brazilian government in dealing with the impact of the COVID-19 pandemic, mainly in the Brazilian Health System (61). However, in this study, only patients without comorbidities were enrolled.

^cThe study also comprised only the first year of the COVID-19 pandemic, when the highest number of deaths (case fatality rates) were observed in Brazil due to the inefficiency of the Brazilian government in dealing with the impact of the COVID-19 pandemic, mainly in the Brazilian Health System (30). However, in this study, only patients without comorbidities were enrolled, and the control sample was restrictive in terms of severity.

^dThe study comprised an overview of the COVID-19 pandemic over 4 years, and the data were presented by the year of notification (39). %, percentage; 95% CI, 95% confidence interval; N, number of individuals; OR, odds ratio. The statistical analysis was performed using the chi-square test.

uncertain. COVID-19 extends beyond being a respiratory illness. As demonstrated by Jin et al. (42), the virus-induced inflammatory response triggers the production of endogenous chemicals that can breach tissue barriers and spread systemically through hematogenic transmission pathways (43).

Giustino et al. (44) reported increased levels of pro-inflammatory cytokines—interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor- α (TNF- α)—in COVID-19-positive patients. These cytokines can trigger immune cell activation in response to vascular changes, leading to increased blood adhesion and coagulation. Consequently, this signaling cascade activates immune cells involved in chronic inflammatory processes, potentially causing pulmonary degeneration, pulmonary fibrosis, loss of function, hypoxemia, and anoxia, which can contribute to unfavorable clinical outcomes.

Patients with cardiopulmonary or metabolic comorbidities, autoimmune diseases such as CD described in our study, or those undergoing treatments that may compromise their immunity (for example, chemotherapy, radiotherapy, or corticosteroid therapy) are at a higher risk of death (45).

The severity of cases and potential consequences in COVID-19 hospitalized patients are important markers for assessing risks and possible prognosis, especially for patients with pre-existing conditions who were left without adequate care due to the suspension of

outpatient treatments (46). The pathophysiology of COVID-19 is complex, affecting various organs and systems. The lungs, considered the target organs of the respiratory system, undergo gradual functional failure, as evidenced by hypoxia and pathological findings from minimal and non-invasive autopsies on patients (47).

The pandemic significantly and disproportionately affected the Brazilian population, marked by geographical differences, socioeconomic inequalities, and low availability of therapeutic resources and healthcare teams. These factors can be important determinants in a pandemic, hindering access to available resources and leading to higher-case fatalities. Furthermore, the unequal distribution of COVID-19 cases among Brazilian regions might have resulted from underreporting (39). The state of São Paulo reported the highest number of notified cases, being a developed state with the main financial and corporate center in South America, which makes it the most influential Brazilian city on the global stage (48).

Although SARS-CoV-2 does not exhibit contagious selectivity, the impacts of infection can manifest differently depending on race, class, and gender. In this study, we observed that individuals of mixed race were the most affected. The Brazilian population, which is the fifth-largest in the world estimated at 211,293 million inhabitants, is classified as White people (45.22%), mixed race (45.06%), Black people (8.86%), Asians (0.47%), and Indigenous peoples (0.38%), which may explain the higher incidence in mixed-race patients (49).

This study focused on analyzing hospitalizations of patients with CD, a chronic and recurrent metabolic disorder that may predispose the body to other comorbidities, including a potentially positive relationship with colorectal cancer, the third leading cause of death. Patients with CD and COVID-19 have been discussed (50). CD, a chronic remittent inflammatory bowel disease, is influenced by genetic predisposition and lifestyle factors and exacerbated by urbanization and industrialization, which disrupt intestinal homeostasis and provoke immune responses, leading to chronic inflammation. This significantly impacts patients' quality of life (51, 52). The CD also has extraintestinal manifestations, including musculoskeletal, ocular, and vascular complications such as cardiovascular disease, thromboembolism, and portal vein thrombosis, contributing to morbidity and mortality (53). Immunosuppressants are commonly used to reduce gastrointestinal inflammation but can increase susceptibility to opportunistic infections and severe illnesses due to compromised immune function (54). A substantial proportion of COVID-19 cases progress to acute respiratory distress syndrome due to critical lung injury. Hyperinflammation following SARS-CoV-2 infection is a key mechanism leading to respiratory failure, multi-organ dysfunction, and mortality (55). The pandemic has raised concerns about managing inflammatory bowel disease patients, as they may experience more severe COVID-19 due to a dysregulated immune state and immunosuppressive medication use (56, 57).

Early epidemiological data indicate a worse prognosis and higher mortality for patients with COVID-19 and chronic diseases, such as heart disease, a relevant complication to our study group. According to the literature, the extreme inflammatory response caused by COVID-19 can lead to cardiac injury through multiple disorders, causing endothelial injury and myocarditis. The cardiovascular system is affected in various ways by severe respiratory tract infections caused by SARS-CoV-2. According to the study by Giustino et al. (44), myocardial injury occurred in 25% of hospitalized COVID-19 patients and is associated with an increased risk of mortality. Increasing clinical and epidemiological evidence has shown that cardiovascular comorbidities are widely associated with an increased risk of death caused by COVID-19.

In our study, another prevalent comorbidity was neurological disorders. According to Mao et al. (56), the short- and long-term impacts of SARS-CoV-2 infection on the central nervous system remain unclear. However, the most commonly reported symptoms of COVID-19 include ageusia, anosmia, hearing loss, headaches, spasms, seizures, confusion, visual impairment, dizziness, decreased consciousness, nausea and vomiting, hemiplegia, ataxia, stroke, and cerebral hemorrhage.

The pathophysiology of SARS-CoV-2 infection involves various essential organ systems for maintaining homeostasis. The direct effect of SARS-CoV-2 hyperinflammation induces the production of endogenous substances that alter vascular hemostasis. Blood coagulation is directly affected by the release of pro-coagulant and pro-inflammatory cytokines, activating disseminated intravascular coagulation and the formation of thromboembolic states that can aggressively affect various tissues, especially those more sensitive to ischemic processes, such as lung, cardiovascular, and cerebrovascular tissues.

According to Zhong et al. (12), inflammatory complications involving the digestive system are not uncommon in individuals affected by COVID-19. Clinical manifestations such as diarrhea, nausea, vomiting, abdominal pain, gastrointestinal bleeding, lack of appetite, and constipation were reported in patients affected by the novel coronavirus, supporting our study, especially in the group that had both COVID-19 and CD, with diarrhea being the main symptom.

Studies suggest that gastrointestinal symptoms caused by SARS-CoV-2 occur because the infection is associated with the lung-intestine-brain axis, where the virus activates intestinal receptors, inducing tissue inflammation and causing a high viral load that leads to the previously mentioned gastrointestinal problems (58).

The infection induces alterations and diminishes the colonies of intestinal microorganisms, precipitating the activation of immune cells and instigating the secretion of pro-inflammatory cytokines. Consequently, this disruption in the individual's microbiota composition, termed dysbiosis, fosters an inflammatory milieu that amplifies systemic inflammation (59, 60). Based on current studies (30, 39, 61, 62), no clear consensus has been reached regarding the impact of COVID-19 on mortality risk in patients with CD. Further research is required to comprehensively assess this relationship.

Patients with autoimmune diseases, when affected by SARS-CoV-2 infection, are at a higher risk of developing severe forms of the disease (63). Immunosuppression can lead to increased production of interferons and interleukins, activation of granulocytes, and tumor necrosis factor, resulting in intravascular inflammation, which causes alterations in angiogenesis and coagulation. In addition to understanding the immune response to COVID-19, the association of symptoms with autoimmune diseases suggests that SARS-CoV-2 may trigger secondary diseases associated with a temporary state of immunosuppression and the presence of the virus.

4.1 Limitations

The present study has several limitations. The key limitations include the following: (a) reliance on a national database, which may contain reporting bias, (b) potential inaccuracies in the diagnosis of CD, (c) limited external validity, as the data are derived exclusively from patients in Brazil, (d) exclusively information regarding the number of COVID-19 vaccinations received, and thus, their potential effect on clinical outcomes in patients with SARI, (e) the absence of crucial epidemiological and clinical markers (e.g., smoking status and daily living habits) in the Open-Data-SUS, which could influence clinical outcomes, (f) the unclear clinical state of the patients with CD at the time of data entry, making it impossible to determine whether the patient was in an exacerbation or remission phase of the disease, and (g) a small sample size, which may increase the risk of a Type II error.

5 Conclusion

The findings of this study revealed that only three Brazilian states, São Paulo, Paraná, and Minas Gerais, accounted for half of the reported cases of COVID-19. Notably, among patients concurrently hospitalized with CD and COVID-19, there was no discernible sex predilection; however, individuals self-identified as mixed-race were the most affected demographic group. The predominant comorbidities observed in these patients included heart disease, diabetes mellitus, and obesity. Additionally, clinical manifestations included symptoms such as cough, oxygen saturation below 95%, fatigue, asthenia, anosmia, ageusia, and headache. An age-based comparison indicated that individuals aged 25 to 60 years were disproportionately affected by both diseases, with this age group exhibiting increased vulnerability to mortality. In addition, the study suggests that the systemic effects of COVID-19 may lead to degenerative changes and prolonged

consequences, highlighting the need for continued research into the long-term implications of the disease.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: <https://opendatasus.saude.gov.br/>.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

LN: Writing – original draft, Writing – review & editing, Investigation, Methodology. FM: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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4. CONCLUSÃO

Os resultados deste estudo revelaram que apenas três estados brasileiros, São Paulo, Paraná e Minas Gerais, foram responsáveis por metade dos casos notificados de Covid-19. Pacientes hospitalizados com DC e Covid-19, observou-se que não houve predileção de sexo, no entanto indivíduos autoidentificados como mestiços foram o grupo demográfico mais afetado.

As comorbidades mais prevalentes foram: doenças cardíacas, diabetes mellitus e obesidade. Outros sinais clínicos apresentados foram: tosse, saturação de oxigênio <95%, fadiga e astenia, perda do olfato, perda do paladar e cefaleia. Na comparação etária, a faixa etária mais acometida foi de 25 a 60 anos e quando avaliada a probabilidade de óbito entre pacientes hospitalizados com DC e pacientes com Covid-19 a mesma faixa etária foi acometida. Além disso, o estudo sugere que os efeitos sistêmicos da Covid-19 podem levar a alterações degenerativas e consequências prolongadas, destacando a necessidade de pesquisas contínuas sobre as implicações de longo prazo da doença.

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