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NELSON PEREIRA MARQUES

CONDIÇÕES ORAIS E SISTÊMICAS ASSOCIADAS A PANDEMIA DE COVID-19

ORAL AND SYSTEMIC CONDITIONS ASSOCIATED WITH THE COVID-19 PANDEMIC

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutor em Estomatopatologia, na Área de Estomatologia.

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Supervisor/Orientador: Prof. Dr. Hercílio Martelli Júnior

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FOLHA DE APROVAÇÃO

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A Comissão Julgadora dos trabalhos de Defesa de Tese de Doutorado, em sessão pública realizada em 30 de junho de 2023, considerou o candidato NELSON PEREIRA MARQUES aprovado.

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A Ata da defesa, assinada pelos membros da Comissão Examinadora, consta no SIGA/Sistema de Fluxo de Dissertação/Tese e na Secretaria do Programa da Unidade.

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RESUMO

A pandemia de COVID-19 emergiu no início do ano de 2020, quando a Organização Mundial da Saúde (OMS) classificou a doença causada pelo vírus SARS-CoV-2 como uma emergência de saúde pública de importância internacional, em razão da sua rápida disseminação que representou um importante desafio para as autoridades de saúde em todo o mundo. A continuidade da pandemia de COVID-19 suscitou preocupações nas áreas da saúde, em razão da dinâmica da doença. Com uma demanda para produzir rapidamente evidências relacionadas a COVID-19, pesquisadores passaram a fornecer dados, visando auxiliar a tomada de decisões clínicas eficazes e o gerenciamento de pacientes. Relatos de possíveis relações de condições sistêmicas e alterações na cavidade oral de pacientes positivos para a COVID-19 passaram a ser discutidos na literatura, tornando necessária uma profunda investigação do impacto da pandemia de COVID-19 no diagnóstico de doenças sistêmicas e na prestação dos serviços essenciais de saúde no Brasil. Com isso, o objetivo deste estudo foi avaliar a produção e a assistência à saúde por estomatologistas durante a pandemia de COVID-19 e comparar com os mesmos dados do período pré-pandêmico, além de avaliar os diagnósticos de doenças sistêmicas no sistema único de saúde brasileiro (SUS) durante o período pandêmico e comparar com os dados anteriores a pandemia de COVID-19. Durante o primeiro período pandêmico (2020), houve uma redução importante nas consultas realizadas por estomatologistas no Brasil. No entanto, em 2021, com o retorno das atividades clínicas, esse dado se normalizou. Os casos de lúpus eritematoso sistêmico, herpes zoster e de síndrome de Guillain-Barré tiveram um aumento contínuo durante a pandemia de COVID-19, o que sugere uma possível relação entre as doenças. Enquanto isso, os diagnósticos de câncer e hanseníase sofreram uma queda durante o período pandêmico, sendo uma fonte de preocupação para o prognóstico desses pacientes. Apesar do fim do período de emergência de saúde pública de importância internacional relacionada à COVID-19, determinado pela OMS, a comunidade científica deve seguir na elaboração de novos estudos relacionados à doença. Atualizações dos dados de diagnósticos das doenças discutidas neste trabalho são essenciais para o melhor entendimento da possível relação entre as condições citadas e a COVID-19, além de determinar se a superação deste período e as medidas implementadas até agora foram suficientes para o controle dessas doenças.

Palavras-chave: Boca. COVID-19. Doenças Autoimunes. Pandemias.

ABSTRACT

The COVID-19 pandemic began in early 2020, when the World Health Organization (WHO) designated the disease caused by the SARS-CoV-2 virus as a public health emergency of international concern for its rapid spread, resenting a major challenge to health authorities around the world. The continuity of the COVID-19 pandemic raised several health concerns, due to the dynamic behavior of the disease. Based on the required demand for scientific evidence of COVID-19, researchers have provided data in order to aid the implementation of effective clinical decisions and manage patients. The literature began to discuss the possible relation between systemic conditions and alterations in the oral cavity in COVID-19 patients, making necessary a detailed investigation into the impact of the pandemic on the diagnoses of infectious and systemic diseases and on the essential health services provision in Brazil. Thus, this study aimed to compare the production and health care by stomatologists during the COVID-19 pandemic with the same data from the pre-pandemic period, in addition to evaluating the diagnoses of systemic and infectious diseases in the Brazilian Unified Healthcare System (SUS) during the pandemic period and compare with pre-COVID-19 pandemic data. During the first pandemic period (2020), the number of consultations carried out by stomatologists dropped significantly in Brazil. However, the rates of oral medicine consultations normalized with the return of clinical activities in 2021. Cases of Systemic Lupus Erythematosus, Herpes Zoster and Guillain-Barré Syndrome have steadily increased during the COVID-19 pandemic, suggesting a possible association between the diseases. Meanwhile, the diagnoses of Cancer and Hansen´s Disease dropped during the pandemic period, concerning the prognosis of patients. Despite the end of the public health emergency of international concern period related to COVID-19, determined by WHO, the scientific community must continue working on further studies related to the disease. Updates of the diagnostic data of the diseases discussed in this study are essential for a better understanding of the possible relationship between the mentioned conditions and COVID-19, in addition to determining whether overcoming this period and the measures implemented so far effectively controlled these diseases.

Keywords: Mouth. COVID-19. Autoimmune Diseases. Pandemics.

SUMÁRIO

1 INTRODUÇÃO

O Centro de Controle e Prevenção de Doenças (CDC) chinês anunciou, no início de 2020, o acometimento da população por uma pneumonia causada por um novo vírus da família Coronavírus (CoV). Este vírus inicialmente foi identificado como 2019-nCoV, e oficialmente como SARS-CoV-2 causador da Síndrome Respiratória Aguda Grave Coronavírus 2, doença denominada posteriormente de Coronavírus-19 (COVID-19) pela Organização Mundial de Saúde (OMS) (DI GENNARO et al., 2020; SHI et al., 2020; WHO, 2020; ZHU et al., 2020).

A COVID-19 apresenta um quadro clínico que varia de infecções assintomáticas a quadros respiratórios grave, cujos sintomas podem incluir, tosse, coriza, mialgia, dor de garganta, dificuldade respiratória e febre (BRASIL, 2020; WHO, 2020). A transmissão desta doença ocorre pela disseminação de gotículas de secreções contaminadas por contato pessoal, ou através de aerossóis, superfícies e objetos contaminados (CHENG et al., 2020).

A contaminação da doença COVID-19 iniciou na cidade de Wuhan, província de Hubei, na China em dezembro de 2019, e a doença estava disseminada em mais de 200 países em março de 2020, sendo classificada pela OMS como uma pandemia (PHELAN; KATZ; GOSTIN, 2020; WHO, 2020). Desde então, medidas restritivas variadas foram estabelecidas na tentativa de controlar a transmissão da doença, incluindo regras de isolamento social, com concomitante fechamento de fronteiras impostas por governos de alguns países, cancelamento de eventos, suspensão de atividades presenciais em comércios e centros educacionais, e até o planejamento e a adoção de medidas de saúde, como, campanhas de conscientização de biossegurança, barreiras sanitárias, e suspensão de serviços especializados de saúde (AQUINO et al., 2020; CORREIA; RAMOS; BAHTEN, 2020; JARVIS et al., 2020; SARAIVA; OLIVEIRA; MOREJON, 2020).

Diante deste cenário, em março de 2020, o Conselho Federal de Odontologia (CFO) e outros conselhos da área de saúde solicitaram ao Ministério da Saúde do Brasil (MS) a suspensão de atendimentos eletivos na rede pública de saúde. Para os serviços particulares recomendou-se o reforço das práticas de biossegurança (CONSELHO FEDERAL DE MEDICINA, 2020; CONSELHO FEDERAL DE ODONTOLOGIA, 2020a). Um levantamento realizado pelo CFO mostrou que 82% dos profissionais mantiveram os atendimentos odontológicos no período pandêmico. Mesmo diante deste cenário, um relatório emitido pelo MS em julho de 2020 mostrou um índice baixo de profissionais da Odontologia contaminados

pela COVID-19 dentre trabalhadores da área da saúde (BRASIL, 2020; CONSELHO FEDERAL DE ODONTOLOGIA, 2020b).

Assim, o MS atualizou a regulamentação do atendimento odontológico no Sistema Único de Saúde (SUS), em conformidade com as recomendações do CFO e CRM, e propôs a retomada gradativa dos atendimentos em serviços especializados, seguindo orientações de gestores, com base em características epidemiológicas locais frente à pandemia da COVID-19 (BRASIL, 2020; CONSELHO FEDERAL DE ODONTOLOGIA, 2020a).

O Conselho Federal de Medicina (CRM) determinou que os gestores de hospitais e outros ambientes de trabalhadores da saúde se preocupassem em tornar acessíveis à toda a equipe de saúde e usuários da unidade, os materiais necessários para proteção individual, como máscaras, luvas, aventais, óculos, bem como materiais de proteção especial para procedimentos invasivos como máscaras N95 e filtros de ar. A infraestrutura para higienização das mãos e "etiqueta respiratória" dos pacientes deveria estar acessível a todos, incluindo os consumíveis, como sabão, álcool gel, lenços e toalhas descartáveis (CONSELHO FEDERAL DE MEDICINA, 2020).

Ainda assim, reconhecendo que o risco de doença grave e da necessidade de hospitalização aumentam com a idade e as comorbidades dos acometidos pela COVID-19, recomendou-se que profissionais de saúde, incluindo médicos, com idade acima de 60 anos ou com doenças crônicas, mesmo que saudáveis, fossem afastados da linha de frente e alocados em outras funções que demandassem atuação de médicos e enfermeiros. Com isso, devido à falta de assistência para outras doenças, comum durante a pandemia de COVID-19, muitos optaram por realizar atendimentos virtuais para a manutenção e controle dos tratamentos e acompanhamentos dos pacientes (CONSELHO FEDERAL DE MEDICINA, 2020).

Durante a pandemia de COVID-19, os programas de telemedicina ou similares foram instrumentos que auxiliaram na troca de informações entre pacientes e profissionais (MACHADO et al., 2020). Alves et al. 2021 observaram um aumento significativo nos atendimentos virtuais em centros oncológicos no período de isolamento social. Além de auxiliar no controle das doenças crônicas e facilitar o diagnóstico precoce, a telemedicina contribuiu para a triagem de pacientes com possíveis sintomas de COVID-19. Uma vez que, esta abordagem permite o rastreamento de casos suspeitos à distância, e torna o atendimento presencial uma opção apenas quando é realmente necessário, evitando a propagação de vírus entre pacientes, profissionais de saúde e comunidade (MACHADO et al., 2020).

Embora programas de telemedicina não possam ser criados repentinamente, a utilização dos aplicativos de mensagens instantâneas e de mídias sociais parece ter sido uma alternativa viável no auxílio de diagnósticos ou esclarecimentos sobre possíveis lesões orais. Recentemente, houve uma melhora significativa na taxa de sobrevida de pacientes com doenças orais, e esse resultado está relacionado ao diagnóstico da doença no estágio inicial, que leva a um melhor prognóstico (MACHADO et al., 2020).

Sabe-se que a falta de assistência, ou ausência de pacientes, comum no período restritivo de isolamento social, pode levar a complicações no tratamento de doenças crônicas. Alves et al. (2021) mostraram uma queda significativa (51,5%) no atendimento de pacientes em acompanhamento de tratamento oncológico em três grandes centros durante o período de isolamento social. É importante ressaltar que o diagnóstico tardio pode levar ao prognóstico desfavorável de lesões malignas (VARELA-CENTELLES; CASTELO-BAZ; SEOANE-ROMERO, 2017). No Brasil e no mundo, a queda no número de diagnósticos de Câncer no período pandêmico também foi consistente, assim como a queda dos atendimentos de profissionais da Medicina Oral (MARTELLI et al., 2021; MACHADO et al., 2022). O tratamento do câncer também foi afetado direta e indiretamente pela pandemia de COVID-19. Em comparação com a população em geral, a taxa de mortalidade específica por COVID-19 foi maior entre os pacientes com câncer. Indiretamente, a sobrecarga do sistema de saúde causou diversas mudanças na prática diária em centros de tratamento oncológico. Protocolos mundiais foram modificados para reduzir a frequência de visitas ou o grau de imunossupressão para manter os serviços de oncologia durante a pandemia (FONSECA et al., 2021).

A cavidade oral foi destacada como um eixo de infecção relevante pelo potencial de disseminação da resposta inflamatória nos tecidos circundantes (MARIZ et al., 2020). Assim, algumas manifestações orais foram observadas em pacientes positivos para à COVID-19, como lesões caracterizadas por placas brancas e eritematosas, úlceras irregulares, pequenas bolhas, petéquias e gengivite descamativa na região da língua, lábios, gengiva e mucosa bucal. A detecção precoce da COVID-19 por meio da compreensão adequada dos sintomas e realização de testes, bem como, o tratamento adequado da doença, foram considerados imprescindíveis para melhorar a condição do paciente (AMORIM DOS SANTOS et al., 2021).

Desde o início da pandemia, os efeitos da COVID-19 em condições infecciosas e autoimunes passaram a ser investigados. Embora o sistema imunológico da infecção por SARS-CoV-2 tenha sido estudado exaustivamente, a comunidade científica não conseguiu explicar

claramente as variações das suas manifestações clínicas e a interação da COVID-19 com outras doenças (ARORA et al., 2021). Manifestações vesiculares de Herpes Zoster (HZ) foram identificadas em pacientes positivos para COVID-19, especialmente em pacientes com linfopenia. Sugeriu-se que a reativação do Vírus varicela-zoster (VVZ) ocorre como consequência de uma disfunção das células T em pacientes com COVID-19. A maioria dos casos de HZ observados durante a pandemia ocorreram dentro de 1 a 2 semanas da infecção por COVID-19 (DIEZ-DOMINGO et al., 2021).

No caso da Hanseníase, que é uma doença infecciosa, crônica e granulomatosa causada pelo *Mycobacterium leprae* que possui alta infectividade e baixa patogenicidade, as preocupações foram ainda maiores quanto a queda ocorrida no diagnóstico e tratamento da doença durante a pandemia pelo mundo, possivelmente devido à redução de apoio financeiro e recursos humanos. Assim como em outras doenças, a pandemia limitou muito o acesso dos pacientes com Hanseníase ao atendimento clínico (MAHATO; BHATTARAI; SINGH, 2020).

Em pacientes com Lúpus Eritematoso Sistêmico (LES), a resposta imune aumentada é caracterizada pela presença de autoanticorpos circulantes, linfopenia, células T aberrantes e citocinas pró-inflamatórias, juntamente com mecanismos regulatórios, levando a danos imunomediados aos tecidos. Os pacientes com LES são frequentemente tratados com imunossupressores e, portanto, são imunocomprometidos e mais suscetíveis a infecções, e consequentemente foram considerados mais vulneráveis ao SARS-CoV-2 (SPIHLMAN et al., 2020). Essa susceptibilidade pode explicar o aumento exponencial de casos de LES observado durante a pandemia de COVID-19 pelo mundo (BOZZALLA CASSIONE et al., 2020; CHUAH et al., 2022).

O SARS-CoV-2 demonstrou ainda um importante potencial neuro invasivo, tendo como manifestações neurológicas tontura, cefaleia, hipogeusia, hiposmia, lesão muscular, acidente vascular cerebral isquêmico e hemorrágico (FILATOV et al., 2020). A síndrome de Guillain-Barré (SGB), uma das complicações do sistema nervoso encontrada em pacientes com diagnóstico prévio de COVID-19, representa a causa mais comum de fraqueza aguda simétrica e flácida dos membros (LI; BAI; HASHIKAWA, 2020). Apesar dos registros de manifestações de doenças neurológicas durante a pandemia, a real associação da COVID-19 com a SGB não foi esclarecida na literatura (SEPIDEH; GORJI; MAVANDADI, 2020).

A OMS declarou recentemente, dia 05 de maio de 2023, o fim da Emergência de Saúde Pública de Importância Internacional pela tendência de queda dos registros de COVID-19. Apesar disso, a COVID-19 ainda é tida como uma importante fonte de preocupação para a população e comunidade científica, devido as frequentes variantes da doença e principalmente as consequências e sequelas relacionadas. O Brasil registrou mais de 37 milhões de casos confirmados e ultrapassou 700 mil óbitos pela COVID-19 (https://covid.saude.gov.br/). Portanto, a investigação do impacto da pandemia de COVID-19 no diagnóstico de doenças sistêmicas e na prestação dos serviços essenciais de saúde no Brasil deve ser realizada continuamente. Com isso, o objetivo deste estudo foi avaliar a produção e a assistência à saúde por estomatologistas durante a pandemia de COVID-19 e comparar com os mesmos dados do período pré-pandêmico, além de avaliar os diagnósticos de doenças sistêmicas no sistema único de saúde brasileiro (SUS) durante o período pandêmico e comparar com os dados anteriores a pandemia de COVID-19.

2 ARTIGOS CIENTÍFICOS

2.1 Artigo científico 1. *Brazilian Oral Medicine and public health system: The enormous impact of the COVID-19 Era*. Publicado no periódico *Oral Diseases* (*Open access* - ANEXO 2).

Brazilian Oral Medicine and public health system: the enormous impact of the COVID-19 Era

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Dear Editor,

Due the Coronavirus disease 2019 (COVID-19), several restrictive measures have been implemented by the government (Simões e Silva, Oliveira, & Martelli Júnior, 2019; Chaudhry et al., 2020; Nussbaumer-Streit et al., 2020). In this way, dentistry services underwent forced changes in their operation and function (Machado, Souza, Oliveira, Martelli Júnior, & Bonan, 2020; Martelli Júnior et al., 2020).

Recent studies highlighted the difficulties and damages from the current COVID-19 pandemic to dental services in general and Oral Medicine (OM) and Oral Pathology particularly. (Alves et al., 2020; Chen et al., 2020; Cunha, Antunes, Martins, Petti, & Hugo, 2020; Izzetti et al., 2020; Machado, Bonan, Martelli, Alves, & Martelli Júnior, 2020). Thus, this investigation aimed to compare Brazilian Unified Healthcare System (SUS) oriented OM clinical care in Brazil before and during the pandemic so far.

To measure OM care in the SUS, we evaluated the number of clinical consultations performed between March and July of 2015 to 2020. The data were extracted and analyzed from the public database (DATASUS) (http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sia/cnv/qauf.def). Table 1 shows the damage caused by the COVID-19 pandemic in OM clinical consultation in the five geographic regions of Brazil. The average number of clinical consultations in the pre-pandemic period compared to the current period is higher in all Regions. The difference in the number of clinical consultations ranged from 28.97% (Northeast) to 74.49% (Midwest). Brazilian general average deficit, 65.59%, representing more than 21,000 clinical consultations. The impact these indicators have on the diagnosis and treatment of oral diseases in the Brazilian population yet unknown.

The number of new cases of oral cavity cancer expected for Brazil for each year of the triennium 2020-2022 will be 11,180 cases in men and 4,010 in women. These values correspond to an estimated risk of 10.69 new cases per 100,000 men, occupying the fifth position. For women, it corresponds to 3.71 for every 100,000 women, being the thirteenth most frequent among all cancers (https://www.inca.gov.br/estimativa).

Considering that the early diagnosis of oral cancer is essential for the effective treatment of the patient, and Brazil does not have legislation that authorizes tele (oral) medicine (Machado, Souza, Oliveira, Martelli-Júnior, & Bonan, 2020, Villa, Sankar, & Shiboski, 2020), this reduction in the number of clinical consultations of OM becomes even more worrying. A recent study on oral biopsies during the COVID-19 pandemic shows an alarming decrease in

mouth biopsies performed in all Brazilian Regions in 2020, showing a decline of over 60% in the entire country (Cunha, Antunes, Martins, Petti, & Hugo, 2020).

Brazil already has approximately 144,600 deaths and more than 4.8 million confirmed cases of contamination (October 1st, 2020) (https://covid.saude.gov.br/), and it is observed that there is a quantitative deficiency of clinical care by OM that significantly compromises the scenario of oral diseases in the SUS. Thus, quick and safe actions are needed to regularize or at least minimize both the critical immediate risks as well as the possible long-term COVID-19 pandemic negative impacts on oral diseases.

Table 1. Difference between the mean of clinical consultations in Oral Medicine, performed in geographical Regions by the Brazilian public health system between March and July of 2015-2019 compared to 2020.

Regions of Brazil	March-July 2015-2019 (n)	March-July 2020 (n)	Difference n (%)
North	915.4	529	386.4 (42.21%)
Northeast	3776	2682	1094 (28.97%)
Southest	22435.2	6148	16287.2 (72.59%)
South	3891.6	1445	2446.6 (62.86%)
Midwest	1478	377	1101 (74.49%)
Total	**32496.2**	**11181**	**21315.2 (65.59%)**

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2.2 Artigo científico 2. *Resumption of Brazilian oral medicine health care during the second period of the COVID-19 pandemic.* Aceito para publicação no periódico *Brazilian Journal of Oral Sciences* (ANEXO 3).

Resumption of Brazilian oral medicine health care during the second period of the COVID-19 pandemic

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Summary

This present study aims to compare the data from the Brazilian Unified Health System on the number of clinical consultations of Oral Medicine from the first 6 months (March-August 2020) of the COVID-19 pandemic in Brazil with the last 6 months (September-February 2020/2021), to update the data, verify the measures' effectiveness to return clinical activities in the following months and perform a literature review of recent articles that report the impact of the COVID-19 pandemic on Oral Medicine. There was an increase in the number of Oral Medicine clinical consultations in the second half of the pandemic throughout Brazil (+64.2%), representing over 9,235 appointments in this period. Therefore, measures for the return of health assistance and the practice of Telemedicine proved to be effective after the second period of the pandemic. Even so, strengthening security measures against the coronavirus is essential to ward off a new wave since the Omicron variant emerged in the country and, consequently, possible new lockdowns that might affect healthcare in Brazil.

Keywords: COVID-19, Dental Care, Oral medicine, Pandemics

Introduction

The COVID-19 pandemic began in early 2020, when the World Health Organization (WHO) designated the disease caused by the SARS-CoV-2 virus as a public health emergency of international concern for its rapid spread, resenting a major challenge to health authorities around the world.[1,2] Since then, the implementation of restrictive measures sought to control disease transmission, including social isolation rules, suspension of face-to-face activities, and the planning and adoption of health measures, such as biosafety awareness campaigns, sanitary barriers, and suspension of specialized health services. [3,4]

Due to this scenario, in March 2020, the Federal Council of Dentistry (CFO) requested the Brazilian Ministry of Health to suspend elective dental care in the public health network and the reinforcement of biosafety practices for private services. Among health professionals on the front line against COVID-19, a low rate of dental professionals becoming contaminated, according to the report published by the Ministry of Health in July 2020. In addition, a survey carried out by the CFO showed that 82% of professionals maintained dental care in this period.[5]

Consequently, the Ministry of Health updated the regulation of dental care in the Unified Health System (SUS), by the recommendations of the CFO, and proposed the gradual resumption of care in specialized services, following guidelines from managers, based on epidemiological characteristics against the COVID-19 pandemic.[5]

In our first study, the data collected from the public database (DATASUS, 2021) showed the damage caused by Brazil's COVID-19 pandemic in Oral Medicine (OM) (Stomatology) practice.[6] The mean number of clinical consultations in the pre-pandemic period compared to the first half of the pandemic (March-August 2020) dropped in all Brazilian regions, and the mean general deficit was 65.59%, representing more than 21,000 clinical consultations.[6]

In this way, this study aimed to perform a literature review of recent papers that report the impact of the COVID-19 pandemic on OM, update the data of the Brazilian OM to the COVID-19 pandemic, and verify the effectiveness of restrictive measures to return to clinical activities, by comparing the data from the Brazilian SUS[7] on the number of clinical consultations of OM from the first 6 months (March-August 2020) of the COVID-19 pandemic in Brazil with the last 6 months (September-February 2020/2021).

Materials and Methods

To measure OM care in the Brazilian SUS, we evaluated the number of clinical consultations performed between March and August 2020 and between September to February

2021. The data from Table 1 were extracted and analyzed from the public database (DATASUS) (http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sia/cnv/qauf.def).

Moreover, a computerized search was performed in the "PubMed" database using the descriptors "ORAL MEDICINE," OR "STOMATOLOGY", AND "COVID-19," OR "SARS-COV 2". Two examiners reviewed the initial list and applied inclusion criteria to determine the final sample. The inclusion criteria for selecting scientific articles covered studies that compared OM data from the pandemic period with previous periods, published from March 2020, in English, with full text available. The exclusion criteria involved studies that did not assess the pandemic period.

The initial search using the descriptors found 60 papers. After reading the abstracts, 20 studies remained for analysis of inclusion criteria. Then, after reading the full text of these studies, only 3 papers[5,8,9] fit the criteria for discussion in Table 2.

Results

Table 1 shows the comparison of the second half of the pandemic period (September 2020-February 2021) with the first half of the COVID-19 pandemic (March-August 2020). The number of OM clinical consultations in the second half of the pandemic increased throughout Brazil (+64.2%), representing over 9,235 appointments in this period. This had repercussions in almost all Brazilian regions, with a significant increase in the Midwest (+112.3%) and Northeast regions (+85.8%), except in the North region where the OM consultations slightly dropped (-21.6%) in this period.

After the second half of the pandemic, even with the increase in COVID-19 cases, the second wave between January 2021 and May 2021, and the arrival of the new variant Omicron in January 2022, the number of consultations in OM remained stable until the most recent data provided by DATASUS (Figure 1).

Table 2 shows the results of the literature review on the impact of the COVID-19 pandemic on oral medicine in the world.

Discussion

As in the first article published by this group, the patient volume reduced considerably in the first period of the COVID-19 pandemic in other countries, such as China and the USA.[8,10] To our knowledge, the present study is the first to assess the data in the second period of the pandemic.

The return of Oral Medicine health assistance is extremely important for critical situations, such as the early diagnosis of oral cancer, an essential condition to provide a favorable prognosis for the patient.[6] These positive numbers become even more relevant since the risk estimated by the National Cancer Institute (INCA) of new cases of oral cancer is the fifth highest among men and thirteenth among women of all cancers (https://www.inca.gov.br/estimativa). The increase in OM performed consultations can be explained by the several implementations that have begun after the lockdown in the 1st half of 2020, mainly due to the return of health assistance, which followed strict hygiene and safety protocols against the dissemination of COVID-19. In the second half of 2020, the Brazilian SUS published a manual for dentistry and released many resources for investment in the adequacy of public dental offices.[11-13] Therefore, the resumption of dental appointments had a great encouragement, especially for emergencies, patients at risk, and mouth injuries, even before starting vaccination in the country.[11-13] The vaccination in Brazil started on 01/17/2021, and the 2nd dose of vaccinations began around April 2021.[14] It is observed that these measures increased OM consultations, and nowadays, the numbers were normalized and stabilized due to the vaccination, which decreased the number of cases and deaths caused by COVID-19.

This increase in the number of OM consultations in the second half of the pandemic can also be elucidated by the importance of the oral cavity for this period. The buccal cavity stands out as a relevant axis of infection due to its potential for dissemination of the inflammatory response in the surrounding tissues.[15] Thus, some oral manifestations affected patients positive for COVID-19, such as lesions characterized by white and erythematous plaques, irregular ulcers, small blisters, petechiae, and desquamative gingivitis in the region of the tongue, lips, gums, and buccal mucosa. Thus, early detection of COVID-19, through proper understanding of symptoms and testing, as well as adequate treatment of the disease, are recommended to improve the patient's condition.[16]

Legislation that authorizes the use of Telemedicine came into force based on the health services restrictions, impacting positively assistance for patients who seek care from OM, with a total of 322 telemedicine consultations since the beginning of the pandemic.[17,18] This instrument helped in the exchange of information between patients and professionals.[18] Virtual consultations increased significantly in cancer centers during the period of social isolation.[19] In addition to assisting in the control of chronic diseases and facilitating early diagnosis, telemedicine has contributed to the screening of patients with possible symptoms of COVID-19. Since this approach allows the tracking of suspected cases at a distance and makes face-to-

face care an option only when it is necessary, preventing, this way, the spread of viruses among patients, health professionals, and the community.[18]

The negative numbers of OM appointments attributed to the Northern region probably occurred due to a delay in the data delivery from the main states in this region or possibly due to the difficulty in accessing the Brazilian Unified Health System care during the COVID-19 pandemic period in this region. The use of telemedicine can minimize the challenges in accessing health care. Delay in data delivery is the main limitation in studies that depend on data from a public system. However, when compared to the previous study by the same authors,[6] the data obtained are consistent and with a good degree of accuracy.

Conclusion

Initially, the first pandemic period dramatically reduced OM clinical consultations in Brazil. However, measures for the return of health assistance and the practice of Telemedicine proved to be effective after the second period of the pandemic. Even so, strengthening security measures against the coronavirus seems to be essential to ward off a new wave since the Omicron variant emerged in the country and, consequently, possible new lockdowns that might affect healthcare in Brazil.

Table Legend

Table 1. Difference between the number of Oral medicine consultations, performed in geographical Regions by the Brazilian public health system between March and August of 2020 compared to September-February of 2020/21.

Source: Ministry of Health Brazil – DATASUS

Table 2. Summary of literature about the impact of the COVID-19 Pandemic on Oral Medicine

Figure Legend

Figure 1. Monthly distribution of clinical consultations in Oral Medicine and COVID-19 cases in Brazil per million population (Jan 2020-Apr 2022).

Source: World Health Organization (WHO) and Ministry of Health Brazil – DATASUS.

Table 1. Difference between the number of Oral medicine consultations, performed in geographical Regions by the Brazilian public health system between March and August of 2020 compared to September-February of 2020/21.

Region of Brazil	Mar-Aug 2020	Sep-Feb 2020/21	Difference	%	p*
North	663	520	-143	-21.6	< 0.001
Northeast	3,435	6,381	+2,946	+85.8	< 0.001
Southeast	8,077	13,048	+4,971	+61.5	< 0.001
South	1,766	2,734	+968	+54.8	< 0.001
Midwest	439	932	+493	+112.3	< 0.001
Total	**14,380**	**23,615**	**+9,235**	**+64.2**	**< 0.001**

*** p-value** - obtained by chi-square Chi2-statistic

Table 2. Summary of literature about the impact of the COVID-19 Pandemic on Oral Medicine

Author / Reference	Country	Data analyzed	Findings	Comment
Dong et al 2021	China	- This paper aimed to reproduce the impacts of the COVID-19 epidemic on the clinical services and academic activities in the department of stomatology of a tertiary hospital in Wuhan, China.	- Was noted a significant decrease in the number of patients seeking outpatient services for the year 2020, which decreased by two-thirds from 2018 to 2020. Emergency cases also decreased significantly in 2020. - The monthly number of teaching hours decreased from 3.8 in 2018 and 4.7 in 2019 to 1.7 during the pandemic period. The number of interns has dropped by more than 77% in 2020.	- Stomatology clinic impacts of the COVID-19 pandemic were significant, with an important decrease in clinical services and education. - It's inescapable to find solutions to keep as many dental professionals as needed remaining on the frontline of oral health care.
Marques et al 2020 (Previous study)	Brazil	- This investigation seeks to compare Brazilian Unified Healthcare System (SUS) Oral Medicine clinical care, before and while the pandemic. - Oral Medicine care in the SUS was measured by assessing the number of clinical consultations performed between March and July 2015 to 2020. - The data was extracted from the public database (DATASUS).	- Clinical consultations number in the pre-pandemic period were higher in all Brazilian Regions when compared to the current period. - The deficit of the general Brazilian average is 65.59%, representing more than 21,000 clinical Oral Medicine consultations.	- Regarding oral cancer, early diagnosis is essential for effective treatment with a good prognosis. As a result, this reduction in the number of Oral Medicine clinical consultations becomes even more worrisome, and the authors suggested quick and safe actions to regularize or at least minimize both critical and immediate risks.
Sandhu et al 2022	USA	- This study aimed to assess Oral Medicine students' perception of the effect of the COVID-19 pandemic on the training experience, education, and psychological well-being of oral medicine residents.	- Most residents reported an important reduction in patient volume at its worst during the pandemic. - Regarding educational activities, the majority of students reported a complete switch of didactic training, academic examinations, and off-site resident rotations to a virtual platform.	- Even with restrictions related to the COVID-19 pandemic, Oral Medicine residency programs continued their clinical activities, didactic training, and research productivity through virtual means.

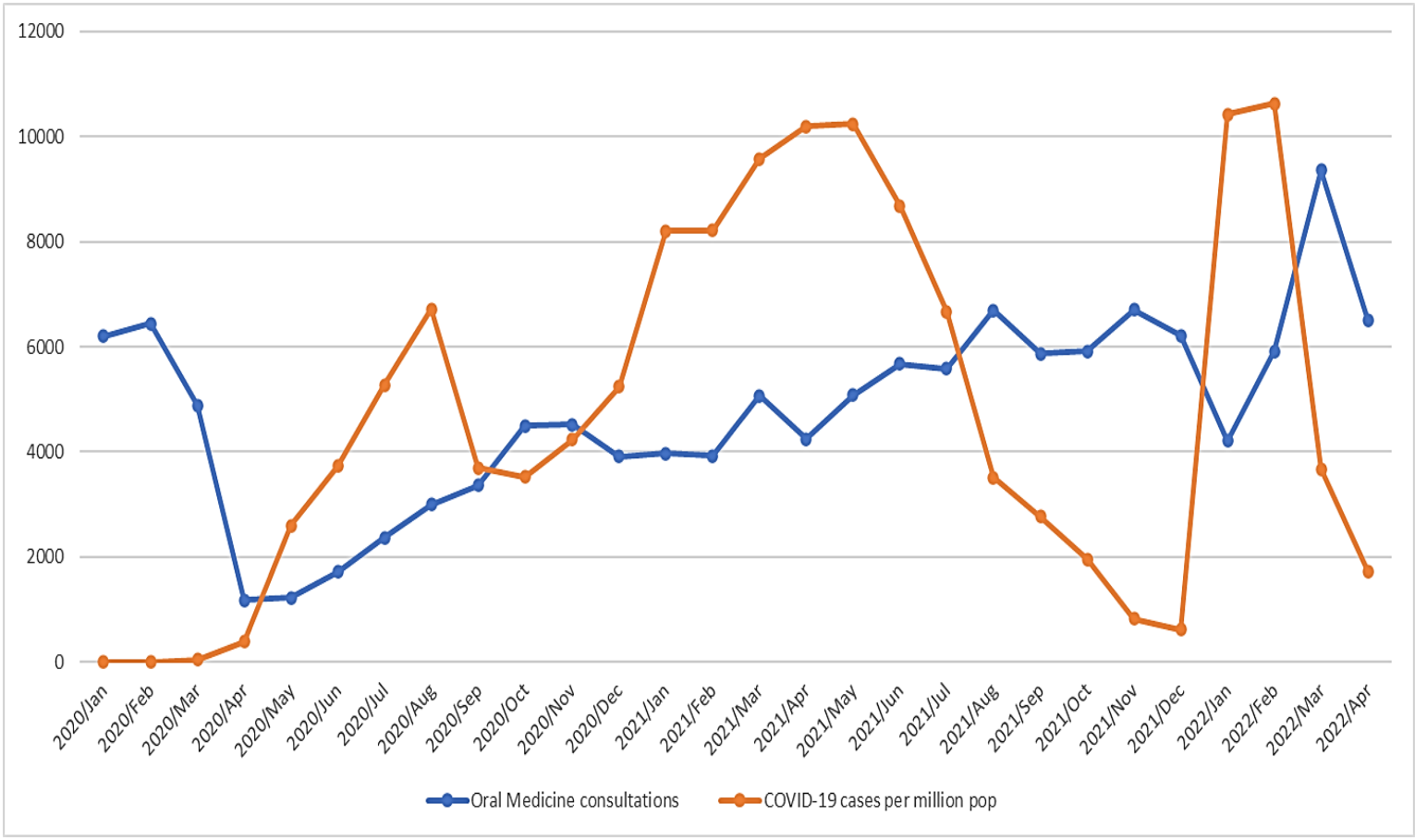

Figure 1. Monthly distribution of clinical consultations in Oral Medicine and COVID-19 cases in Brazil per million population (Jan 2020-Apr 2022).

Source: World Health Organization (WHO) and Ministry of Health Brazil – DATASUS

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2.3 Artigo científico 3. *Cancer diagnosis in Brazil in the COVID-19 era*. Publicado no periódico *Seminars in Oncology* (*Open access* - ANEXO 4).

Cancer diagnosis in Brazil in the COVID-19 Era

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Conflicts of Interest: None to declare

Abstract

The comprehensive care and treatment for cancer patients in Brazil, regulated by the National Cancer Prevention and Control Policy, is provided by Brazilian Unified Healthcare System (SUS) in certified health institution. Due the COVID-19 pandemic, several restrictive measures have been implemented by the State federations governments, and cancer diagnosis reference centers were also impacted by these measures. Thus, this study aimed to compare SUS-oriented cancer diagnosis in Brazil before and during the pandemic so far. The average number of cancer diagnoses has dropped considerably in all Brazilian Regions since the pandemic period started. The number of new cancer cases has plunged in all regions, ranged from -24.3% in the North to -42.7% in Northeast region. The overall Brazilian average deficit reached 35.5%, corresponding to about 15,000 undiagnosed cases of cancer monthly. The pandemic period has dramatically reduced the diagnosis of new cases of cancer in Brazil, since consultations in public health services were compromised by restrictive measures. Therefore, effective measures must be urgently put in action in order to minimize the damage, and consequently, the negative health impacts caused by the COVID-19 pandemic in the care of cancer patients.

Introduction

The Coronavirus disease (COVID-19), caused by the virus SARS-CoV-2, was detected in Brazil on February 26, approximately two months after the first case have been reported in China. The first death by COVID-19 in Brazil occurred on March 17, when this disease has already turned into a pandemic [1]. COVID-19 pandemic has been severely impacting health systems worldwide [2], affecting the care of various chronic diseases, including cancer diagnosis and treatment [3,4]. Recent studies have shown the effects of COVID-19 on health professionals' routine responsible for diagnosing and treating patients with cancer [5,6,7,8]. A set of security measures has been proposed to relieve this problem, even so it is an alarming situation [9,10,11].

Brazilian Unified Healthcare System

Brazilian Unified Healthcare System (SUS) is the world largest universal healthcare system, funded by federal, state and municipal resources and serves over 209,000 million inhabitants (https://censo2010.ibge.gov.br) (access in October 2020). Qualifying the service network and guaranteeing access to users is a daily challenge faced by SUS managers, whom, in 2011, developed the largest institutional evaluation program of its history, the Access and Quality Improvement Program (PMAQ) (http://189.28.128.100/dab/docs/portaldab/documentos/instrumento_ae_sb.pdf) (access in October 2020). SUS decentralization provided more focused evaluation of regional health problems and identified involved health determinants, thus allowing adequate management aimed at population needs.

These characteristics provides municipalities with more power and concomitant responsibility, which makes planning essential and situational, as opposed to the centralized and normative planning of public management until 1990. However, due to daily work required demands, this practice is sometimes neglected and actions are improvised to solve emerging problems [11]. This management weakness limits our critical cases responding capacity, which is very heterogeneous across the 26 States and Federal District [1,13]. Regarding oncology treatment, the National Cancer Prevention and Control Policy regulates comprehensive care for the patient in a regionalized and decentralized way and set that cancer treatments by SUS are performed in certified health institutions as the High Complexity Assistance Unit in Oncology (UNACON) or the High Complexity Assistance Center in Oncology (CACON (https://www.inca.gov.br/onde-tratar-pelo-sus) (access in October 2020).

Effects of COVID-19 on public health assistance

Due the COVID-19, several restrictive measures have been implemented by the various States of federation governments, such as physical distancing, leisure areas and non-essential commerce closure in order to reduce contamination rate, and cancer diagnosis reference centers were also impacted by these measures [1,3,14,15]. Interestingly, Alves et al. (2020) [3] revealed a considerable reduction in follow-up and treatment consultations of oral cancer patients at three reference cancer centers located respectively in Brazil, Canada, and the United States, comparing to the first six weeks of restrictive measures with the six weeks prior to the pandemic period. Thus, the aim of this study was to compare SUS-oriented cancer diagnosis in Brazil before and during the pandemic so far.

Summary of literature

A computerized search was performed in the *"PubMed"* database. The research descriptors used were "CANCER", "COVID-19" AND "DIAGNOSIS". Two examiners reviewed the initial list of articles and applied inclusion criteria to determine the final sample of articles.

The inclusion criteria for selecting articles were studies that compared general cancer diagnosis data from the pandemic period with previous periods, published from March 2020, in English, with full text available. Studies that did not assess the pandemic period or restricted to a specific single cancer type were excluded.

Initially, 163 articles were found using the descriptors. After reading the abstracts, 20 studies remained for analysis of inclusion criteria. Then, after reading the full text of these studies, only five articles [16-20] were selected for discussion in Table 1.

Impact of COVID-19 on cancer diagnosis in Brazil

In order to assess the impact of the COVID-19 pandemic in Brazil, we compared the monthly average of new cancer cases diagnosed in 2019 to the monthly average of January-August of 2020, from the five geographic Regions of Brazil (North, Northeast, Southeast, South and Midwest), representing the Brazilian States (26 States and the Federal District), through data extracted and analyzed from the public database of SUS (DATASUS)(http://tabnet.datasus.gov.br/cgi/dhdat.exe?PAINEL_ONCO/PAINEL_ONCOLOGIABR.def). In Brazil, cancer only became mandatory notification in 2018, with effect from 2019. Thus, searches carried out before 2019 are not representative (https://legis.senado.leg.br/norma/27410223) (access in October 2020).

Table 2 shows the negative impact from the COVID-19 pandemic in the diagnosis of cancer in Brazil. The average number of cancer diagnosis has dropped considerably in all Brazilian Regions since the pandemic period started. The number of new cancer cases has plunged in all regions, ranged from -24.3% in the North to -42.7% in Northeast region. The overall Brazilian average deficit reached 35.5%, corresponding to about 15,000 undiagnosed cases of cancer monthly. The long-term impact of these indicators on the diagnosis and treatment of cancer patients in the Brazilian population remains uncertain.

Just as an example, when analyzing the situation of cancer in the country, the numbers are worrying, since the decrease of consultations. The number of new cases of cancer expected for Brazil for each year of the triennium 2020-2022 would be 387,980 cases in men and 297,980 in women. These values correspond to an estimated risk of 371.11 new cases per 100,000 men, and for women, it corresponds to 277.11 for every 100,000 (https://www.inca.gov.br/estimativa).

Brazil has seen approximately 6.2 million cases of COVID-19 and over 172,500 deaths currently (November 28th, 2020) (https://covid.saude.gov.br/), and the end of the pandemic cannot yet be predicted, which leads us to believe that more patients undergoing cancer treatment or undiagnosed cases will still be affected by this critical period. One of the best alternatives cares for patients with cancer during the COVID-19 pandemic is the telemedicine practice, which was recently regularized in Brazil. This approach allows communication at a distance between health professionals, assisting in diagnosis and case discussions [21].

Conclusion

The pandemic period has dramatically reduced the diagnosis of new cases of cancer in Brazil, possibly by the restrictive measures including limitation of consultations in public health services. Therefore, effective measures must be urgently put in action in order to minimize the damage, and consequently, the negative health impacts caused by the COVID-19 pandemic in the care of cancer patients.

Table legend

Table 1. Summary of literature about general cancer diagnosis in the COVID-19 pandemic compared to previous periods.

Table 2. Difference between the monthly average of cancer diagnosis (excluding oral cancer), performed in all geographical Regions from Brazil of 2019 compared to January-August of 2020.

Table 1. Summary of literature about general cancer diagnosis in the COVID-19 pandemic compared to previous periods

Author / Reference	Country	Data analyzed	Findings	Comment
De Vincentiis et al 2020	Italy	• This study analyzed the number of cytopathological and histopathological diagnosis of primary and metastatic malignancies, made between the 11th and the 20th weeks of the 2020, corresponding to the most severe lockdown period, in comparison to average number of diagnosis in the same period of 2018 and 2019	• The diagnosis of new metastatic malignancy and pancreatic cancer increased, • Different types of cancer exhibited varied reduction in the number of diagnosis. Colon-rectum (62%), bladder (66%) and prostate (75%) cancer underwent the greatest reduction	• The authors were concerned about the decrease in the number of diagnosis of colon-rectum cancer (CRC) (62%), due to the higher risk of death in this type of lesion, independent of tumor stages or interval between the diagnosis to treatment interval. • Corrective actions are recommended for CRC, such as: triage of patients by family physicians according to standard guidelines and reintroduction of mass screening through fecal occult blood testing,
Ferrara et al 2020	Italy	• Compared the number of pathologic diagnosis of malignant lesions, at seven anatomic pathology units serving secondary care hospitals, during the most severe lockdown period (11th to 20th week of the year) in northern-central Italy with the same period of 2018 and 2019	• The average number recorded of cancer diagnosis fell 44.9% in 2020, compared to the previous periods • Skin cancers represented the main undiagnosed lesions (56.7%), followed by colorectal (46.6%), prostate (45%), and bladder (43.6%) cancer. High-grade prostate tumors were not strongly affected by the lockdown period, with 21.7% drop in diagnosis	• The most severe lockdown period in Italy affected the diagnosis of malignant lesions, mostly of skin, colorectal and invasive bladder cancer • The authors pointed out the importance of the mass screening programs return, as well, the application of corrective actions, mainly for the diagnosis of colorectal cancer and invasive bladder cancer
Kaufman et al 2020	USA	• Weekly changes in the number of patients with newly identified cancer before and during the COVID-19 pandemic • Study included 278,778 patients, 258,598 (92.8%) from the baseline period and 20,180 (7.2%) from the COVID-19 period • Six cancers were investigated: breast colorectal, lung, pancreatic, gastric, and esophageal cancer.	• During the pandemic, weekly number fell 46.4% for the 6 cancers combined, with significant declines in all cancer types, ranging from 24.7% for pancreatic cancer (from 271 to 204; P=.01) to 51.8% for breast cancer (from 2208 to 1064; P<.001)	• The interruption of medical services and the reduction in assiduity of patients during the social isolation period can compromise the diagnosis of cancer • To minimize this situation, the authors suggested urgent planning, including the use of digital technology, such as the practice of telehealth and virtual interactions between healthcare professionals and patients

Table 1. (continued)

Maluchnik et al 2020	Poland	• Patients with suspected neoplastic diseases receive the so-called DiLO card in Poland, since 2015 • This investigation included data referring to all oncological patients in Poland, registered by The National Health Fund from the beginning of the DiLO program to 25 May 2020	• During the pandemic period analyzed, the distribution of DiLO cards decreased by 33% compared to the same period of the previous year, mainly in primary care. Due to the difficulty of accessing cancer diagnostic tests during the COVID-19 pandemic, the number of preliminary diagnosis, extended diagnostic procedures, decreased, respectively, by 31% and 19% in 2020 compared to 2019.	• The authors suggest disclosing information to make patients aware that the risk of delaying diagnosis and treatment of cancer is most damaging than a possible COVID infection • The restrictive measures of COVID-19 pandemic affected oncological treatments in Poland. This investigation highlights the role of telemedicine and virtual consultations to mitigate the limitations of this period
Zadnik et al 2020	Slovenia	• Monthly changes in the number of cancer notifications before and during the COVID-19 pandemic • Analyzed data were extracted from the Slovenian Cancer Registry, the e-referral system of Slovenia managed by the National Institute of Public Health (NIPH), and the Institute of Oncology Ljubljana	• Compared to November 2019 – February 2020 average, the decrease in April was respectively about 43% and 29% for histopathological and clinical cancer notifications • In the same period, the average decrease in first outpatient visits was 19%, 43% and 20% at the radiotherapy, surgery and medical oncology sectors.	• The authors conclude that significant drops in oncological referrals, outpatient visits, imaging exams, as well as, in the cancer notifications, may point to a delay in diagnosis and treatment of cancer during the COVID-19 period in Slovenia
Marques et al 2020 (Current study)	Brazil	• Monthly average of new cancer cases diagnosed in 2019 compared to the monthly average of January – August of 2020 • Data extracted and analyzed from the public database of Brazilian Public Health System (DATASUS)	• This study included the average of 69,404 cancer diagnosis monthly, 42,186 (60.78%) of which registered in 2019, and 27,218 (39.21%) from the COVID-19 period • The number of new cancer cases has plunged in all Brazilian regions, this drop ranged from 24.3% and 42.7% in the North to Northeast region, respectively. The overall Brazilian average deficit reached 35.5%, corresponding to about 15,000 undiagnosed cases of cancer monthly	• The pandemic period has considerably harmed the diagnosis of new cases of cancer in Brazil, in consequence of restrictive measures in public health services, or even for patient insecurities • Effective measures must be implemented to minimize the negative impacts, caused by the COVID-19 pandemic, in the care of cancer patients

Table 2. Difference between the monthly average of cancer diagnosis (excluding oral cancer), performed in all geographical Regions from Brazil of 2019 compared to January-August of 2020.

Regions of Brazil	2019 (n)	2020 (n)	Difference (n) (%)
North	1454	1101	-353 (24.3)
Northeast	10113	5798	-4315 (42.7)
Southwest	17688	11560	-6128 (34.6)
South	10276	7102	-3174 (30.9)
Midwest	2654	1655	-999 (37.6)
Total	**42,186**	**27,218**	**-14,968 (35.5)**

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2.4 Artigo científico 4 *Increased number of Herpes Zoster cases in Brazil related to the COVID-19 pandemic*. Publicado no periódico *International Journal of Infectious Diseases* (*Open access* - ANEXO 5).

Increased number of Herpes Zoster cases in Brazil related to the COVID-19 pandemic

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Article type: Short Communication

Running title: Herpes Zoster and COVID-19

Keywords: COVID-19; Herpes Zoster; Pandemics;

Abstract

Coronavirus 2019 (COVID-19), caused by the pathogen SARS-CoV-2, was declared a pandemic in March 2020. Recently, studies have discussed reports of patients infected with COVID-19 associated with vesicular manifestations of Herpes Zoster. The objective of this study was to compare the data from the Unified Health System (SUS), on the number of diagnoses of Herpes Zoster from March to September 2017 to 2019, with the same period of 2020, in the five Brazilian regions (North, Northeast, Southeast, South and Midwest). The analyzed data were extracted from the public database (DATASUS) of the Ministry of Health of Brazil. The data showed an increase in the number of Herpes Zoster diagnoses over the years, and the negative impact from the COVID-19 disease, revealing an increase corresponding to an average of over extra 10.7 cases per million of inhabitants during the COVID-19 pandemic in all Brazilian Regions. Therefore, although the association between HZ and COVID-19 is not well stablished, we observed in this study an increase in HZ cases during the COVID -19 pandemic, which suggests a correlation between these diseases.

Coronavirus 2019 (COVID-19), caused by the pathogen SARS-CoV-2, was declared a pandemic by the World Health Organization (WHO) in March 2020 (Recalcati, 2020). Studies have discussed reports of patients infected with COVID-19 associated with vesicular manifestations of Herpes Zoster (HZ) (Fernandez-Nieto et al., 2020; Llamas-Velasco et al., 2020; Marzano et al., 2020; Ortega-Quijano et al., 2020; Recalcati, 2020). Recalcati (2020) reported for the first time the involvement of skin manifestations with the COVID-19 infection.

Varicella and Herpes zoster are diseases caused by the varicella-zoster virus (VZV) (Elsaie and Nada, 2020), which in its initial phase causes chickenpox ("Chickenpox"). This virus remains latent within the dorsal root of the trigeminal ganglion, and after its reactivation, it manifests itself as HZ (Elsaie and Nada, 2020). The objective of this study was to compare the data from the Unified Health System (SUS) on the number of diagnoses of Herpes Zoster from March to September 2017 to 2019, with the same period of 2020, in the five Brazilian regions (North, Northeast, Southeast, South and Midwest).

The analyzed data were extracted from the public database (DATASUS) (http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sia/cnv/qauf.def) of the Ministry of Health of Brazil. Table 1 shows an increase in the number of HZ diagnoses over the years, and Table 2 shows the negative impact from the COVID-19 disease, revealing an increase in the number of HZ diagnoses in all Brazilian Regions. A descriptive analysis showed that the percentage of new HZ cases per million of inhabitants has increased in all Brazilian regions, ranged from +23.6% in the Northwest to +77.2% in Midwest Region. The overall Brazilian average increase reached +35.4%, corresponding to an average of over extra 10.7 cases per million of inhabitants during the COVID-19 pandemic.

The association between HZ and COVID-19 is not well-known so far, but an increase in HZ infections during the COVID-19 outbreak has been observed (Llamas-Velasco et al., 2020). The COVID-19 infection can cause changes in leukocyte levels, resulting in a decrease in cell count, mainly of CD4 + T cells, CD8 + T cells, B cells, and natural killer cells (Tartari et al., 2020). The interference of SARS-COV-2 in the dysregulation of the immune system associated with physical and mental stress may be one factor involved in the reactivation of VZV (Pona et al., 2020). In the presence of vesicular lesions, we emphasize the importance of HZ diagnoses through Tzanck smear, PCR test from vesicular fluid or skin biopsy to exclude any infection by other viruses (Llamas-Velasco et al., 2020).

Regarding COVID-19 in Brazil, the updated data on 01/02/2021 from the Brazilian Ministry of Health, Coronavirus//BRAZIL (https://covid.saude.gov.br/COVID-19) (Coronavírus//BRASIL, n.d.) reported a total of 9.204.731 confirmed cases; 8.027.042

recovered cases; 224.504 confirmed deaths; incidence/100 thousand inhab.: 4380,1; mortality/100 thousand inhab.: 106,8. Out of the limitations of this study, we can mention cases that are not notified to Brazilian public health system, suggesting that the real incidence could be higher.

Therefore, although the association between HZ and COVID-19 is not well stablished, we observed in this study an increase in HZ cases during the COVID -19 pandemic, which suggests a correlation between these diseases. Thus, controlled clinical studies are necessary to define whether this relationship exists.

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Ethical approval: None.

Table legend

Table 1. Number of Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2017-2020.

Table 2. Difference between the average per million of inhabitants with Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2017-2019 compared to the same period in 2020.

Table 1. Number of Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2017-2020.

Regions of Brazil	State	Mar-Aug 2017 (n)	Mar-Aug 2018 (n)	Mar-Aug 2019 (n)	Mar-Aug 2020 (n)
North	Acre Amapá Amazonas Pará Rondônia Roraima Tocantins	474	583	630	708
Northeast	Alagoas Bahia Ceará Maranhão Paraíba Pernambuco Piauí Rio Grande do Norte Sergipe	2086	2272	2218	2709
Southeast	Espírito Santo Minas Gerais Rio de Janeiro São Paulo	1676	2053	2446	3003
South	Paraná Rio Grande do Sul Santa Catarina	1161	1185	1078	1447
Midwest	Distrito Federal Goiás Mato Grosso Mato Grosso do Sul	294	463	649	828
Total		**5691**	**6556**	**7021**	**8695**

Table 2. Difference between the average per million of inhabitants with Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2017-2019 compared to the same period in 2020.

Regions of Brazil	Mar-Aug 2017-2019 (n/per million)	Mar-Aug 2020 (n/per million)	Difference (%/per million)*
North	2.65	3.33	+25.7%
Northeast	10.32	12.75	+23.6%
Southwest	9.69	14.13	+45.8%
South	5.38	6.81	+26.6%
Midwest	2.2	3.9	+77.2%
Total	**30.2**	**40.9**	**+35.4%**

*Increase in the number of Herpes Zoster diagnoses in 2020.

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2.5 Artigo científico 5 Continuous increase of herpes zoster cases in Brazil during the COVID-19 pandemic. Publicado no periódico *Oral Surgery, Oral Medicine, Oral Pathology Oral Radiology* (*Open access* - ANEXO 6).

Continuous increase of herpes zoster cases in Brazil during the COVID-19 pandemic

Running head: Herpes Zoster and COVID-19

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Dear Editor,

With the continuation of the Coronavirus 2019 (COVID-19) pandemic throughout the world, clinical and epidemiological evidence of the occurrence and increase in the number of other diseases, such as herpes zoster (HZ), continue to be discussed, but the real association between HZ and COVID-19 is not well stablished.

An important narrative review identified 27 cases of HZ following 1–2 weeks of COVID-19 in non-vaccinated patients. Most patients showed a typical manifestation of HZ, clinically characterized by painful unilateral rash, compromising the patients' quality of life. Other cases, including patients with lymphopenia, exhibited atypical presentations of HZ, with necrotic tissue injuries and severe neurological involvement. The authors suggest that T cell dysfunction, such as lymphopenia and lymphocyte exhaustion, reactivates the varicella zoster virus (VZV), which causes the HZ disease[1].

Conversely, recent studies reported cases of VZV reactivation in patients who were vaccinated with mRNA or inactivated COVID-19 vaccines[2-5]. The COVID-19 vaccines most common adverse reactions are pain, local redness and swelling, fatigue, headache, fever, chills, nauseas and vomiting[3,5,6], which does not include the main clinical findings of VZV reactivation, that were painful multiple grouped vesicles on an erythematous base and pruritic lesions, which are manifested in patients from 4-14 days after vaccination. These clinical manifestations of HZ may ensue spontaneously, following activation by a trigger, as fever and immunosuppression[2-4].

In order to ascertain this issue further, this study aims to compare the data from the Brazilian Unified Health System (SUS) on the number of diagnoses of HZ from the pre-pandemic period with the pandemic period, as well as compare the first 6 months of the COVID-19 pandemic in Brazil with the last 6 months, so as to update the data and verify if HZ disease control measures were effective in the following months.

The analyzed data were extracted from the public database (DATASUS) (http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sia/cnv/qauf.def) of the Ministry of Health of Brazil. Table 1 presents the previous study by the same research group (Maia et al., 2021)[7] and shows an increase in the number of HZ diagnoses in all Brazilian regions in the months March-August from 2020, compared to the mean number of same months in 2017-2019. The growth increase ranged from +24% in the Northwest to +77% in Midwest Region. The overall Brazilian average increase reached +35%, corresponding to an average of over 2,274 cases in excess.

Table 2 shows the comparison of the second half of the pandemic period (September 2020-February 2021) initially with the first half of the COVID-19 pandemic (March-August 2020) and after with the same months of the pre-pandemic. There was a trend towards an increase in the number of HZ cases in the second half of the pandemic throughout Brazil (+11%), with attention to the Northeast region, the least affected in the first study and now the one with the biggest increase (+15%) during the pandemic. When comparing the following period of the pandemic (September 2020-February 2021) with the same months in the pre-pandemic, the increase in the number of HZ cases was similar to the previous study, keeping the Midwest region as the most impacted (+82%) and an increase of 3,350 cases throughout Brazil (+53%).

Table 3 shows the comparison of the incidence rate adjusted per million population for the five geographic Regions of Brazil and throughout the whole country. There was a consistent and significant increase in the incidence rate all over Brazil, between first and second pandemic periods and between the pre pandemic and the second pandemic periods. Limitations of this article include lack of information regarding the criteria for confirmation of HZ diagnoses in the public database from the SUS, and the unavailability of larger clinical COVID-19 vs HZ studies.

The relation between the manifestation of HZ disease and COVID-19 remains to be established. Only case reports and case series have been published showing this coexistence until now, and this evidence is not sufficient to assert this association. However, we observed in this study a continued increase in HZ cases during the COVID-19 pandemic, with a tendency towards an increase in subsequent months, which may suggest a correlation among these diseases, as demonstrated in the previous study[7]. Furthermore, this new data suggests that measures to control the increase in HZ cases in the first period of the pandemic were not effective, including the assessment of access to medicines, healthcare-seeking behavior, telemedicine consultations, aware of practitioners about possible increased risk of HZ during the pandemic period and the application of timely preventive and therapeutic measures against HZ. Thus, it is necessary to have larger clinical studies with different populations to better understand the relationship between these two conditions and find measures to raise the control of this disease.

Table legend

Table 1. Difference between the average of Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2017-2019 compared to the same period in 2020. (Previous study - Maia et al., 2021)

Table 2. Difference between the average of Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2020 (previous study) compared to September to February – 2020/21 and from of the pre-pandemic with the pandemic period.

Table 3. Incident cases of herpes zoster per million population in Brazilian macroregions according to the periods 2017-2019 vs. 2020.

Table 1. Difference between the average of Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2017-2019 compared to the same period in 2020. (Previous study - Maia et al., 2021)

Regions of Brazil	**Mar-Aug 2017-2019 (n)**	**Mar-Aug 2020 (n)**	**Difference (n)**	**%**
North	562	708	+146	+26%
Northeast	2192	2709	+517	+24%
Southeast	2058	3003	+945	+46%
South	1141	1447	+305	+27%
Midwest	468	828	+360	+77%
Total	**6421**	**8695**	**+2274**	+35%

Table 2. Difference between the average of Herpes Zoster diagnoses reported by the Brazilian public health system in all geographical regions between March and August 2020 (previous study) compared to September to February – 2020/21 and from of the pre-pandemic with the pandemic period.

Regions of Brazil	Mar-Aug 2020 (n)	Sep-Feb 2020/21 (n)	Sep-Feb 2017-20 (n)	Difference (%) Mar-Aug 2020 Sep-Feb 2020/21	Difference (%) Sep-Feb 2017-20 Sep-Feb 2020/21
North	708	751	719	+43 (6.1%)	+32 (4.5%)
Northeast	2709	3126	2128	+417 (15.4%)	+998 (46.9 %)
Southeast	3003	3336	2086	+333 (11.1%)	+1250 (59.9%)
South	1447	1532	873	+85 (5.9%)	+659 (75.5%)
Midwest	828	909	498	+81 (9.8%)	+411 (82.5%)
Total	**8695**	**9654**	**6304**	**+959 (11%)**	**+3350 (53.1%)**

Mar-Aug 2020: Previous study (Maia et al., 2021)
Sep-Feb 2017-20: Pre-pandemic period
Sep-Feb 2020/21: Pandemic period (This study)

Table 3. Incident cases of herpes zoster per million population in Brazilian macroregions according to the periods 2017-2019 vs. 2020.

Regions of Brazil	Pre-pandemic period Incidence rate (95% CI)	First pandemic period Incidence rate (95% CI)	Second pandemic period Incidence rate (95% CI)	P*	P**
North	40.0 (37.2 – 43.1)	39.5 (36.6 - 42.5)	41.9 (38.9 – 44.9)	0.77	0.40
Northeast	37.2 (35.6 – 38.8)	47.3 (45.5 – 49.1)	54.6 (52.7 – 56.5)	< 0.001	< 0.001
Southwest	24.0 (22.9 – 25.1)	34.4 (33.3 – 35.8)	38.4 (37.0 – 39.7)	< 0.001	< 0.001
South	29.5 (27.5 – 31.5)	48.8 (46.3 – 51.4)	51.7 (49.1 – 54.3)	0.12	< 0.001
Midwest	31.4 (28.7 – 34.2)	52.2 (48.7 – 55.8)	57.3 (53.6 – 61.1)	0.052	< 0.001
Total	**30.4 (29.6 – 31.1)**	**41.9 (41.0 – 42.8)**	**46.5 (45.6 – 47.5)**	**< 0.001**	**< 0.001**

*Comparison between first and second pandemic periods

** Comparison between the pre pandemic and the second pandemic periods

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2.6 Artigo científico 6. *Impact of the coronavirus disease 2019 on the diagnoses of Hansen's disease in Brazil.* Publicado na Revista da Sociedade Brasileira de Medicina Tropical (*Open access* - ANEXO 7).

Impact of the coronavirus disease 2019 on the diagnoses of Hansen's disease in Brazil

Marques NP et al. - COVID-19 and Hansen's disease cases in Brazil

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) has limited the access of patients with Hansen's disease (HD) to care due to changes in routine health services. Methods: To ascertain this, we compared the number of HD cases diagnosed before and after the COVID-19 pandemic. Results: The decrease in HD cases in Brazil reached 18,223 (-48.4%), corresponding to an average reduction of 1,518 cases per month during the COVID-19 pandemic. Conclusion: Therefore, effective measures should be implemented to minimize the damage and the consequent negative health impact of COVID-19 on the care of HD patients.

Keywords: COVID-19, Hansen's disease, Pandemics.

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic in March 2020[1]. In Brazil, the first COVID-19 case was reported on February 26, 2020. Just a year after that, 18.7 million people have been diagnosed with COVID-19 and approximately 524,000 deaths have been reported[2]. The high infection and hospitalization rates caused by SARS-CoV-2 have led to several disturbances in health systems around the world, including the Brazilian Unified Health System (SUS)[3,4].

In response to the increase in the number of COVID-19 cases, non-urgent consultations and hospital admissions have been discouraged or postponed, leading to a change in the priorities of hospital care[4,5]. The high infectivity of SARS-CoV-2 raises important questions about COVID-19 risk groups[6]. Mortality seems to be higher in men, older adults, people who do not receive assistance from health services, and people with chronic diseases, such as hypertension, diabetes, coronary heart disease, and pulmonary obstructive diseases[6,7]. However, there is still a lack of information regarding how COVID-19 affects people with chronic infectious diseases[6].

The pandemic has limited the access of patients with Hansen's disease (HD) to care[5]. HD is an infectious, chronic, and granulomatous disease caused by *Mycobacterium leprae* (with high infectivity and low pathogenicity), which was quite prevalent in Europe during the 16th century and currently affects 200,000 people globally[1,8]. Clinically, HD cases are classified as paucibacillary (PB), with up to five lesions on the body, or multibacillary (MB), with more than five lesions; the latter has greater potential for transmission due to the high bacillary load and the spread of bacillus through the upper airways[1,8].

HD mainly affects the peripheral nervous system, skin, and mucosa, with symptoms varying depending on the immune response of the patient to bacterial infection. During transmission by droplets, *Mycobacterium leprae* affects the nasal mucosa capillary endothelial cells and, subsequently, reaches the Schwann cells of the nervous system. This way, infection of the olfactory bulb can occur and lead to olfactory dysfunction, which is clinically characterized as hyposmia or anosmia and is similar to some of the symptoms of COVID-19[8].

HD is curable; however, it can progress to severe neural damage and lead to amputation of the limbs if not treated early; this makes early diagnosis even more important for preventing worse outcomes. Besides, Mahato et al. (2020) affirmed that the prevalence of HD is higher among people of low social status; these are the same people most affected by the measures for mitigating the COVID-19, such as restrictions of non-essential services and recommendations

of social isolation, which favor the increase in social inequalities. Because of this condition, several people cannot maintain appropriate hygienic measures to prevent SARS-CoV-2 infection, including frequent washing of hands and the use of alcohol gel and masks, among other measures. If contaminated by Hansen's bacillus, they may develop severe leprosy reactions and possibly co-infection with SARS-CoV-2[5,7].

To further ascertain this, we evaluated the number of cases of HD diagnosed between January 2010 and December 2020 using data collected from the National Disease Notification System (SINAN)[9]. We also compared the data for the pre- and peri-pandemic periods. The diagnoses of the disease were already declining within 2010-2019, as shown by the Mann-Kendall trend test (-0.6444, P = 0.012). **Figure 1** shows a decline in HD diagnoses between 2010 and 2015 with a tendency to stabilize during the subsequent years, followed by a steep drop in 2020. Considering the average number of newly diagnosed cases of HD in 2010-2019 compared with 2020, the reduction was consistent across all five Brazilian macroregions, ranging from 41% in the Midwest to 56.4% in the Southeast macroregion. The decrease in the number of Brazilian cases reached 18,223 (-48.4%), corresponding to an average reduction of 1,518 cases per month during the COVID-19 pandemic **(Table 1)**. **Table 2** shows the comparison between the mean rates during the pre-pandemic years and 2020 across Brazilian geographic macroregions and the entire country. The rates of HD diagnoses significantly decreased during the pandemic period throughout Brazil (IRR= 0.51, 95% CI 0.50-0.52, P<0.0001)**.**

In conclusion, our study showed a reduction in the number of HD cases diagnosed in Brazil during the pandemic. Concerns about the diagnoses and treatment of neglected tropical diseases have heightened during the pandemic period, possibly due to the reduction of financial support and human resources[10]. Therefore, effective measures, including the advancement of COVID-19 vaccination, dissemination of information about protective measures by health care professionals, and awareness of the population about the importance of HD control should be urgently prioritized to minimize the negative impact of COVID-19 on health services for HD.

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Authors' contribution

NPM: Conception and design of the study, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted; **NCTM**: Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted; **IMC:** Conception and design of the study, Acquisition of data, Drafting the article; **EGL**: Acquisition of data, Analysis and interpretation of data; **DRBM**: Conception and design of the study, Analysis and interpretation of data, Final approval of the version to be submitted; **EAO**: Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted; **HMJ**: Conception and design of the study, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be submitted.

Conflict of Interest

The authors declare that there is no conflict of interest.

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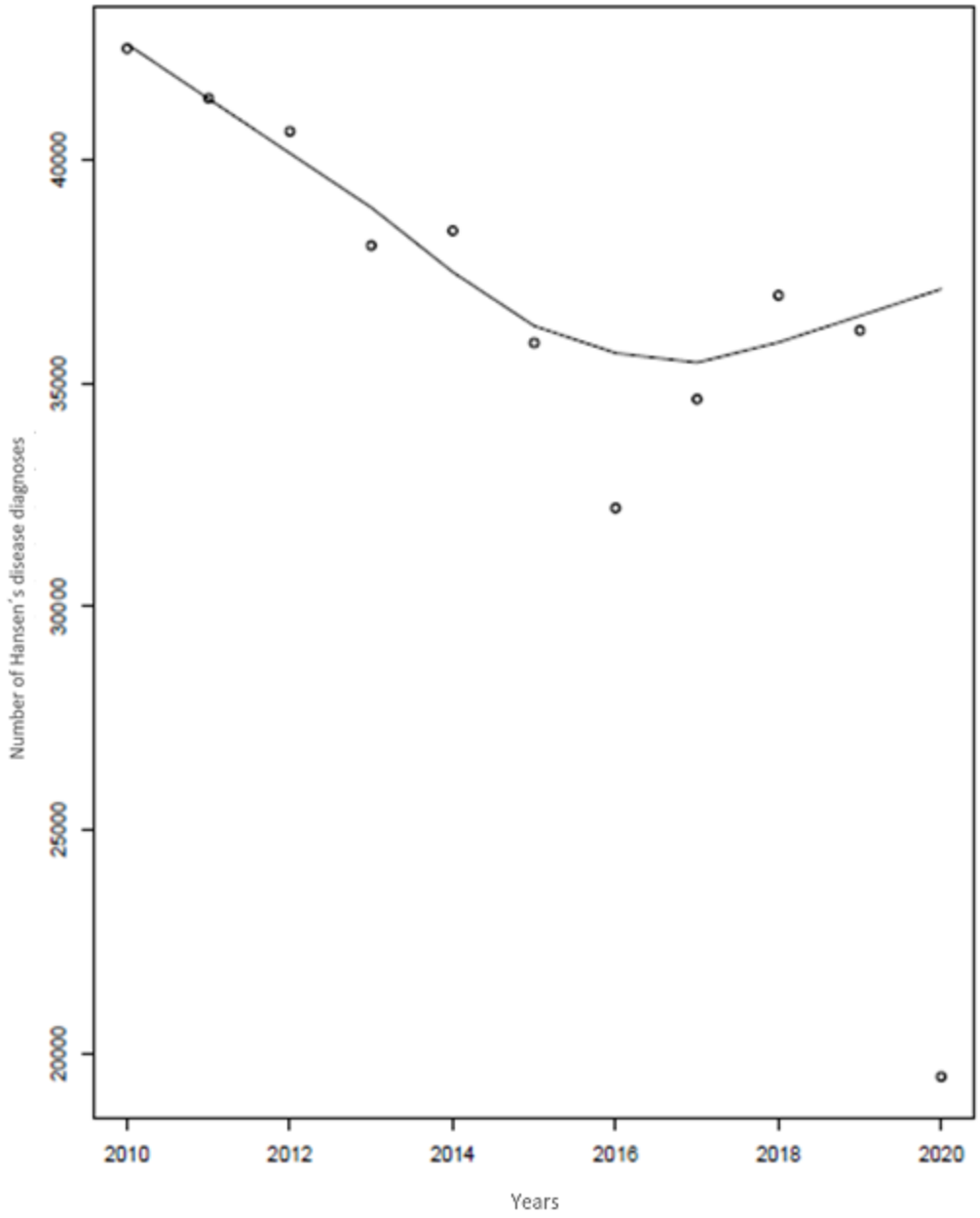

Figure 1: Plot of the number of diagnoses of Hansen's disease in Brazil by the Brazilian public health system (2010-2020).

Table 1: Comparison of the diagnoses of Hansen's disease in Brazil by the Brazilian public health system within 2010-2019 and in 2020.

Macroregions of Brazil	2010-2019	2020	Difference (%)
North	7,409	3,876	-3,533 (-47.7)
Northeast	15,877	8,190	-7,687 (-48.4)
Southwest	5,657	2,408	-3,249 (-57.4)
South	1,349	638	-711 (-52.7)
Midwest	7,409	4,366	-3,043 (-41.0)
Total	**37,701**	**19,478**	**-18,223 (-48.4)**

Source: Notifiable Diseases Information System - Sinan Net (http://portalsinan.saude.gov.br/).

Table 2: Incident cases of Hansen's disease per million population in Brazilian macroregions within 2010-2019 and in 2020.

Macroregions of Brazil	2010-2019 Incidence rate (95%CI)	2020 Incidence rate (95%CI)	Incidence ratio (95%CI)	*p**
North	413 (403 - 422)	216 (209 – 223)	0.52 (0.50 – 0.54)	< 0.001
Northeast	277 (273 – 281)	143 (140 – 146)	0.51 (0.50 - 0.53)	< 0.001
Southwest	65 (63 – 67)	27 (26 – 28)	0.42 (0.40 - 0.44)	< 0.001
South	45 (43 – 48)	21 (19 – 23)	0.47 (0.43 - 0.52)	< 0.001
Midwest	46 (44 – 47)	27 (26 – 28)	0.59 (0.56 - 0.61)	< 0.001
Total	**181 (179 – 183)**	**94 (92 – 95)**	**0.51 (0.50 - 0.52)**	**< 0.001**

HD - Hansen's disease

CI - Confidence interval

*** *p*-value -** obtained by chi-square Chi^2-statistic

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2.7 Artigo científico 7. *Correspondence on 'Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine' Increase in the number of systemic lupus erythematosus cases in Brazil in the COVID-19 era*. Publicado no periódico *Annals of Rheumatic Diseases* (ANEXO 8).

Correspondence on 'Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine' Increase in the number of systemic lupus erythematosus cases in Brazil in the COVID-19 era

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Running Title: COVID-19 on systemic lupus erythematosus cases in Brazil

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The SARS-CoV- 2 disease 2019 (COVID-19) pandemic deeply affected all Brazilian regions. Brazil has seen approximately 12 million cases of COVID-19 and over 294 042 deaths to date (21 March 2021) (https:// COVID- 19. saude. gov. br/), and the end of the pandemic cannot yet be predicted. The COVID-19 pandemic scenario represents a source of concern for the management of patients with chronic diseases and comorbidities, including autoimmune diseases, such as systemic lupus erythematosus (SLE).[1] The new viral infection caused by SARS-CoV- 2 seems to lead to the onset or exacerbation of autoimmune diseases in genetically predisposed patients.[2–4] SLE is an autoimmune disease prone to flare-ups that are linked to significant morbimortality. Immunosuppression-related infections are one of the leading causes of premature death in patients with SLE. However, there are currently no data to support a higher infection rate or an increased risk for fatal outcome related to COVID-19 in these patients.[2–5] One could even speculate the SLE treatment can protect against the serious complications related to COVID-19.[2]

In this regard, we read the relevant paper by Mathian et al[1] who evaluated the clinical course of COVID-19 in patients with SLE treated with hydroxychloroquine. Although these preliminary data have shown a lack of clarity about the incidence and severity of COVID-19 in patients with SLE, it is suggested that patients with comorbidities, such as chronic kidney disease and obesity, may suffer from severe forms of COVID-19, regardless of the chronic use of hydroxychloroquine. Similarly, Wallace et al[6] suggests that patients with SLE may develop more severe manifestations of COVID-19 infection, especially when other comorbidities and predisposing factors are associated, including obesity, smoking and chronic use of medications, such as immunosuppressants. On the other hand, Favalli et al[7] consider the impact of COVID-19 in patients with SLE very low, since most patients with chronic diseases are used to take measures in order to reduce infection risks, even before the outbreak of COVID-19. Accordingly, Caso et al[5] claim that different strategies followed for the management of rheumatic diseases are currently included in the treatment protocol for SARS-CoV- 2 infection.

However, it is believed that autoinflammatory and autoimmune syndromes can have triggering factors, such as viruses, which stimulate the activation of an exacerbated immune response, with increased synthesis of proinflammatory cytokines. Due to similar pathogenic mechanisms and clinical–radiological aspects in hyperinflammatory diseases and COVID-19, it can be suggested that SARS-CoV-2 could act as a triggering factor for the development of rapid autoimmune and/or autoinflammatory dysregulation.[5] In order to ascertain this issue further, we evaluated the number of cases of SLE diagnosed from January 2017 to December

2020 over all the five Brazilian macroregions and compared the prepandemic and transpandemic period of COVID-19.

Over the triennium 2017–2019, the average number of new diagnosed cases of SLE was 23 422, while in 2020 this figure reached 36 549, an increment of about 56% during the time frame analysed. The increment was consistent across all five Brazilian macroregions, ranged from +23.4% in Southeast to +108.9% in the Northeast region. The increase in the overall Brazilian cases reached +13 107 (+55.9%) cases, corresponding an addition of an average of 1092 cases per month during the COVID-19 pandemic (table 1). Table 2 shows a significant increase in the incident cases of SLE per million population in Brazil ($p<0.001$).

In conclusion, our findings have shown an increase in the number of new cases of SLE in Brazil during the pandemic period. Conversely, we recently reported that the pandemic period has dramatically reduced the diagnosis of new cases of cancer in Brazil, possibly by the limitation of consultations in public health services.[8] Many aspects of the association between SLE and COVID-19 are not yet well established. Further prospective clinical studies are needed to define whether these conditions are really related.

Table legend

Table 1. The average number of diagnosed systemic lupus erythematosus cases, across Brazilian geographical macroregions, according to different periods (2017-2019 vs. 2020). Source: Health Information System for Primary Care – SISAB (https://sisab.saude.gov.br/paginas/acessoRestrito/relatorio/federal/saude/RelSauProducao.xhtml).

Table 2. Incident cases of systemic lupus erythematosus per million population in Brazilian macroregions according to the periods 2017-2019 versus 2020.

Table 1. The average number of diagnosed systemic lupus erythematosus cases, across Brazilian geographical macroregions, according to different periods (2017-2019 vs. 2020).

Macroregions of Brazil	2017-2019 (n)	2020 (n)	Difference (n) (%)
North	1296	2221	+925 (71.3%)
Northeast	5119	10697	+5578 (108.9%)
Southwest	10320	14526	+4206 (40.7%)
South	4750	5863	+1113 (23.4%)
Midwest	1957	3242	+1285 (65.6%)
Total	**23,442**	**36,549**	**+13,107 (55.9%)**

Table 2. Incident cases of systemic lupus erythematosus per million population in Brazilian macroregions according to the periods 2017-2019 vs. 2020.

Macroregions of Brazil	2017-2019 Incidence rate (95%CI)	2020 Incidence rate (95%CI)	Incidence ratio (95%CI)	*p*
North	69.4 (65 - 73)	118.9 (114 – 124)	1.71 (1.59 – 1.83)	< 0.001
Northeast	89.2 (86 – 91)	186.4 (183 – 190)	2.08 (2.02 - 2.16)	< 0.001
Southwest	115.9 (113 – 118)	163.2 (160 – 165)	1.40 (1.37 - 1.44)	< 0.001
South	157.3 (152 – 162)	194.2 (189 – 199)	1.23 (1.18 - 1.28)	< 0.001
Midwest	118.6 (113 – 124)	196.4 (189 – 203)	1.65 (1.56 - 1.75)	< 0.001
Total	**111.6 (110 – 113)**	**171.7 (170 – 174)**	**1.54 (1.52 – 1.57)**	**< 0.001**

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2.8 Artigo científico 8. *The continuous increase in the number of systemic lupus erythematosus cases in Brazil in the COVID-19 Era*. Aceito para publicação no periódico *Brazilian Oral Research* (ANEXO 9).

The continuous increase in the number of systemic lupus erythematosus cases in Brazil in the COVID-19 era

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Abstract: This study aims to reevaluate and compare the data from the Brazilian Unified Health System (SUS) on the number of diagnoses of systemic lupus erythematosus (SLE) in the pre-pandemic period with those in the pandemic period, as well as to compare the first year (2020) of the COVID-19 pandemic in Brazil with the last year (2021), to update the data, and to verify whether SLE disease control measures were effective in 2021. There was a consistent and significant increase in the incidence of SLE cases all over Brazil between the first and second pandemic years and between the pre-pandemic triennium and the second pandemic year. Therefore, it is inescapable to have larger clinical studies with different populations to better understand the relationship between these two conditions and find measures to improve the control of this disease.

Introduction

As the Coronavirus 2019 (COVID-19) pandemic goes on around the world, clinical and epidemiological evidence of the incidence and increase in the number of systemic lupus erythematosus (SLE) continues to be discussed, but the real association between SLE and the risk factors associated with worse COVID-19 outcomes in this population are not well established.[1,2] Even with the expansion of vaccination in Brazil, with full immunization of 171 million (80.6%) people, COVID-19 variants such as OMICRON have impacted and increased COVID-19 cases. Brazil has experienced approximately 34 million cases of COVID-19 and over 682,358 deaths to date (August 19, 2022) (https://covid.saude.gov.br/).

This scenario still represents a cause for concern about the management of patients with autoimmune diseases, such as SLE. Ugarte-Gil et al.[1] demonstrated that more severe COVID-19 outcomes in individuals with SLE are largely driven by factors such as untreated or active SLE. Patients on glucocorticoids also have more severe outcomes. The concern becomes even greater when studies conducted during the pandemic showed a decrease in the hospitalization rate of patients with SLE but an increase in the mortality rate due to the measures implemented to mitigate the pandemic, such as negligence in medical assistance for other diseases.[2,3]

A number of orofacial manifestations have also been reported in patients with SLE, such as nonspecific ulcerations, involvement of salivary glands, and temporomandibular joint disorders.[4] A recent study has highlighted the difficulties and damage from the current COVID-19 pandemic to dental services in general and to oral medicine and oral pathology particularly, which makes the possible number of undiagnosed SLE cases even more concerning.[5]

Materials and methods

The data on the number of diagnoses of SLE in 2017 – 2019, 2020, and 2021 from five Brazilian regions (north, northeast, southeast, south, and midwest), representing 26 states and the Federal District were extracted from SISAB (Health Information System for Primary Care), a public database maintained by the Brazilian Ministry of Health (https://sisab.saude.gov.br/paginas/acessoRestrito/relatorio/federal/saude/RelSauProduc Re.xhtml).

Statistical analyses were performed using the BioEstat 5.0 statistical software (Biostatistical Institute of Science and Technology). The number of diagnoses of SLE was compared between the pre-pandemic period and the pandemic period. The number of diagnoses of SLE in the first year (2020) of the COVID-19 pandemic in Brazil was compared with the

last year (2021). The study also aimed to update the data and verify whether SLE disease control measures were effective in 2021. In addition, binomial regression was used to analyze the longitudinal associations between the impact of the COVID-19 pandemic and the number of diagnoses. Percentage changes were calculated by dividing the change in value by the original value and then multiplying the obtained value by 100. In all analyses, the data were disaggregated by Brazilian regions.

Results

Table 1 presents the previous study by the same research group[6] and shows an increase in the number of SLE diagnoses in all Brazilian regions in 2020, compared to the mean number of the pre-pandemic triennium (2017–2019). The increase ranged from +23.4% in the south to +108.9% in northeastern region. The overall Brazilian average increase amounted to 55.9%, corresponding to 13,107 more cases in the first year of the pandemic period.

Table 2 shows the comparison of the second year of the pandemic period (2021) initially with the first year of the COVID-19 pandemic (2020) and then with the pre-pandemic period. There was a trend towards an increase in the number of SLE cases in the second year of the pandemic throughout Brazil (+20.4%), giving special attention to the southern region, the least affected in the first study and now the one with the largest increase (+28.1%) during the pandemic. When comparing the subsequent period of the pandemic (2021) with the mean number in the pre-pandemic period (2017–2019), the increase in the number of SLE cases was higher compared to the previous study, showing the northeastern region was the most widely affected (148.4%), in addition to an increase of 20,550 cases throughout Brazil (+87.7%).

Table 3 shows the comparison of the incidence rate adjusted per million people for the five Brazilian regions and throughout the country. There was a consistent and significant increase in the incidence rate all over Brazil between the first and second pandemic years and between the pre-pandemic triennium and the second pandemic year.

Discussion

SLE is clearly an important risk factor for the development of more severe COVID-19.[2,7] Patients with SLE develop more severe manifestations of COVID-19, especially when they have other comorbidities and predisposing factors, including smoking, obesity, and chronic use of medications, such as immunosuppressants.[2] It has been suggested that SARS-CoV-2 could act as a triggering factor for the development of rapid autoimmune and/or

autoinflammatory dysregulation due to similar pathogenic mechanisms and clinico-radiological aspects in hyperinflammatory diseases and COVID-19.[2,8]

At the beginning of the pandemic period, telemedicine came into use because of health service restrictions, having a positive impact for patients who sought rheumatology care.[9] Nevertheless, it is still unclear why SLE cases continue to increase during the pandemic even after the adoption of these preventive measures and the decrease in COVID-19 cases.[1,2]

The fear of patients of seeking medical services during the pandemic, difficulties related to technology and telemedicine, routine care cancellations, difficulties in accessing healthcare, and pandemic-related stress seem to contribute to the physical deterioration of SLE patients and might also have increased the number of patients diagnosed with the disease.[10]

Conclusion

Therefore, given the increase of rheumatic diseases, such as SLE,[9] described in the literature during the pandemic and demonstrated in this paper, it is inescapable to have larger clinical studies with different populations to better understand the relationship between these two conditions and find measures to improve the control of this disease.

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Tables

Table 1. Average number of diagnosed systemic lupus erythematosus cases across Brazilian geographical macroregions in different periods (2017–2019 *vs*. 2020). Previous study – *Martelli-Junior et al., 2021*.

Source: Health Information System for Primary Care – SISAB (https://sisab.saude.gov.br/paginas/acessoRestrito/relatorio/federal/saude/RelSauProducRe.xhtml).

Table 2. Difference between the number of diagnosed systemic lupus erythematosus cases reported by the Brazilian public health system in all geographical regions in 2020 (previous study) compared to 2021 and comparison of the average number of SLE cases in the pre-pandemic and pandemic periods.

Table 3. Incidence of systemic lupus erythematosus per million people in Brazilian macroregions in 2017–2019 *vs*. 2021 and 2020 *vs.* 2021.

Table 1. Average number of diagnosed systemic lupus erythematosus cases across Brazilian geographical macroregions in different periods (2017–2019 *vs*. 2020). Previous study – *Martelli-Junior et al., 2021*.

Macroregions of Brazil	**2017-2019 (n)**	**2020 (n)**	**Difference (n) (%)**
North	1,296	2,221	+925 (71.3)
Northeast	5,119	10,697	+5,578 (108.9)
Southwest	10,320	14,526	+4,206 (40.7)
South	4,750	5,863	+1,113 (23.4)
Midwest	1,957	3,242	+1,285 (65.6)
Total	**23,442**	**36,549**	**+13,107 (55.9)**

Table 2. Difference between the number of diagnosed systemic lupus erythematosus cases reported by the Brazilian public health system in all geographical regions in 2020 (previous study) compared to 2021 and comparison of the average number of SLE cases in the pre-pandemic and pandemic periods.

Macroregions of Brazil	**2020 (n)**	**2021 (n)**	**2017-2019 (n)**	**Difference (%) 2020 *vs* 2021**	**Difference (%) 2017-2019 *vs* 2021**
North	2,221	2,772	1,296	+551 (24.8)	+1,476 (113.9)
Northeast	10,697	12,716	5,119	+2,019 (18.9)	+7,597 (148.4)
Southeast	14,526	17,122	10,320	+2,596 (17.9)	+6,802 (65.9)
South	5,863	7,508	4,750	+1,645 (28.1)	+2,758 (58.1)
Midwest	3,242	3,874	1,957	+632 (19.5)	+1,917 (98)
Total	**36,549**	**43,992**	**23,442**	**+7,443 (20.4)**	**+20,550 (87.7)**

2020: Previous study (Martelli-Junior et al., 2021).
2017-19: Pre-pandemic period.
2021: Pandemic period (*This study*).

Table 3. Incidence of systemic lupus erythematosus per million people in Brazilian macroregions in 2017–2019 vs. 2021 and 2020 vs. 2021

Regions of Brazil	**2017-2019 Incidence rate (95%CI)**	**2020 Incidence rate (95%CI)**	**2021 Incidence rate (95%CI)**	**Incidence ratio* (95%CI)**	***p***
North	1,296 72.2 (68.4- 76.3)	2,221 123.8 (118.7- 129.1)	2,772 154.5 (148.8 – 160.6)	1.92 (1.80 – 2.06)	< 0.001
Northeast	5,119 97.4 (93.1 – 107.4)	10,697 186.8 (183.3 – 190.4)	12,716 222.1 (218.3 – 226.0)	2.28 (2.21 - 2.36)	< 0.001
Southeast	10,320 48.4 (44.8 – 51.9)	14,526 167.1 (164.4 – 169.8)	17,122 196.9 (194.0 – 199.9)	1.53 (1.49 – 1.57)	< 0.001
South	4,750 160.2 (155.7 – 164.9)	5,863 197.8 (192.7 – 202.9)	7,508 253.3 (247.6 – 259.1)	1.40 (1.35 - 1.46)	< 0.001
Midwest	1,957 123.3 (117.9 – 128.9)	3,242 204.2 (197.4 – 211.4)	3,874 244.0 (236.4 – 251.8)	1.82 (1.72 – 1.91)	< 0.001
Total	**23,442** **112.9 (111.4 – 114.3)**	**36,549** **176.0 (174.2 – 177.8)**	**43,992** **221.8 (209.9 – 213.8)**	**1.72** **(1.69 - 1.74)**	**< 0.001**

*Comparison between the average figures for post-pandemic (2020-2021) and pre pandemic (2017-2019) periods.

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2.9 Artigo científico 9. *Assessment of Guillain-Barre Syndrome Cases in Brazil in the COVID-19 Era*. Publicado no periódico *Neurologist* (*Open access* - ANEXO 10).

Assessment of Guillain-Barre syndrome cases in Brazil in the COVID-19 Era

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Letter to the Editor,

There has been amounted evidence of the neuroinvasive potential of the SARS-CoV-2. The main neurological manifestations reported include dizziness, headache, hypogeusia, hyposmia, muscle damage, ischemic and hemorrhagic stroke.[1] Guillain-Barre syndrome (GBS) represents the most common cause of acute symmetrical flaccid limb weakness. GBS encompasses a wide range of clinical syndromes with an acute inflammatory polyradiculoneuropathy.[2] GBS is one of the neurological complications that has been found in patients with previous diagnosis of COVID-19.[3]

The possible mechanism that has been associated with GBS in patients with COVID-19 is similar to the pathogenesis involved in typical GBS, consisting of demyelination of peripheral nerve roots. Peripheral nerve damage can be caused by the immune response to SARS-CoV-2, driven by the production of self-reactive antibodies (anti-ganglioside).[4] It is recognized that viral infections can disrupt immune tolerance by exposing antigen epitopes that induce cross-reactive antibodies. There are many reports indicating antigenic mimicry between viral and human proteins that cause autoimmune diseases. As autoimmune diseases are linked to a deregulated immune system, this dysregulation can lead to damage and dysfunction in target organs. Autoimmune and immune-mediated diseases can play a pathogenic role in COVID-19 and some patients have reported the appearance of autoimmune diseases such as GBS and lupus erythematosus after coronavirus infection.[5]

To investigate the impact of the pandemic of COVID-19 in the GBS diagnosis in Brazil, the main goal of this study was compare data from the Brazilian Unified Health System (SUS) on the number of annual GBS cases between the pre-pandemic period (March 2018 – May 2019) and the pandemic (March 2020 – May 2021), from the 5 Macroregions of Brazil (North, Northeast, Southeast, South, and Midwest), representing the Brazilian States (26 States and the Federal District), through data extracted and analyzed from the public database of SUS (http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sia/cnv/qauf.def).

Table 1 shows the increase in GBS diagnosis in all five Brazilian Macroregions since the pandemic period began, ranging from +27.5% in the North region and +1.6% in the Midwest region. In Brazil the rise reached +15,8% diagnosis of GBS, representing more than 240 cases during COVID-19 pandemic compared with the pre-pandemic period. Table 2 shows the comparison between the mean incident rates of GBS in the pre pandemic and trans pandemic periods, across Brazilian geographic macroregions and for the country as a whole. The incident

rates of GBS diagnoses significantly increased in the pandemic period throughout Brazil (IRR= 1.16, 95%CI 1.08-1.24, P<0.0001), especially in regions Northeast and Southeast.

The literature also includes reports on the correlation between COVID-19 and GBS.[3] A systematic review analyzed 73 cases of GBS that included only patients who had a laboratory test confirming the COVID-19 infection.[6] The authors revealed that most patients showed respiratory and systemic symptoms and developed GBS manifestations after COVID-19.[6] Vaccination has been investigated as a possible trigger for GBS.[7] A study carried out in United Kingdom in the first wave of COVID-19, did not show a significant increase on GBS cases and, therefore, no relation between the diseases[8], which differs from this present data, that shows a significant increase in the number of GBS cases during the COVID-19 pandemic.

A recent study reported the time to onset of GBS symptoms in patients with COVID-19 was five to ten days, similar interval observed when GBS occurs during or after other infections.[9] On the other hand, cerebrospinal fluid protein levels seem higher in COVID-19 patients.[10] The treatment given for these cases used immunoglobulin IV or plasmapheresis, supportive care, and antiviral drugs.[4]

The pandemic period has significantly increased the number of GBS diagnoses in Brazil, and measures to raise the control of this disease must be carried out. In addition, physicians and patients who have already undergone COVID-19 should be aware of this this possible relation between COVID-19 and GBS increased cases.

Table legend

Table 1. Difference in the number of Guillain-Barre syndrome cases in all five Brazilian geographical regions between the pre-pandemic period (March 2018 – May 2019) and the pandemic period (March 2020 – May 2021)

Table 2. Incident cases of Guillain-Barre syndrome cases per million population in Brazilian macroregions according to the periods pre pandemic and pandemic periods.

Table 1. Difference in the number of Guillain-Barre syndrome cases in all five Brazilian geographical regions between the pre-pandemic period (March 2018 to May 2019) and the pandemic period (March 2020 to May 2021).

Region	Pre-pandemic Period	Pandemic Period	Difference	%
North	109	139	+30	+27,5%
Northeast	251	319	+68	+27,1%
Southeast	614	752	+138	+22,5%
South	410	419	+9	+2,2%
Midwest	183	186	+3	+1,6%
Total	**1,567**	**1,815**	**+248**	**+15,8%**

Table 2. Incident cases of Guillain-Barre syndrome cases per million population in Brazilian macroregions according to the periods pre pandemic and pandemic periods.

Regions of Brazil	COVID-19 cases per million pop	2017-2019 GBS Incidence rate (95%CI)	2020-2021 GBS Incidence rate (95%CI)	Incidence ratio (95%CI)	P
North	100,618	6.2 (5.0 - 7.4	7.8 (6.6 – 9.2)	1.27 (0.98 – 1.65)	0.057
Northeast	84,509	4.4 (3.8 – 4.9)	5.6 (5.0 – 6.2)	1.26 (1.07 – 1.50)	0.0044
Southeast	95,790	7.1 (6.6 – 7.5)	8.7 (8.1 – 9.3)	1.22 (1.09 – 1.36)	0.0002
South	139,995	13.9 (12.6– 23)	14.2 (12.9 – 15.7)	1.02 (0.88 – 1.17)	0.754
Midwest	141,915	11.7 (10.0 – 13.5)	11.9 (10.2 – 13.7)	1.01 (0.82 – 1.25)	0.875
Total	103,032	**7.0 (6.9 – 7.6)**	**8.4 (8.0 – 8.7)**	**1.16 (1.08 – 1.24)**	**< 0.001**

*P-value obtained by χ2statistic.
CI indicates confidence interval; COVID-19, coronavirus disease-2019; GBS, Guillain-Barre syndrome; Pop, population.

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3 CONCLUSÕES

Como as discussões foram abordadas em cada artigo, seguiremos diretamente para as conclusões, visando contextualizar nossos resultados e avaliar as perspectivas futuras para novos estudos.

1. Inicialmente, o primeiro período de pandemia (2020) reduziu drasticamente as consultas clínicas de Estomatologia no Brasil. No entanto, as medidas para o retorno da assistência à saúde e a prática da telemedicina na Odontologia se mostraram muito eficazes após o segundo período da pandemia (2021). Porém, é necessário que essas práticas e os cuidados básicos sejam mantidos, a fim de evitar novas medidas restritivas devido às variantes da doença.

2. Com relação à assistência de pacientes oncológicos, o período de pandemia reduziu drasticamente o diagnóstico de novos casos de câncer no Brasil, possivelmente pelas medidas restritivas, incluindo a limitação de consultas nos serviços públicos de saúde. Apesar do retorno da procura de pacientes pela assistência à saúde, estudos futuros para avaliar as consequências dessa queda de diagnósticos de câncer se tornam extremamente necessários, uma vez que quanto mais precoce o diagnóstico de neoplasias, melhor o prognóstico do paciente oncológico.

3. Mesmo com o alerta aos profissionais de saúde sobre o aumento de casos de HZ durante o período pandêmico em 2020, bem como, acerca da aplicação de medidas preventivas e terapêuticas contra a doença, houve um aumento contínuo e exponencial de casos de HZ durante o segundo tempo pandemia de COVID-19. Além disso, a relação entre estas doenças segue sem um esclarecimento concreto, e os pacientes que tiveram COVID-19 continuam a apresentar sintomas da HZ através de uma possível reativação do VVZ. Assim, são necessários estudos clínicos maiores, com diferentes populações, para melhor compreensão da relação entre essas duas condições e para definição de medidas mais eficazes que fortaleçam o controle da HZ.

4. As doenças infecciosas também se tornaram fonte de preocupação em períodos pandêmicos, uma vez que a queda no número de diagnósticos de Hanseníase no Brasil, observada no presente trabalho, parece estar relacionada à falta de apoio financeiro e recursos humanos para o diagnóstico e tratamento desta doença. Medidas efetivas, incluindo a continuidade da vacinação contra a COVID-19 e suas variantes, além da divulgação de informações sobre medidas de proteção pelos profissionais de saúde e a conscientização da população sobre a importância do controle da Hanseníase devem ser priorizadas, visando minimizar o impacto negativo destas afecções na população.

5. O aumento contínuo de casos de LES, tanto no primeiro período pandêmico (2020), quanto no segundo (2021) sugere uma possível relação entre as doenças. Este dado é extremamente alarmante, uma vez que pacientes com LES podem desenvolver manifestações mais graves da COVID-19, principalmente quando outras comorbidades e fatores predisponentes estão associados, como o uso crônico de imunossupressores. Portanto é inevitável a realização de novos estudos clínicos para entender melhor a relação entre essas duas condições e encontrar medidas a fim de minimizar a ocorrência do LES.

6. O período de pandemia ainda aumentou significativamente o número de diagnósticos de SGB no Brasil. A população que teve COVID-19 deve estar ciente dessa possível relação, principalmente pelas consequências neurológicas tardias relacionadas à infecção pelo SARS-CoV-2.

7. Apesar de decretado o fim da Emergência de Saúde Pública relacionada à COVID-19, a comunidade científica deve seguir na proposição de novos estudos sobre este tema. Atualizações dos dados de diagnósticos das doenças discutidas neste trabalho são essenciais para o melhor entendimento da possível relação entre as condições citadas e a COVID-19, além de determinar se a superação deste período e as medidas implementadas até agora foram suficientes para o controle dessas doenças. As complicações tardias em pacientes que foram positivos para COVID-19 não podem ser negligenciadas, principalmente por se tratar de uma doença relativamente nova e com muitas variantes a serem investigadas.

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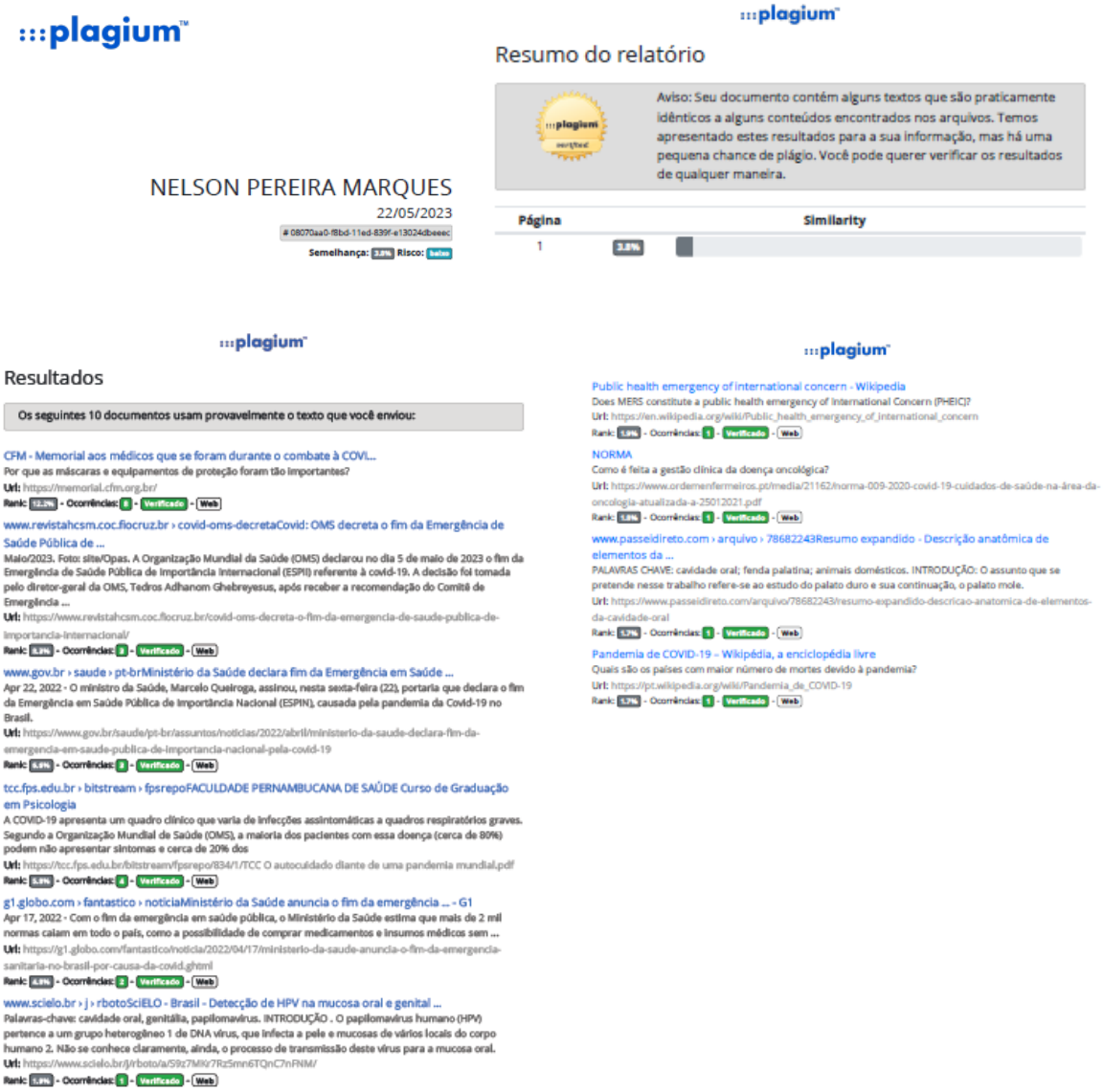

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Anexo 3 - Carta de aceite - Artigo científico 2

Dear author(s): Nelson Pereira Marques, Denise Maria Silveira, Nádia Carolina Teixeira Marques, Edson Hilan Lucena, Daniella Reis Barbosa Martelli, Danyel Elias da Cruz Perez , Hercílio Martelli-Junior
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Kind regards,
Altair A Del Bel Cury
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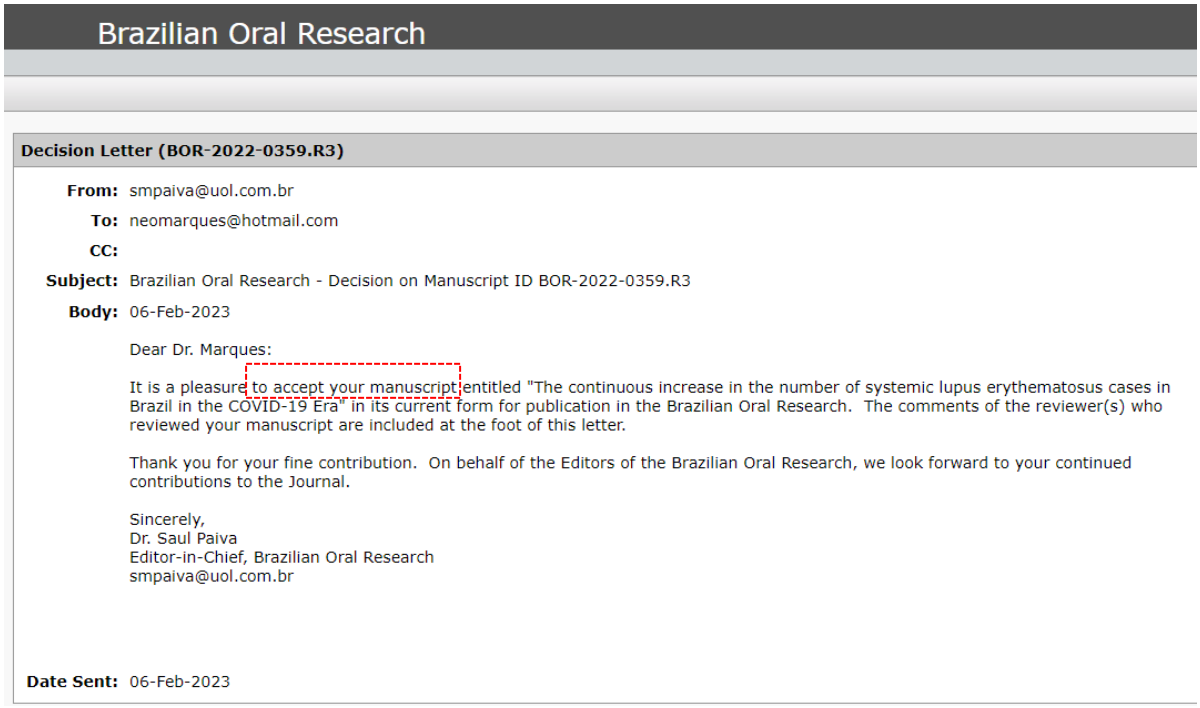

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Body: 06-Feb-2023

Dear Dr. Marques:

It is a pleasure to accept your manuscript entitled "The continuous increase in the number of systemic lupus erythematosus cases in Brazil in the COVID-19 Era" in its current form for publication in the Brazilian Oral Research. The comments of the reviewer(s) who reviewed your manuscript are included at the foot of this letter.

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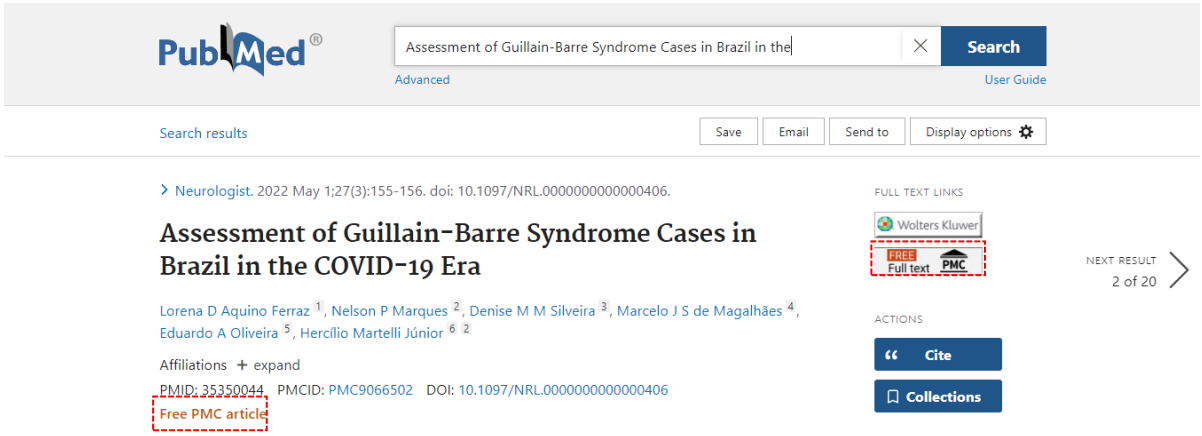

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