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Interrupção Voluntária da Gravidez nos Cuidados de Saúde Primários em Portugal: Problemas e Desafios Futuros

Medical Abortion in Primary Health Care in Portugal: Problems and Future Challenges

Mariana CASTRO GUIMARÃES✉[1], Raquel BAPTISTA LEITE[2], Vítor TRINDADE PEDROSA[3], Nuno BASÍLIO[4]
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Palavras-chave: Aborto Induzido; Aborto Legal; Acesso aos Serviços de Saúde; Cuidados de Saúde Primários; Portugal
Keywords: Abortion, Induced; Abortion, Legal; Health Services Accessibility; Portugal; Primary Health Care

A partir da aprovação da lei n.º 16/2007 de 17 de abril de 2007, a interrupção voluntária da gravidez (IVG) passou a não ser punível por lei em Portugal, se realizada com o consentimento da mulher grávida nas primeiras 10 semanas de gestação.[1] Entre 2008 e 2021 realizaram-se, em Portugal, 238 301 interrupções da gravidez.[2] Considerando os mais recentes dados disponíveis, relativos a 2021, realizaram-se 12 159 interrupções de gravidez, das quais 11 640 foram IVG.[3]

Desde 2007 a IVG é realizada em estabelecimentos oficiais ou oficialmente reconhecidos e, segundo a lei, antes do procedimento é necessária a realização de uma consulta prévia, destinada a fornecer informação relevante para tomada de decisão e um período de reflexão de três dias. Importa destacar que no período de reflexão deve ser disponibilizado acompanhamento em consulta de psicologia e/ou assistente social. Após a interrupção da gravidez deve ser agendada uma consulta médica de reavaliação e uma consulta de planeamento familiar.[1]

Quanto a esta realidade, são diversas as questões éticas e organizacionais.

Problemas atuais

À data de hoje, ao abrigo da norma n.º 001/2013 de 29/01/2013, a IVG pode ser realizada, por opção da mulher, até às 10 semanas e seis dias de gravidez.[4] Os médicos de família e enfermeiros de família dos Cuidados de Saúde Primários (CSP) são confrontados diariamente com vários desafios. Estes desafios são agudizados pelo facto de, simultaneamente, o tempo médio de espera após encaminhamento pelos CSP ou outra porta de entrada no Serviço Nacional de Saúde (SNS) para a realização da IVG se encontrar entre os 6,22 e os 6,42 dias, com uma mediana de cinco dias.[3] Não são assim tão raras as vezes em que, aquando da IVG, a idade gestacional legal para a realização do procedimento se encontra no limite das 10 semanas e seis dias ou já foi largamente ultrapassada.

Outro ponto prende-se com a ausência de clarificação de como orientar uma mulher que solicite a IVG nas primeiras 12 semanas de gravidez, de forma a "evitar perigo de morte ou de grave e duradoura lesão para o corpo ou para a saúde física ou psíquica da mulher grávida".[1] No caso de estarmos perante, por exemplo, uma utente não frequentadora ou sem médico de família/médico assistente, quem atesta e como atesta este perigo? Qual o papel da equipa de enfermagem, da equipa médica ou da psicologia nesta situação?

Uma outra questão que se levanta relaciona-se com o mapeamento de profissionais objetores de consciência para a IVG. Este mapeamento existe a nível nacional? Está atualizado? É público? Perante a transferência de um profissional de saúde para outro serviço, este pedido transitará com ele? Ou justifica-se que apresente um novo documento que comprove a sua objeção?

O Relatório dos Registos das Interrupções da Gravidez[5] de 2018, que apresenta os dados mais recentes relativos às mulheres que realizaram mais do que uma interrupção da gravidez em Portugal, refere que 21,1% já tinha efetuado uma interrupção anteriormente, 5,8% já tinha efetuado duas e 2,4% já tinha efetuado três ou mais. Que estratégias têm sido criadas para diminuir a realização de mais do que uma IVG? E que reflexão tem vindo a ser feita sobre a possibilidade ilimitada de realizar IVG? Que apoio é fornecido a estas mulheres?

Desafios futuros

No dia 5 de abril de 2023, foi anunciada a possibilidade de alargar o recurso à IVG por via da sua realização nos CSP. Esta medida surge com o objetivo de ultrapassar os casos em que a distância ao estabelecimento oficial ou

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oficialmente reconhecido para realização de IVG constitui uma barreira ao acesso ao procedimento.

Sabe-se que os CSP são, por excelência, a porta de entrada para os utentes no SNS. A afluência aos CSP é elevada, resultando numa enorme pressão sobre as equipas de saúde familiares, que têm dificuldade em prestar uma acessibilidade adequada às consultas e procedimentos disponíveis, dada a dimensão das suas listas de utentes. Acresce ainda o desafio da resposta, hoje desigual em qualidade e acessibilidade, aos utentes sem médico de família.

Assim, num contexto de rotura do SNS, com derrapagens frequentes do tempo máximo de resposta garantido, de que forma os mesmos profissionais conseguirão dar ainda resposta atempada às IVG, sobretudo as que vêm no limite da idade gestacional legal para a sua realização? Perante a escassez de recursos humanos nas áreas de Psicologia e apoio social no SNS, como poderão estes profissionais responder à lei em tempo útil?

Passando a executar IVG nos CSP e face ao elevado tempo de espera para realização de ecografias de datação nas redes convencionadas com o SNS, quais as estratégias pensadas para ultrapassar a necessidade da sua realização dentro do limite de tempo legal para a IVG, sobretudo quando pela data da última menstruação (DUM) poderemos estar perante uma situação-limite, ou seja, perante uma grávida com idade gestacional próxima das 10 semanas e seis dias? Será a DUM suficiente para aferir o tempo da gravidez?

Face a possíveis complicações da IVG, tais como hemorragia grave, febre ou cólicas abdominais intensas, como gerir adequadamente nos CSP com cuidados de saúde secundários a grandes distâncias?

Se a objeção de consciência existente atualmente em vários hospitais públicos atingir de igual forma os CSP, e se esta objeção implica que não se possa realizar a consulta prévia à interrupção, tal como mencionado na lei, de que forma será realizado o primeiro apoio à mulher grávida?

Colocando o olhar nos relatos internacionais, são várias as dificuldades na aplicabilidade das IVG nos CSP. A ser implementado implicará a resolução de problemas crónicos acima identificados, bem como uma planificação e formação adequada. No Chile,[6] verificou-se que a falta de conhecimento da lei, de respostas adequadas e a objeção de consciência levou a que os CSP falhassem nos seus objetivos. Na Austrália,[7] verificou-se que a falta de formação dos profissionais relativamente à IVG levou à baixa taxa de realização destes procedimentos. Por outro lado, no Canadá[8] foram demonstrados melhores resultados face ao investimento na formação adequada dos profissionais e adoção de estratégias que permitiram garantir respostas atempadas, como por exemplo, o desenvolvimento de protocolos com clínicas para a realização de ecografias de datação.

Conclui-se, portanto, que antes da inclusão dos CSP na realização de IVG, importa ver esclarecidas diversas questões de índole ética, de planeamento de recursos humanos e de acesso aos meios complementares de diagnóstico, bem como investir na formação de todos os profissionais de saúde que estarão envolvidos neste processo.

CONTRIBUTO DOS AUTORES

MCG: Conceptualização e desenho do artigo. Recolha e análise de dados. Redação do artigo. Elaboração e revisão crítica de todos os conteúdos.

RBL: Conceptualização e desenho do artigo. Análise de dados. Elaboração e revisão crítica de todos os conteúdos.

VTP, NB: Conceptualização e desenho do artigo. Análise de dados. Revisão crítica de todos os conteúdos.

CONFLITOS DE INTERESSE

NB recebeu pagamentos individuais da Dr. Share para palestras sobre a COVID-19; recebeu pagamentos individuais da MSD por participar num fórum de peritos sobre a COVID-19; é um membro não remunerado da Assembleia Geral da Associação Portuguesa de Medicina Geral e Familiar (APMGF).

Os restantes autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Long COVID Symptoms in Non-Hospitalised Patients: A Retrospective Study

Sintomas *Long* COVID em Doentes Não Hospitalizados: Um Estudo Retrospetivo

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ABSTRACT

Introduction: The COVID-19 pandemic has presented numerous challenges to healthcare systems. As the number of affected individuals continues to rise, it is crucial to find preventive, diagnostic, and therapeutic approaches. This study aims to describe different COVID-19 sequelae within a Primary Health Care population.

Methods: A retrospective cohort study was conducted in adults diagnosed with COVID-19 from March 2020 to April 2022, excluding pregnant women, minors, nursing home residents, hospitalizations, and deaths. Data was gathered from surveillance records on the Trace COVID-19® platform, a pre-set original questionnaire (which included the Portuguese version of the World Health Organization's Quality of Life Assessment Instrument), and, if needed, patient electronic health records. Information on sociodemographic and clinical characteristics of acute COVID-19 was collected along with long COVID symptoms.

Results: This study included 284 patients, aged 19 to 99 years old. The five most prevalent acute COVID-19 symptoms were fever (50.0%), tiredness (48.2%), myalgias (44.7%), dry cough (37.7%) and odynophagia (36.3%). Symptoms related to the neurological system (23.2%) and tiredness (22.9%) were the most prevalent in long COVID symptoms. Acute tiredness and arthralgia were associated with all long COVID outcomes. The associations between acute COVID-19 symptoms with long COVID outcomes were stronger for anosmia [OR = 5.07, 95% confidence interval (CI) 2.49 - 10.36, $p < 0.001$] on a neurological chapter, acute tiredness for long lasting tiredness (OR = 4.07, 95% CI 2.07 - 8.02, $p = 0.041$), fatigue for muscles and/or bones chapter (OR = 7.55, 95% CI 3.06 - 18.66, $p < 0.001$), tiredness on an endocrine/hormonal chapter (OR = 6.54, 95% CI 2.37 - 18.04, $p < 0.001$), dyspnea for respiratory symptoms (OR = 5.67, 95% CI 1.92 - 16.74, $p = 0.002$) and fever for stomach or intestine symptoms (OR = 8.06, 95% CI 2.55 - 25.47, $p < 0.001$). Almost all quality of life dimensions were negatively associated with the number of long COVID symptoms.

Conclusion: A higher number of acute symptoms, as well as the presence of specific COVID-19 symptoms were associated with reported symptoms ≥ 12 weeks after infection. In the studied population, an increased number of symptoms in both acute and long COVID had a significant negative impact on the perception of overall quality of life. The identification of these relationships could provide a new perspective for post-COVID care.

Keywords: COVID-19/complications; Post-Acute COVID-19 Syndrome; Primary Health Care

RESUMO

Introdução: A pandemia de COVID-19 trouxe desafios aos serviços de saúde. À medida que o número de indivíduos afetados aumenta, é crucial encontrar abordagens preventivas, diagnósticas e terapêuticas. Este estudo tem como objetivo descrever diferentes sequelas de COVID-19 numa população dos Cuidados de Saúde Primários.

Métodos: Estudo de coorte retrospetivo de indivíduos adultos diagnosticados com COVID-19 entre março 2020 e abril 2022, excluindo grávidas, menores, residentes em Estrutura Residencial para Pessoas Idosas, internados e óbitos. Colheu-se informação através da plataforma Trace COVID-19®, um questionário pré-estabelecido (que incluiu a versão portuguesa do Instrumento Abreviado de Avaliação da Qualidade de Vida da Organização Mundial da Saúde) e, quando necessário, registos clínicos dos utentes. Foi obtida informação sobre as características sociodemográficas e clínicas no momento de infeção aguda juntamente com sintomas de *long* COVID.

Resultados: Estudaram-se 284 doentes com COVID-19, entre os 19 e os 99 anos. Os cinco sintomas agudos de COVID-19 mais prevalentes foram febre (50,0%), cansaço (48,2%), mialgias (44,7%), tosse seca (37,7%) e odinofagia (36,3%). Os sintomas relacionados ao sistema neurológico (23,2%) e cansaço (22,9%) foram os mais prevalentes na *long* COVID. Cansaço e artralgia agudos foram associados a todas as situações de *long* COVID. Associações entre sintomas agudos e sintomas de *long* COVID foram maiores entre anosmia e capítulo neurológico [OR = 5,07, intervalo de confiança (IC) 95%, 2,49 – 10,36, $p < 0,001$], cansaço agudo e cansaço prolongado (OR = 4,07, IC 95%, 2,07 – 8,02 p =0,041), fadiga e capítulo músculo/esquelético (OR = 7,55, IC 95%, 3,06 – 18,66, $p < 0,001$), cansaço e capítulo endócrino/hormonal (OR = 6.54, IC 95%, 2,37 – 18,04, $p < 0,001$), dispneia e sintomas respiratórios (OR = 5,67 IC 95% 1,92 – 16,74, $p = 0,002$) e por fim febre e capítulo gastrointestinal (OR = 8,06, IC 95%, 2,55 – 25,47, $p < 0,001$). Quase todas as dimensões da qualidade de vida foram associadas negativamente ao número de sintomas de *long* COVID.

Conclusão: Um maior número de sintomas agudos, bem como a presença de sintomas específicos de COVID-19, foram associados a sintomatologia ≥ 12 semanas após a infeção. Na população estudada, um aumento no número de sintomas, quer na COVID aguda quer na *long* COVID, teve um impacto negativo significativo na perceção da qualidade de vida geral. A identificação dessas relações poderá trazer uma nova perspetiva de cuidados pós-COVID.

Palavras-chave: COVID-19/complicações; Cuidados de Saúde Primários; Síndrome Pós-COVID-19 Aguda

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a multisystem infectious disease caused by the SARS-CoV-2 virus. It was first identified in Wuhan, China,[1] and was declared a global pandemic by the World Health Organization (WHO) on March

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11, 2020.[2] By November 2022, there were 630 million confirmed cases and 6 million deaths worldwide, which included 5.53 million cases and 25 319 thousand deaths reported in Portugal.[2,3] Although many cases of COVID-19 were mild and asymptomatic, approximately 5% of patients developed severe symptoms and became critically ill.[4] Most individuals returned to their baseline health status after acute infection, while some experienced persistent health issues.[5]

Primary Health Care (PHC) in Portugal has been adapting to the COVID-19 pandemic by improving its response to infected patients. Family doctors (FD) have played a crucial preventive role by participating in the country's immunization campaign and monitoring asymptomatic and mild to moderate cases, as well as following up hospitalized patients after discharge.

The Portuguese national health system faces a new challenge, namely the possibility of long-term sequelae in individuals following discharge. To address this, an online national platform called Trace COVID-19® was created to monitor exposed or suspected cases as well as infected individuals. This platform served as a critical tool for storing and analyzing data related to exposed, suspected, and infected individuals, allowing the follow-up of these patients.[6] As with other post-acute coronavirus syndromes, persistent and prolonged effects have been reported after acute COVID-19.[4,5,7] Therefore, it is essential to obtain information on possible sequelae and to define the best diagnostic and therapeutic approaches, in addition to controlling the infection itself.

A WHO-endorsed Delphi consensus has established that individuals with a prior confirmed or probable SARS-CoV-2 infection may develop a post-COVID-19 syndrome. The latter was defined as persistent symptoms and/or delayed/prolonged complications extending beyond 12 weeks that cannot be attributed to an alternative diagnosis.[8,9] It can affect normal functioning due to symptoms such as fatigue, shortness of breath, and cognitive impairment. These symptoms can either emerge after an initial recovery phase from acute COVID-19 or continue from the prior illness. Furthermore, the symptoms can reappear or fluctuate over time.[5] Some studies on individuals with COVID-19 after hospital discharge found that respiratory function and quality of life can be affected by lingering symptoms.[10-12] However, there is limited research on the long-term effects of COVID-19 in patients who did not require hospitalization and were followed up in PHC. This knowledge gap has prompted this study to investigate the chronic sequelae of SARS-CoV-2 infection. In the future, interventions that promote recovery and quality of life (QoL) may reduce the overall socioeconomic costs of long COVID.

The study aimed to identify sequelae of COVID-19 among a population monitored in PHC.

The specific objectives were to:

- Describe individuals infected with SARS-CoV-2 followed up in PHC;
- Describe symptoms in the acute phase;
- Identify and characterize sequelae of SARS-CoV-2;
- Determine the association between acute symptoms and long COVID symptoms;
- Determine the association between COVID-19 and influenza immunization with long COVID symptoms;
- Assess perceived quality of life impairment of long COVID.

METHODS

Study type

Retrospective cohort study carried out at Ria Formosa Family Health Unit (FHU) – Algarve Central Group of Health Centers – Algarve Regional Health Administration (RHA).

Study population

The study population consisted of 4194 individuals who were diagnosed with COVID-19 and followed at Ria Formosa FHU. The Trace COVID-19® platform survey was accessed on July 26, 2022, at 10:49 pm to collect the population data.

Inclusion and exclusion criteria

The inclusion criteria were:

- Individuals aged ≥ 18 years, under clinical surveillance on the Trace COVID-19® platform;
- Time range from March 2020 to April 2022;
- Prior laboratory diagnosis of SARS-CoV-2 by real-time-polymerase chain reaction (RT-PCR) ≥ 12 weeks;
- Informed consent to participate, being able to withdraw at any time. The authors also guarantee the protection of individuals with regard to the processing of personal data;
- Cognitive ability to answer the questionnaires.

The exclusion criteria were:

- Pregnancy;
- Under 18 years of age;
- Resident in nursing home facilities;
- Death;
- Hospital admission for COVID-19;
- Individuals not reachable for follow-up.

Sample size, sample selection and recruitment process

Sample size calculation was performed with G-Power, version 3.1. For the purpose of calculations, the overall QoL continuous variable was selected as a main outcome. Selected parameters for sample size calculation were $\alpha = 0.05$, $\beta = 0.80$, respectively for type I error and statistical power, a

standard deviation of 1 for predictor and independent variable and minimum effect size of 0.17, in this case related to the slope of the linear regression. The minimum sample size that was expected to detect a minimum effect size of 0.17 under these conditions was 266. The magnitude of the effect size was selected after reviewing other studies with similar objectives.[13]

Individuals classified as 'cured' and followed at Ria Formosa FHU, that fit the inclusion criteria, were selected, and were also subjected to a careful and rigorous evaluation of exclusion criteria leading to a total sample population of 2891. This sample was obtained using a website designed for random selection and a total of 300 individuals selected (target number defined by the authors, surpassing the minimum of 266 individuals. The individuals not eligible for follow-up (n = 16) were excluded and the final sample size for the study was 284 patients (Fig. 1).

For those with more than one COVID-19 infection, only the last episode was considered, if the diagnosis by RT-PCR was at least 12 weeks before the time of contact.

Instruments

Information was collected from questionnaires applied at least 12 weeks after the date of diagnosis. Questions included 119 items within four main domains (Table 1) where long COVID symptoms were clustered in chapters, compiled by the International Classification of Primary Care 2 (ICPC-2). One of these domains included the WHOQOL-Bref-Portuguese version of the WHO's Abbreviated Quality of Life Assessment Instrument to assess QoL, validated for the Portuguese population.[14] SClinico®, an electronic health record system used in Portugal, was used as a tool to obtain/confirm additional data (contact information, usual medication, immunization status and chronic diseases). Questionnaires were applied online through email or verbally by telephone through a qualified health worker (physician). The approximate time for completion was 20 minutes.

Information management

A database was created using Microsoft Office 365 Excel®. A code was assigned to each eligible subject, ensuring confidentiality and data protection, according to the Portuguese Law 58/2019, August 8. The storage of the information is foreseen for a maximum period of five years.

The present study was submitted and approved by the Algarve RHA Ethics Committee.

Statistical analysis

Statistical analyses were performed with R, version 4.4.1. and some of the packages used were {stats}, {ggplot2} and {msm}. Descriptive statistics were presented as mean and standard deviation (SD) for continuous variables with symmetrical distribution and median with quartiles, otherwise. Criteria for symmetry was the skewness coefficient [-1, 1] and observation of histograms. Categorical variables were described as frequencies (n) and proportions (%). Reliability was assessed with Cronbach's alpha considering > 0.70 as a criterion for good reliability.[15] Logistic regression models were used for binary outcomes, Poisson regression was used for right skewed discrete (countable) outcomes, namely the total number of long COVID symptoms. Linear regressions with the least squares method were used for continuous outcomes, following the necessary assumptions of residuals normality, independence, and homoscedasticity. All regressions were adjusted to sets of covariates according to each outcome. All independent variables were entered simultaneously in the regression models. Effect sizes were calculated for each type of regression, namely

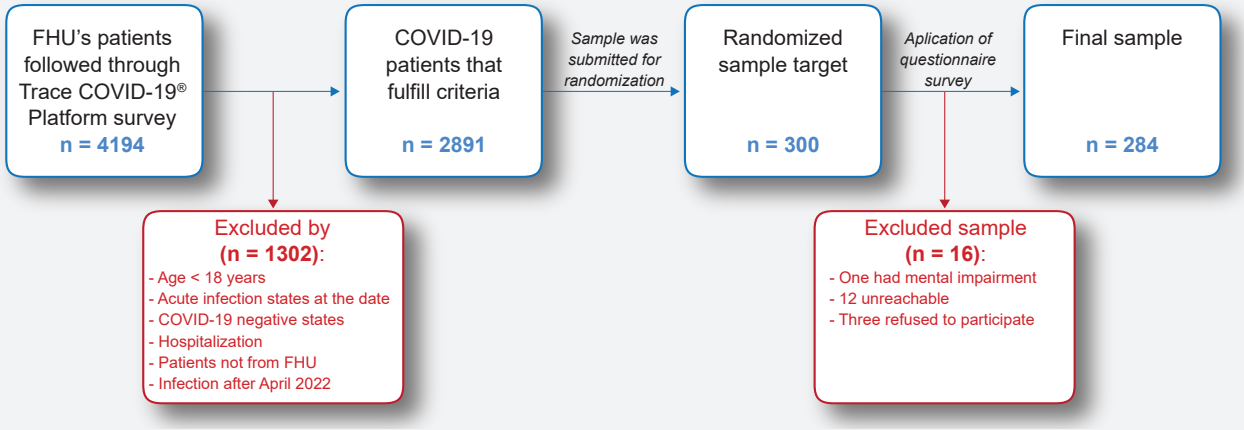

Figure 1 – Study flowchart
FHU: family health unit

Table 1 – Questionnaire main domains (part 1 of 2)

Acute phase		
1 - Social and demographic characteristics, clinical and immunization status (Influenza and COVID-19)		
2 - Acute symptoms: No symptoms, fever, tiredness, myalgias, dry cough, odynophagia, headache, nasal congestion/obstruction, ageusia, anosmia, fatigue, productive cough, arthralgia, diarrhea, nausea, dyspnea, chest pain, vomiting, other symptoms		
Long COVID		
3 - Long COVID symptoms (≥ 12 weeks after acute infection)	Neurological system	Headache Face pain Tingling fingers/feet/toes Sensation disturbance other Convulsion/seizure Abnormal involuntary movements Disturbance of smell/taste Vertigo/dizziness Paralysis/weakness Speech disorder Limited function/disability
	General and unspecified	Tiredness
	Muscles and/or bones	Neck symptom/complaint Back symptom/complaint Chest symptom/complaint Shoulder symptom/complaint Arm symptom/complaint Elbow symptom/complaint Wrist symptom/complaint Hand/finger symptom/complaint Hip symptom/complaint Leg/thigh symptom/complaint Knee symptom/complaint Ankle symptom/complaint Foot/toe symptom/complaint
	Endocrine/hormonal system	Excessive thirst Excessive appetite Loss of appetite Weight gain Weight loss
	Respiratory system	Shortness of breath/dyspnea Wheezing Cough Nosebleed/epistaxis Sneezing/nasal congestion Throat symptom/complaint Voice symptom/complaint Haemoptysis Abnormal sputum/phlegm Fear of respiratory disease, other
	Stomach or intestines	General abdominal pain/cramps Heartburn Rectal/anal pain Dyspepsia/indigestion Flatulence/gas/belching Nausea Vomiting Diarrhea Constipation Jaundice Haematemesis/vomiting blood Melaena Rectal bleeding Incontinence of bowel Changes in faeces/bowel movements Abdominal mass Abdominal distension

Table 1 – Questionnaire main domains (part 2 of 2)

Long COVID		
3 - Long COVID symptoms (≥ 12 weeks after acute infection)	Psychological and/or sexual	Feeling anxious/nervous/tense Feeling depressed Feeling/behaving irritable/angry Senility, feeling/behaving old Sleep disturbance Reduced sexual desire Reduced sexual fulfilment Memory disturbance Fear of mental disorder
	Heart/circulation	Heart pain Pressure/tightness of heart Palpitations/awareness of heart Prominent veins Swollen ankles/oedema Fear of heart disease
	Eyes	Eye pain Red eye Eye discharge Visual floaters/spots Abnormal eye sensation Abnormal eye movements Abnormal eye appearance Eyelid symptom/complaint Fear of eye disease
	Skin	Pain/tenderness of skin Pruritus Lump/swelling Rash Skin colour change Infected finger/toe
	Ears	Ear pain/earache Hearing complaint Tinnitus, ringing/buzzing ear Ear discharge Bleeding ear Clogged ear
	Mouth	Teeth/gum symptom/complaint Mouth/tongue/lip symptom Swallowing problem
4 - WHOQOL-Bref-Portuguese version of the WHO's Abbreviated Quality of Life Assessment Instrument to assess QoL Two weeks prior (date of the survey)		24 items distributed in 4 domains: - Physical health - Psychological health - Social relationships - Environment Two items on overall QoL Score: linear between 0 and 100 (a higher score indicates a better QoL)

odds ratios (OR) for logistic regressions, risk ratios (RR) for Poisson regression and non-standardized coefficients for linear regression (β). Statistical significance was decided for a 95% confidence interval (CI).

The long COVID symptoms were clustered because of the low prevalence in a way to preserve the sampling power.

RESULTS

A total of 284 patients with COVID-19 were enrolled in this study, 168 (59.2%) were female, aged from 19 to 99 years old, mean 46.94 years old (SD = 13.37). Most patients were white (n = 273, 96.1%) and 158 (55.6%) were married or in a common law marriage. More than one third of the sample had a tertiary level of education: a bachelor of science degree (graduation, n = 87, 30.6%) or a master of science degree (post-graduation, n = 23, 8.1%). Body mass index (BMI) ranged from 16.49 to 45.20, mean of 24.75 (SD = 4.11). More than half of the individuals in the study had a BMI classified as normal weight (n = 60, 56.3%). Overweight had a prevalence rate of 28.5% (n = 81) (Table 2).

Table 2 presents the patients' clinical history, the type and distribution of acute symptoms felt during COVID-19 infection, and the perceived long COVID symptoms.

Table 2 – Social and demographic characteristics, clinical and immunization status, type, and number of acute symptoms experienced during COVID-19 infection and long COVID symptoms (part 1 of 2)

Characteristic	n	%
Sex		
Female	168	59.2%
Male	116	40.8%
Age	$\bar{x}$ 46.94	(13.37) [19 - 99]
Race		
White	273	96.1%
Black	4	1.4%
Others	7	2.5%
Marital status		
Single	81	28.5%
Married/common law marriage	158	55.6%
Divorced/separated	29	10.2%
Widowed	16	5.6%
Education		
No education	5	1.8%
4 years of education	26	9.2%
6 years of education	18	6.3%
9 years of education	44	15.5%
Secondary education	81	28.5%
Graduation	87	30.6%
Post-graduation	23	8.1%
BMI (WHO)	$\bar{x}$ 24.75	(4.11) [16.49 - 45.20]
18.5 - 24.9 Normal weight	160	56.3%
< 18.5 Low weight	12	4.2%
25.0 - 29.9 Overweight	81	28.5%
≥ 30.0 Obesity	31	10.9%
Clinical history	**n**	**%**
Current smoking	53	18.7%
Regular physical exercise[a]	116	40.8%
Prevalence of the following diseases[b]		
None	147	51,8%
Cancer	18	6.3%
Diabetes	18	6.3%
Hypertension	64	22.5%
Chronic Kidney Disease	4	1.4%
Neurological diseases	5	1.8%
Psychiatric diseases	15	5.3%
Autoimmune diseases	16	5.6%
Cardiovascular disease	15	5.3%
COPD - Chronic Obstructive Pulmonary Disease	5	1.8%
Asthma	19	6.7%
HIV/Immunodeficiency	1	0.4%
Other	34	12.0%

The most prevalent chronic conditions observed were hypertension (n = 64, 22.5%) and autoimmune diseases (n = 16, 5.6%). Less than one third of the sample had been immunized against the influenza virus in the year before they were infected with COVID-19 (n = 86, 20.3%). A complete immunization schedule before COVID-19 infection was

Table 2 – Social and demographic characteristics, clinical and immunization status, type, and number of acute symptoms experienced during COVID-19 infection and long COVID symptoms (part 2 of 2)

Immunization against influenza the year before COVID-19 infection	**n**	**%**
No	198	69.7%
Yes	86	30.3%
Immunization plan before COVID-19 infection		
Complete immunization plan	145	51.1%
Incomplete	72	25.4%
No	67	23.6%
Type and number of acute symptoms felt during COVID-19 disease	**n**	**%**
No symptoms	30	10.6%
Fever	142	50.0%
Tiredness	137	48.2%
Myalgias	127	44.7%
Dry cough	107	37.7%
Odynophagia	103	36.3%
Headache	89	31.3%
Nasal congestion/obstruction	83	29.2%
Ageusia	58	20.4%
Anosmia	56	19.7%
Fatigue	55	19.4%
Productive cough	45	15.8%
Arthralgia	41	14.4%
Diarrhea	26	9.2%
Nausea	26	9.2%
Dyspnea	21	7.4%
Chest pain	16	5.6%
Vomiting	11	3.9%
Other symptoms[c]	30	10.6%
Number of acute symptoms		
Median = 4.0	P_{25} = 2.0	P_{75} = 6.0
Long COVID symptoms	**n**	**%**
Neurological system	66	23.2%
Tiredness	65	22.9%
Muscles and/or bones	40	14.1%
Endocrine/hormonal system	33	11.6%
Respiratory	31	10.9%
Stomach or intestines	30	10.6%
Psychological and/or sexual	25	8.8%
Heart/circulation	23	8.1%
Eyes	13	4.6%
Skin	10	3.5%
Ears	9	3.2%
Mouth	8	2.8%
Number of long COVID symptoms		
Median = 1.0	P_{25} = 0.0	P_{75} = 2.0

a: 150 min of moderate exercise/week (e.g., walking, dancing, gymnastics) or 75 minutes of intense exercise/week (e.g., running, crossfit);
b: total is not 100% because patients can have more than one disease;
c: other symptoms including abdominal pain, eye pain or vision alterations, loss of appetite, dysgeusia, dizziness, anxiety, excessive sweating, earache, low blood pressure, sleep disorders and toothache.

present in 145 (51.1%) patients (Table 2).

Regarding type and distribution of acute symptoms felt during COVID-19 disease, the five most prevalent symptoms were fever (n = 142, 50.0%), tiredness (n = 137, 48.2%), myalgia (n = 127, 44.7%), dry cough (n = 107, 37.7%) and odynophagia (n = 103, 36.3%). The median of overall number of acute symptoms was 4, ranging from 1 to 20 (P_{25} = 2.0; P_{75} = 6.0).

Table 2 includes the prevalence rate and distribution of long COVID symptoms. The two most frequently reported symptoms were related to the neurological system (n = 66, 23.2%) and tiredness (n = 65, 22.9%). A prevalence rate above 10% was found for muscles and/or bones chapter (n = 40, 14.1%), endocrine/hormonal system (n = 33, 11.6%), respiratory symptoms (n = 31, 10.9%) and stomach/intestines chapter (n = 30, 10.6%). Likewise in the distribution of acute symptoms, an asymmetrical distribution was observed. The median of total long COVID symptoms was 1, ranging from 0 to 9 (P_{25} = 0.0; P_{75} = 2.0).

Reliability results, assessed with Cronbach's alpha showed good internal consistency for all domains assessed with WHOQOL-Bref-Portuguese version. Cronbach's alpha values were 0.79 (Overall QoL), 0.85 (Physical health), 0.83 (Psychological health), 0.74 (Social relationships) and 0.78 (Environment), all above the recommended threshold of 0.70. These and other descriptive results are presented in Table 3.

Table 4 presents results for long COVID symptoms in association with acute symptoms. All the long COVID symptoms considered had a prevalence rate above 10%. Each regression included one acute symptom, up to a prevalence rate higher than 7% (Table 2) in the sample and was adjusted for the following covariates: sex, age, BMI, smoker or non-smoker, regular physical activity, history of cancer, diabetes mellitus (DM), high blood pressure (HBP), chronic kidney disease (CKD), chronic respiratory disease including chronic obstructive pulmonary disease (COPD) and asthma, neurological/psychiatric disease, or cardiovascular disease, influenza vaccine in the year before COVID infection and complete COVID-19 immunization schedule before infection.

Decisions for implementing regressions to assess long COVID outcomes with a prevalence rate of at least 10% in the sample and to include COVID-19 acute symptoms with a prevalence rate higher than 7% were based on the recommendations of Gelman and Hill (2006)[16] to ensure better statistical power. The included 13 covariates respected more conservative criterion of 20 observations per variable.

The main findings presented in Table 4 included acute tiredness associated with all long COVID outcomes, namely neurological system (OR = 4.20, $p < 0.001$), tiredness (OR = 4.07, $p < 0.001$), muscles and/or bones chapter (OR = 5.28, $p < 0.001$), endocrine/hormonal system (OR = 6.54, $p < 0.001$), respiratory system (OR = 3.82, p = 0.006) and stomach/intestines chapter (OR = 3.96, $p = 0.007$). Acute arthralgia was associated with almost all outcomes, namely neurological system (OR = 2.74, $p = 0.012$), tiredness (OR = 2.25, $p = 0.041$), muscles and/or bones chapter (OR = 5.47, $p < 0.001$), endocrine/hormonal system (OR = 3.13, $p = 0.025$) and stomach/intestines chapter (OR = 4.08, $p = 0.003$). The strongest association of each acute COVID-19 symptom with each long COVID outcome were anosmia for neurological system (OR = 5.07, $p < 0.001$), acute tiredness for long lasting tiredness (OR = 2.25, $p = 0.041$), fatigue for muscles and/or bones chapter (OR = 7.55, $p < 0.001$), tiredness for endocrine/hormonal system (OR = 6.54, $p < 0.001$), dyspnea for respiratory symptoms (OR = 5.67, $p = 0.002$) and fever for stomach/intestine chapter (OR = 8.06, $p < 0.001$), the largest effect size of this analysis. Particularly for muscles and/or bones other important effect sizes were arthralgia (OR = 5.47, $p < 0.001$) and tiredness (OR = 5.28, $p < 0.001$) whereas for endocrine/hormonal system was tiredness (OR = 6.54, $p < 0.001$) and diarrhea (OR = 5.86, $p = 0.002$). For stomach/intestine chapter, other large effect sizes were found for diarrhea (OR = 7.32, $p < 0.001$) and nausea (OR = 6.77, $p < 0.001$).

Results of the number of long COVID symptoms associated with the number of acute symptoms and immunization schedules were obtained. These results were adjusted for sex, age, BMI, smoking, regular physical activity, history of cancer, DM, HBP, CKD, chronic respiratory disease (COPD/asthma), neurological/psychiatric disease and cardiovascular disease. The three independent variables of interest: number of acute symptoms, influenza vaccine before COVID-19 infection and COVID-19 immunization schedule

Table 3 – WHOQOL-Bref-Portuguese version descriptive statistics

WHOQOL-Bref-Portuguese version dimensions	Range	M (SD)	Cronbach's alpha
Overall QoL	12.50 - 100.00	71.26 (18.35)	0.79
Physical health	17.86 - 10.00	76.99 (17.23)	0.85
Psychological health	16.67 - 100.00	73.40 (16.58)	0.83
Social relationships	8.33 - 100.00	75.76 (17.36)	0.74
Environment	25.00 - 100.00	72.50 (13.08)	0.78

Table 4 – Long COVID symptoms association with acute COVID-19 symptoms

	Long COVID Binary Outcomes [OR (95% CI) *p*-value]					
Acute COVID-19 symptoms	**Neurological system**	**Tiredness**	**Muscles and/or bones**	**Endocrine/hormonal system**	**Respiratory**	**Stomach or intestines**
Fever	**3.45 (1.80 - 6.61) *p* < 0.001**	1.93 (1.06 - 3.52) *p* = 0.032	1.84 (0.86 - 3.92) *p* = 0.115	2.77 (1.18 - 6.49) *p* = 0.019	2.11 (0.89 - 4.97) *p* = 0.088	**8.06 (2.55 - 25.47) *p* < 0.001**
Tiredness	**4.20 (2.08 - 8.47) *p* < 0.001**	**4.07 (2.07 - 8.02) *p* < 0.001**	**5.28 (2.16 - 12.95) *p* < 0.001**	**6.54 (2.37 - 18.04) *p* < 0.001**	**3.82 (1.47 - 9.97) *p* = 0.006**	**3.96 (1.46 - 10.75) *p* = 0.007**
Myalgias	**2.02 (1.08-3.78) *p* = 0.029**	1.51 (0.82 - 2.78) *p* = 0.184	1.67 (0.76 - 3.68) *p* = 0.199	1.55 (0.69 - 3.52) *p* = 0.289	**3.13 (1.27 - 7.73) *p* = 0.013**	**2.81 (1.15 - 6.86) *p* = 0.023**
Dry cough	1.44 (0.77 - 2.69) *p* = 0.250	0.77 (0.41 - 1.44) *p* = 0.415	1.38 (0.64-2.99) *p* = 0.411	1.23 (0.53 - 2.82) *p* = 0.633	**3.81 (1.52 - 9.52) *p* = 0.004**	**3.33 (1.42 - 7.85) *p* = 0.006**
Odynophagia	**2.24 (1.16 - 4.33) *p* = 0.016**	1.36 (0.72 - 2.55) *p* = 0.339	1.38 (0.61 - 3.11) *p* = 0.435	0.98 (0.41 - 2.34) *p* = 0.963	1.53 (0.65 - 3.59) *p* = 0.325	1.75 (0.74 - 4.11) *p* = 0.202
Headache	1.70 (0.91 - 3.17) *p* = 0.098	**2.19 (1.19 - 4.02) *p* = 0.012**	**2.15 (1.02 - 4.57) *p* = 0.046**	1.21 (0.53 - 2.77) *p* = 0.651	0.75 (0.31 - 1.87) *p* = 0.543	1.61 (0.70 - 3.66) *p* = 0.260
Nasal congestion/obstruction	1.22 (0.63 - 2.35) *p* = 0.549	1.17 (0.62 - 2.22) *p* = 0.628	1.11 (0.49 - 2.48) *p* = 0.803	1.06 (0.44 - 2.56) *p* = 0.896	1.61 (0.68 - 3.81) *p* = 0.277	1.79 (0.76 - 4.20) *p* = 0.182
Ageusia	**4.10 (2.06 - 8.16) *p* < 0.001**	**2.01 (1.00 - 4.04) *p* = 0.050**	0.40 (0.14 - 1.15) *p* = 0.089	1.32 (0.54 - 3.21) *p* = 0.538	1.43 (0.53 - 3.88) *p* = 0.481	1.01 (0.37 - 2.81) *p* = 0.978
Anosmia	**5.07 (2.49 - 10.36) *p* < 0.001**	**2.60 (1.28 - 5.28) *p* = 0.008**	0.50 (0.18 - 1.37) *p* = 0.177	1.38 (0.56 - 3.37) *p* = 0.485	1.25 (0.44 - 3.56) *p* = 0.682	1.11 (0.39 - 3.13) *p* = 0.842
Fatigue	**4.24 (2.02 - 8.87) *p* < 0.001**	0.99 (0.47 - 2.09) *p* = 0.988	**7.55 (3.06 - 18.66) *p* < 0.001**	**6.00 (2.34 - 15.38) *p* < 0.001**	2.25 (0.87 - 5.78) *p* = 0.094	**5.52 (2.22 - 13.70) *p* < 0.001**
Productive cough	1.56 (0.71 - 3.42) *p* = 0.265	1.52 (0.71 - 3.24) *p* = 0.282	0.86 (0.28 - 2.59) *p* = 0.784	0.92 (0.30 - 2.76) *p* = 0.877	2.32 (0.92 - 5.87) *p* = 0.074	0.52 (0.15 - 1.78) *p* = 0.296
Arthralgia	**2.74 (1.24 - 6.03) *p* = 0.012**	**2.25 (1.04 - 4.89) *p* = 0.041**	**5.47 (2.18-13.75) *p* < 0.001**	**3.13 (1.16 - 8.48) *p* = 0.025**	2.24 (0.85 - 5.95) *p* = 0.104	**4.08 (1.60 - 10.39) *p* = 0.003**
Diarrhea	**2.99 (1.18 - 7.58) *p* = 0.021**	1.41 (0.55 - 3.63) *p* = 0.473	2.73 (0.95 - 7.84) *p* = 0.062	**5.86 (1.96 - 17.49) *p* = 0.002**	1.23 (0.35 - 4.32) *p* = 0.743	**7.32 (2.69 - 19.92) *p* < 0.001**
Nausea	**3.32 (1.33 - 8.26) *p* = 0.010**	1.58 (0.64 - 3.95) *p* = 0.323	1.37 (0.45 - 4.19) *p* = 0.576	2.84 (0.92 - 8.73) *p* = 0.069	2.90 (0.96 - 8.82) *p* = 0.060	**6.77 (2.50 - 18.35) *p* < 0.001**
Breathing difficulty	**4.72 (1.66 - 13.44) *p* = 0.004**	1.29 (0.44 - 3.75) *p* = 0.641	2.08 (0.60 - 7.20) *p* = 0.250	3.17 (0.95 - 10.53) *p* = 0.060	**5.67 (1.92 - 16.74) *p* = 0.002**	**5.92 (1.93 - 18.19) *p* = 0.002**

Binary logistic models adjusted for sex, age, BMI, current smoking, regular physical activity, history of cancer, history of DM or HBP, history of chronic kidney disease, history or respiratory disease (COPD or Asthma), history of neurological or psychiatric disease, history of cardiovascular disease, influenza vaccine in the year before getting COVID infection and complete immunization plan before COVID-19 infection; Results presented as aOR (95% CI for aOR) and *p*-value.

were entered simultaneously in a single Poisson regression model after confirming no evidence of multicollinearity between the number of acute and long COVID symptoms. The Spearman correlation coefficient between these two variables was $r_s = 0.44$ ($p < 0.001$), placing the effect size in the low to moderate bound of strength of association. The number of acute COVID-19 symptoms was associated with a higher risk of an increased amount of long COVID symptoms [RR = 1.16, (95% CI 1.12 - 1.19) $p < 0.001$]. A complete COVID-19 immunization schedule was associated with a lower risk of an increased number of long COVID symptoms [RR = 0.73, (95% CI 0.56 - 0.96) $p = 0.022$] while there was no statistically significant association between COVID-19 incomplete immunization schedule and lower risk of increased number of long COVID symptoms [RR = 0.85, (95% CI 0.63 - 1.14), $p = 0.276$]. Influenza immunization was not associated with the number of long COVID symptoms ($p = 0.276$).

Finally, the association between QoL and the number of long and acute COVID-19 symptoms was assessed by conducting a series of linear regressions, one per dimension of QoL, entering simultaneously the number of long and acute symptoms as independent variables and adjusting for sex, age, education, BMI, smoking, regular physical activity, history of cancer, history of DM or HBP, history of CKD, history of chronic respiratory disease (COPD/asthma), history of neurological or psychiatric disease and history of cardiovascular disease (Table 5).

The main findings were that almost all QoL dimensions were negatively associated with the number of long COVID symptoms, suggesting lower QoL for increased number of long COVID symptoms, namely in overall QoL (β = -1.88, $p = 0.003$), physical health (β = -2.24 $p < 0.001$), psychological health (β = -1.94, $p = 0.002$) and environment (β = -2.15, $p < 0.001$). Low overall QoL was also associated with the number of acute symptoms (β = -0.70, $p = 0.049$). The social relationship dimension was not associated with the number of acute or long COVID symptoms.

DISCUSSION

The impact of mild to moderate COVID-19 infection was studied in a sample of 284 patients followed in PHC after confirmed SARS-CoV-2 infection through an RT-PCR test.

The most common symptoms during acute SARS-CoV-2 infection were fever, tiredness and myalgia. Furthermore, a specific group of acute COVID-19 symptoms were associated with more prevalent symptoms ≥ 12 weeks after infection. In particular, anosmia was associated with long-term neurological complaints, acute fatigue with chronic fatigue and endocrine/hormonal dysfunction, dyspnea with respiratory complaints, and fever with gastrointestinal symptoms. A complete COVID-19 immunization plan had demonstrated a protective effect, associated with a decreased risk of long COVID symptoms.

Fever was the most prevalent symptom during acute COVID-19, followed by tiredness, myalgia, and dry cough. These findings align with previous systematic reviews and meta-analyses.[17,18] However, the percentages of reported

Table 5 – Number of long and acute COVID-19 symptoms association with Quality of Life

		Outcome
		General health and overall QoL
Model 1	Number of long COVID symptoms	**-1.88 (-3.11; -0.65), $p = 0.003$**
	Number of acute COVID-19 symptoms	**-0.70 (-1.40; -0.002), $p = 0.049$**
		Physical health
Model 2	Number of long COVID symptoms	**-2.24 (-3.37; -1.10), $p < 0.001$**
	Number of acute COVID-19 symptoms	-0.51 (-1.16; 0.13), $p = 0.117$
		Psychological health
Model 3	Number of long COVID symptoms	**-1.94 (-3.14; -0.74), $p = 0.002$**
	Number of acute COVID-19 symptoms	-0.58 (-1.26; 0.10), $p = 0.095$
		Social relationships
Model 4	Number of long COVID symptoms	-1.12 (-2.47; 0.24), $p = 0.105$
	Number of acute COVID-19symptoms	-0.74 (-1.51; 0.03), $p = 0.060$
		Environment
Model 5	Number of long COVID symptoms	**-2.15 (-3.14; -1.16), $p < 0.001$**
	Number of acute COVID-19 symptoms	-0.39 (-0.95; 0.17), $p = 0.174$

Linear regression models 1 to 5 adjusted for sex, age, education, BMI, current smoking, regular physical activity, history of cancer, history of DM or HBP, history of chronic kidney disease, history or respiratory disease (COPD or Asthma), history of neurological or psychiatric disease and history of cardiovascular disease; Results presented as β (95% CI for β) and *p*-value; β is a non-standardized coefficient; (a) include all symptoms presented in Table 2;
REF: reference category

symptoms differ from previous studies.[19,20] For instance, a recent meta-analysis showed that the percentage of non-hospitalized patients who reported the four most common acute symptoms varied between 52.5% to 71.9%,[18] while the present study ranged from 37.7% to 50.0%. This variation may be due to a potential memory bias since the questionnaire was completed at different periods after the onset of symptoms or a positive RT-PCR test. Additionally, the diversity of viral variants may also contribute to these differences. Nonetheless, the study data supports previous assumptions that the severity of early COVID-19 symptoms is linked to an increased risk of long-term symptoms.[21]

Most studies reveal that the percentage of symptoms progressively decreases with time, and at the time of a 12-week follow up, almost 25% still exhibited at least one symptom.[11,22,23] The present study showed that 52.1% (n = 148) of patients reported symptoms 12 weeks after acute infection. Concerning long COVID, the study presented an asymmetrical distribution regarding the number of symptoms, with some patients reporting no symptoms, while others had up to nine, with a median of one symptom. The results showed that the most common chronic symptoms were related to the neurological chapter (n = 66, 23.2%) and tiredness (n = 65, 22.9%), while other studies identified fatigue, dyspnea, and cognitive symptoms[11,24-26] as well as depression and anxiety symptoms among the most frequently reported problems.[27] Over 10% of individuals in the present study reported muscle and/or bone symptoms (n = 40, 14.1%), endocrine/hormonal chapter symptoms (n = 33, 11.6%), respiratory symptoms (n = 31, 10.9%) and stomach/intestine symptoms (n = 30, 10.6%). According to some systematic reviews, the prevalence rate of these symptoms was higher than that found in the present study.[28,29] In this study, some chronic symptoms were clustered in chapters, making it impossible to compare them with single symptoms. In particular, the neurological chapter showed an overall prevalence rate of 23.2%. Compared with the literature, in long COVID, the prevalence rate of memory loss, forgetfulness, and concentration difficulties was around 17%, while for insomnia and sleep difficulties it was 12%.[30] The prevalence rate of headache (18%), altered sense of smell (14% - 60%) and taste (7% - 11%) in the literature[31] was lower compared to the present study results. The symptom 'tiredness', in the present study, fell within the range already reported in the literature (10% - 87%).[29] Respiratory symptoms (including dyspnea, abnormal breath sounds, cough, sneezing, throat/voice disorders, and nasal congestion) were experienced by 10.9% of participants, showing a lower prevalence rate compared to those found in the literature – dyspnea (4.6% - 24.0%) and cough (18.0% - 74.1%).[32] In the present study, 10.6% of the studied population reported symptoms concerning the gastroenterology chapter. The literature shows a different percentage (19.0% - 36.0%), with anorexia, dyspepsia, abdominal pain, diarrhea and obstipation being the most common symptoms.[18,24,33]

The present study found 37 positive associations between acute COVID symptoms and long COVID outcomes. Certain acute symptoms were linked to experiencing symptoms more than 12 weeks after infection. The causes of long COVID symptoms are still being studied, but recent evidence showed that they can be triggered by an atypical response of the immune system, caused by a prolonged pro-inflammatory response related to SARS-CoV-2 infection, which can affect multiple systems.[32,34-37] This may explain why results revealed acute tiredness and breathing difficulties associated with chronic respiratory symptoms. Similarly, acute tiredness, fever, arthralgia and diarrhea were associated with chronic gastrointestinal symptoms – namely diarrhea and vomiting.[29,34,38] In the case of acute fatigue, tiredness, and arthralgia the strongest association was found for chronic muscles and/or bones related symptoms (all with p-value < 0.001). Regarding chronic endocrine/hormonal complaints during long COVID, the most important effect was found with tiredness, fatigue, and diarrhea during acute COVID. A strong association was found between acute and long-lasting tiredness (p-value < 0.001). Acute neurological symptoms, such as headaches, sensitivity changes, weakness, and speech disorders were found to be strongly associated with long COVID. The correlation observed between the loss of taste and smell during acute infection and neurological symptoms experienced in long COVID provides evidence that the condition persists in the central nervous system.

The present study found that a complete COVID-19 immunization schedule was associated with a lower risk of experiencing an increased number of long COVID-19 symptoms, as compared to one dose only. This enhances the importance of completing the full course of immunization to reduce the risk of long-term effects, as previously reported.[19,39] One study even found that symptoms of long COVID were reduced after the first dose of COVID-19 vaccine.[40]

An increase in the number of symptoms in both acute and long COVID had a significant adverse effect on the overall quality of life, as has been reported for hospital-based studies.[40-44] It is challenging to assess the functional impact, particularly when the baseline state is unknown. Moreover, because there are different methodologies capable of assessing subjective perception, it is difficult to compare the obtained results.[45] When analyzing the different evaluated QoL aspects (environment, physical and psychological health), each one was negatively influenced by the increased number of long COVID symptoms, which was not noticed with acute symptoms. Such discrepancy may be evidence of the influence of long COVID on

long-term QoL, regardless of the severity of the initial infection. No statistically significant results have been obtained in the social dimension.

The difficult ability to discern whether the impact on QoL was due to previous infection with SARS-CoV-2 or new conditions related to their health status, evolution of pre-existing comorbidities or social changes can also provide biased feedback.

Study limitations include the possible lack of control over confounding variables, such as recall bias due to temporal gaps between infection and data collection, despite the consistent findings with other studies on long COVID.

The aim of identifying long-term sequelae of COVID-19 was achieved. Furthermore, the study is innovative in PHC, and the protocol can be applied in other units. In the studied population, an increased number of symptoms of both acute and long COVID had a significant negative impact on the perception of the overall QoL. The identification of the relationships between acute and long COVID symptoms may provide a new perspective to patient care. In fact, the acquired clinical data can be used to plan tighter patient follow-up in the short, medium, and long term, allowing early interventions and facilitating recovery. Additionally, this will enhance action protocols, whose objective is to reduce and/or avoid symptoms in the future.

CONCLUSION

By comparing the symptoms experienced during acute SARS-CoV-2 infections and the ones felt in long COVID, the present study contributes to a more comprehensive understanding of the disease and may help to identify individuals at risk of long COVID, even during the acute phase.

More than half of the patients had symptoms at least 12 weeks after the COVID-19 disease. This study supports the assumption that more symptoms during the acute phase are associated with a higher risk of developing long COVID.

The study serves as an important starting point for further research into the long-term effects of COVID-19 and how they can be mitigated to improve patient outcomes.

AUTHOR CONTRIBUTIONS

AMO, CFC, FL, ICP, JA, RC, RP: Study design, data collection and interpretation, writing and critical review of the manuscript.

EM: Statistic analysis and data interpretation, writing and critical review of the manuscript.

DT, PM, VG: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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The Prevalence of COVID-19 Fog and the Impact on Quality of Life After SARS-CoV-2 Infection (QoL-COVID): A Cross Sectional Study

A Prevalência de COVID-19 Fog e Impacto na Qualidade de Vida da Infeção SARS-CoV-2 (QoL-COVID): Um Estudo Transversal

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ABSTRACT

Introduction: Coronavirus has an impact on both the physical and mental health of individuals. The literature regarding the patient's health status post-SARS-CoV-2 is still scarce with limited data on the prevalence of residual symptoms and quality of life (QoL) after the infection. The aim of this study was to understand the impact of SARS-CoV-2 on patient QoL, and remaining symptoms.

Methods: Single center cross-sectional study of patients who had been admitted to our COVID-19 ward between March 2020 and March 2021. By applying a QoL questionnaire (EQ-5D-5L) we assessed the overall sample, at three time points and in different groups of patients: those admitted to the intensive care unit (ICU) and the elderly.

Results: A total of 125 participants were included in our study. Most patients who were admitted had a severe course of disease (51%), with 22% of admissions to the ICU, with 8% requiring prone ventilation, 10% experiencing thrombotic complications and 18% of nosocomial infections throughout the admission. As for persistent symptoms related with COVID-19 fog, the most frequent were fatigue (57%), memory loss (52%) and insomnia (50%). Regarding QoL, the average decrease was 0.08 ± 0.2 in the index and 8.7 ± 19 in the Visual Analogue Scale (VAS). The QoL index decrease correlated with age, chronic obstructive pulmonary disease, asthma and heart failure, and all persistent symptoms, significantly. QoL VAS correlated significantly with fatigue, mood changes, difficulty concentrating and memory loss. The decrease in QoL and the persistent symptoms remained overall stable over the three time points. The ICU group showed no statistically significant difference in QoL, but the most frequently persistent symptoms were mood changes and attention disturbances. However, the elderly experienced a worsening in QoL expressed by index (0.69 ± 0.3 *vs* 0.8 ± 0.2, *p*-value = 0.01).

Conclusion: A decrease in QoL was observed following SARS-CoV-2 infection, correlating with both chronic conditions and persistent symptoms. The lack of difference through time points of both QoL and persistent symptoms suggests a long-standing effect.

Keywords: COVID-19; Mental Fatigue; Mental Status and Dementia Tests; Patient Reported Outcome Measures; Quality of Life; SARS-CoV-2

RESUMO

Introdução: O coronavírus tem um impacto negativo sobre os indivíduos afetados tanto a nível físico como mental. A literatura sobre o estado de saúde pós SARS-CoV-2 ainda é escassa, com poucos dados sobre a prevalência de sintomas residuais e a qualidade de vida (QoL) após a infeção. O objetivo deste estudo foi compreender o impacto da infeção SARS-CoV-2 na QoL dos doentes e em sintomas residuais.

Métodos: Estudo transversal observacional em doentes admitidos em enfermaria COVID-19 entre março 2020 e março de 2021. Aplicação de um questionário QoL (EQ-5D-5L) com avaliação de toda a amostra, em três pontos temporais e grupos de doentes: admitidos numa unidade de Cuidados Intensivos (UCI) e idosos.

Resultados: Foram incluídos 125 participantes. A maioria foi admitida por curso grave de doença (51%), tendo-se registado 22% admissões na UCI, 8% com necessidade de ventilação ventral, 10% com complicações trombóticas e 18% com infeções nosocomiais. Quanto aos sintomas persistentes associados ao COVID-19 *fog*, os mais frequentes foram fadiga (57%), perdas de memória (52%) e insónia (50%). Em relação à QoL, houve uma diminuição média de 0,08 ± 0,2 no índex e 8,7 ± 19 na *Visual Analogue Scale* (VAS). A diminuição do índex relacionou-se significativamente com a idade, doença pulmonar obstrutiva crónica, asma e insuficiência cardíaca, e todos os sintomas persistentes. O VAS correlacionou-se significativamente com fadiga, alterações do humor, dificuldades de concentração e perdas de memória. A diminuição da QoL e os sintomas persistentes permaneceram estáveis ao longo dos três pontos no tempo. Não se verificaram diferenças estatisticamente significativas na QoL do grupo de UCI, afetado sobretudo por sintomas persistentes relacionados com alterações do humor e perturbações da atenção. Os idosos apresentaram agravamento da QoL segundo o índex (0,69 ± 0,3 *vs* 0,8 ± 0,2, valor-*p* = 0,01).

Conclusão: Observou-se uma diminuição na QoL após a infeção por SARS-CoV-2, correlacionando-se com comorbilidades e sintomas persistentes. A ausência de variação da QoL e sintomas persistentes entre pontos temporais sugere efeito a longo prazo.

Palavras-chave: COVID-19; Fadiga Mental; Medidas de Resultados Relatados pelo Doente; Qualidade de Vida, SARS-CoV-2; Testes de Estado Mental e Demência

INTRODUCTION

The new beta coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in December 2019 in Wuhan, China. Most patients experience mild symptoms, but some could develop a more serious condition, such as pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ failure. The worldwide mortality rate in 2020 was estimated to be 4.1%.[1] In Portugal, on the 22nd July 2021, there had been 943 244 notified

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cases, with 17 248 deaths and an estimated mortality rate of 1.8%.[2] Now that the COVID-19 pandemic has reached its third year, the focus is changing towards the long-term impact of the disease, in particular quality of life (QoL) and COVID-19 fog.[3]

The impact of COVID-19 on quality of life (QoL) has been assessed in a variety of settings. Firstly, in non-infected people that experienced higher levels of anxiety and lower QoL during quarantine, particularly women and the elderly.[4] Secondly, COVID-19 patients that did not require hospitalization also revealed a decrease in QoL compared to the general population, mainly in the domains of mobility and usual activities.[5] As for hospitalized COVID-19 patients, different populations have been evaluated, ranging from those who were clinically stable, to cardiovascular patients with severe complications or patients requiring intensive care unit (ICU) admission. They have all exhibited a lower quality of life,[6,7] that was frequently associated with persistent depression/anxiety.[3,8,9] This decline in QoL has also been reported in Portugal, where patients also exhibited physical and emotional disability.[10] In fact, a neurological condition, which consists of mood change, fatigue, headache, memory impairment, attention disturbances and sleep disorders, has been described as a consequence of COVID-19 disease, defined as COVID-19 fog.[3,7,11–13]

However, there are still some gaps in understanding the QoL deterioration following SARS-CoV-2 infection. For example, the duration or time frame, as most studies focus on up to three months and only in one time point. Also, in certain populations, such as the elderly, QoL has been mostly evaluated in relation to lockdown and quarantine, but not to infection requiring hospital admission.[14,15]

The aim of this study was to assess the prevalence of COVID-19 fog persistent symptoms as well as the impact of SARS-CoV-2 infection in the quality of life of patients admitted to a COVID-19 ward.

METHODS

We performed a cross sectional observational study of patients who had been admitted to our COVID-19 ward between March 2020 and March 2021.

We included patients with SARS-CoV-2 (positive PCR for SARS-CoV-2), within all the spectrum of disease severity, including asymptomatic patients admitted to hospital for other causes. Patients were included if they were admitted to our COVID-19 ward, coming directly from the emergency department, other wards (not dedicated to COVID-19), or ICU. Recruited patients had been admitted at our ward three (3M), six (6M) and 12 (12M) months before. Furthermore, we included all patients who were fluent in Portuguese, and with absence of diagnosed dementia.

We applied a health-related quality-of-life questionnaire (EQ-5D-5L,[16] both Index and Visual Analogue Scale-VAS), that had been translated, validated and with normative values for the Portuguese Population.[17] This QoL questionnaire used for cost-utility and estimation of quality-adjusted life years, assesses five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), at five levels (no problems, slight problems, moderate problems, severe problems and extreme problems). We also evaluated COVID-19 fog using a questionnaire developed by us for assessing persistent symptoms previously described elsewhere (fatigue, mood changes, headaches, attention disturbances, insomnia, and memory impairment) (Fig. 1).[3,11,12]

Finalmente, gostaríamos de lhe perguntar se após a infeção COVID, mantém atualmente algum dos seguintes sintomas (coloque um círculo em redor da opção correta):

1. Fadiga
Sim Não

2. Alterações do humor
Sim Não

3. Dores de cabeça
Sim Não

4. Dificuldades de concentração
Sim Não

5. Dificuldades a dormir/insónias
Sim Não

6. Perdas de memória/esquecimentos
Sim Não

Muito obrigado pelo tempo dispensado a participar no nosso estudo.

Figure 1 – COVID-19 fog persistent symptoms questionnaire

The questionnaires were sent by mail, for self-administration by patients, together with a presentation letter regarding the project, and informed consent form, as well as an envelope for return.

The EQ-5D-5L questionnaire was filled twice, firstly concerning the status before the SARS-CoV-2 infection (pre-test), and secondly regarding the patient's current status (post-test). We used the retrospective test or *thentest* method,[3] which has been shown to be as valid as a prospective method,[4] despite some bias, such as the *recall bias.*[5]

After receiving the patient questionnaires, we collected each patients' information from the medical records: demographics and relevant medical history according to the guidelines of the Directorate General of Health, Portugal's Public Health authority (chronic obstructive pulmonary disease, asthma, heart failure, type 2 diabetes mellitus, cirrhosis, renal failure, obesity, neoplasia, post-solid organ transplant status, and immunosuppression),[18] chronic medication, degree of autonomy for activities of daily living (ADL), according to the KATZ scale, symptoms, cause for hospital admission (COVID-19 disease or other), and severity of SARS-CoV-2 infection. Severity markers such as need for ventilation (both noninvasive and invasive), and prone ventilation, ICU admission, nosocomial infections, and thrombotic complications, need for renal replacement therapy (RRT) and length of stay (LOS) were also collected. Two different LOS were considered: total (from hospital admission to discharge) and SARS-CoV-2 (refers exclusively to time when SARS-CoV-2 infection was considered active). Severity was assessed at admission, according to the guidelines of the Directorate General of Health[18]: asymptomatic, slight, moderate (fever and dyspnea), severe (requiring oxygen) and critical (ARDS or hemodynamic instability).

The study was approved by the Hospital's Ethics Committee and all data was anonymized.

Data was analyzed comparing both the previous and current quality of life, but also according to its difference, both with index and VAS from EQ-5D-5L. We also performed subgroup analysis according to three different time points (three, six or 12 months after SARS-CoV-2 infection), ICU admission and elderly population (65 years old or older).

Continuous data were expressed as mean and standard deviation if they presented a normal distribution and median and interquartile range (IQR), if otherwise. The chi-square or the Fisher exact test were used in the comparison of categorical variables. The *t*-Student test was used for continuous parametric variables and the Wilcoxon test for non-parametric continuous variables. ANOVA was performed for parametric data, when more than two groups were assessed, and Spearman for correlations. We performed the Bonferroni correction if more than two groups were being compared. Logistic regression was performed to account for bias.

Statistical analysis was performed using STATA® (StataCorp. Stata statistical software: release 14. College Station, TX: StataCorp LP). A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 400 patients fulfilled the criteria and were included in the study, out of 478 patients admitted during the study time frame. Letters were sent according to the time frame: 82 to the 3M, 187 to the 6M and 131 to the 12M group. Out of those 400, 125 patients responded: 31 at 3M, 58 at 6M and 36 at 12M post admission, yielding about a 30% response rate (Fig. 2).

Of the 125 participants, 51% were female (n = 64), about 93% were white (n = 116) and 82% (n = 102) were independent in their ADL. Average age was 70 ± 13 years old [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Most patients were admitted due to COVID-19 disease (77%, n = 96), but 29 patients were admitted due to other clinical conditions and tested positive for SARS-CoV-2 infection at hospital admission or during their stay in other hospital wards [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

The most common comorbidities were diabetes mellitus (37%, n = 46), heart failure (22%, n = 27) and obesity (21%, n = 26). Most patients had a severe course of disease (51%, n = 64) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Regarding severity markers: 22% (n = 28) of patients were admitted in the ICU, and 8% (n = 10) required prone ventilation. We present two different lengths of stay: 18.8 ± 13 days total LOS and 14 ± 10 days SARS-CoV-2 LOS. During the admission 10% (n = 13) experienced thrombotic complications and 18% (n = 22) nosocomial infections [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

As for persistent symptoms related with COVID-19 fog, the most frequent were fatigue (57%, n = 71), memory impairment (53%, n = 65) and insomnia (50%, n = 62). Attention disturbances (38%, n = 48), mood changes (30%, n = 37) and headaches (29%, n = 36), although less frequently, were also prevalent (Table 1).

Considering quality of life, the index varied significantly from 0.81 ± 0.26 to 0.73 ± 0.26 (p-value < 0.001), as well

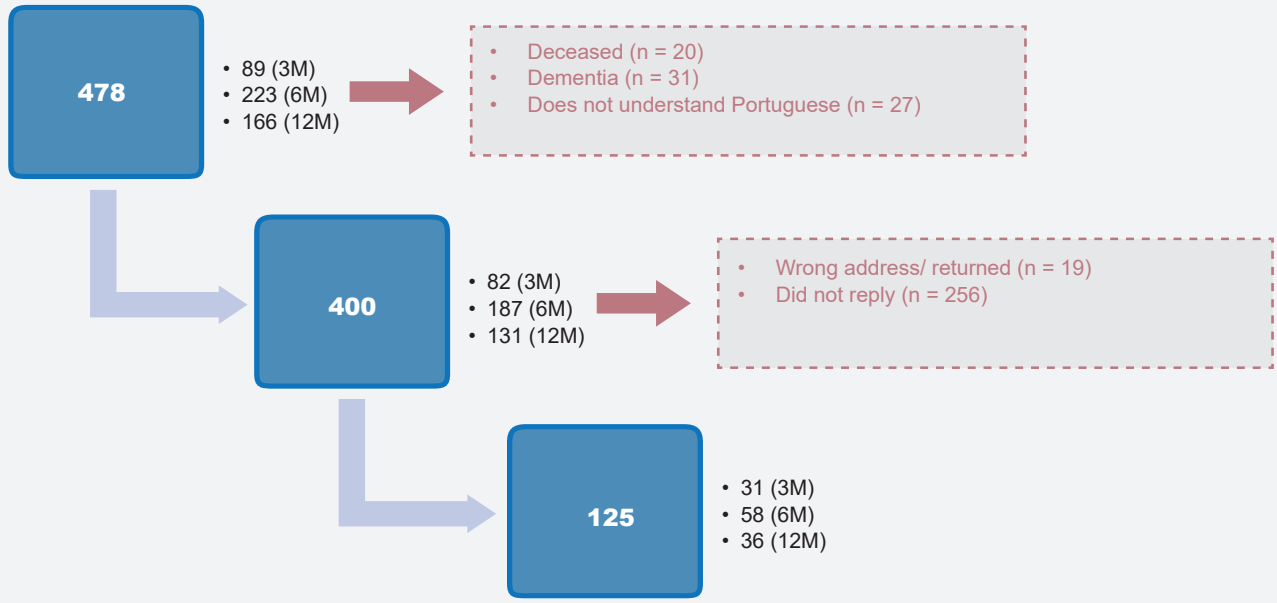

Figure 2 – Flowchart of the study participants

as the VAS from 72 ± 20 to 64 ± 22 (*p*-value < 0.001). The average decrease in QoL was 0.08 ± 0.2 in the index and 8.7 ± 19 in the VAS (Table 2). QoL index decrease correlated significantly with age (r = -0.18, *p*-value < 0.05), COPD (r = -0.24, *p*-value < 0.05), asthma (r = -0.19, *p*-value < 0.05) and heart failure (r = -0.23, *p*-value < 0.05), and all the evaluated persistent symptoms (fatigue: r = -0.33, *p*-value < 0.01; mood changes: r = -0.31, *p*-value < 0.01; headaches: r = -0.2, *p*-value < 0.05; attention disturbances: r = -0.31, *p*-value < 0.01; insomnia: r = -0.24, *p*-value < 0.05; and memory impairment: r = -0.29, *p*-value < 0.01). QoL VAS correlated with fatigue (r = -0.4, *p*-value < 0.01), mood changes (r = -0.24, *p*-value < 0.05), attention disturbances (r = -0.31, *p*-value < 0.01) and memory impairment (r = -0.32, *p*-value < 0.01), but not with age, LOS, comorbidities, or severity markers.

Time point subgroup analysis

As previously mentioned, a total of 31, 58 and 36 patients participated in the 3M, 6M and 12M time points. Demographic data was well-adjusted, with the exception of gender, which showed predominance of the male gender at 3M and 12M (58%, n = 18 and 61%, n = 22), and females at 6M (64%, n = 37). The admission diagnosis and the comorbidity distribution throughout the time points followed the overall distribution. However, there was a difference in SARS-CoV-2 LOS which was higher in the 12M group (12 ± 13 *vs* 12 ± 6.7 *vs* 19 ± 12), *p*-value = 0.007). SARS-CoV-2 severity also varied by time point, with less prevalence of severe disease in this last group (65% (n = 20) *vs* 57% (n = 33) *vs* 31% (n = 11), *p*-value = 0.006). In contrast, ICU admission was also higher at 12 months (19% *vs* 14% *vs* 39%, *p*-value = 0.016), along with mechanical ventilation (19% *vs* 9% *vs* 33%, *p*-value = 0.01) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

COVID-19 fog symptoms were similar throughout the three time points (Table 1). Regarding QoL, there was little difference between the three time points either in index or difference. However, current VAS QoL at 6M was significantly lower, even after Bonferroni *post-hoc* (69 ± 20 *vs* 58 ± 22 *vs* 67 ± 20, *p*-value = 0.039). (Table 2). A logistic regression was performed to adjust for gender and SARS-CoV-2 severity as potential confounders for COVID-19 fog symptoms and QoL as assessed by index and VAS, before, after and difference. As for COVID-19 fog symptoms, headache was affected by both gender and the severity of the infection (*p*-value = 0.003 and 0.008, respectively). Gender was also a confounding factor for VAS before and after the SARS-CoV-2 infection (*p*-value = 0.02 and 0.002, respectively). However, it had no influence on the VAS variation (*p*-value = 0.6).

ICU subgroup analysis

From the 125 patients, 28 (22%) were admitted to the ICU. There was a slight predominance in male gender admissions [64% (n = 18) *vs* 44% (n = 43)], but not statistically significant. There was also a difference in autonomy

Table 1 – COVID-19 fog persistent symptoms: total and by subgroup analysis

COVID-19 fog persistent symptoms	Total	3M	6M	12M	*p*-value	ICU	Ward	*p*-value	Elderly	Young	*p*-value
Fatigue	71 (57%)	15 (48%)	35 (60%)	21 (58%)	0.500	18 (64%)	53 (55%)	0.360	54 (63%)	17 (44%)	0.045
Mood changes	37 (30%)	6 (19%)	19 (33%)	12 (33%)	0.300	15 (54%)	22 (23%)	0.020	25 (29%)	12 (31%)	0.800
Headache	36 (29%)	9 (29%)	16 (28%)	11 (31%)	0.900	10 (36%)	26 (27%)	0.360	26 (30%)	10 (26%)	0.600
Attention disturbances	48 (38%)	11 (36%)	23 (40%)	14 (40%)	0.900	17 (61%)	31 (32%)	0.006	34 (40%)	14 (36%)	0.700
Insomnia	62 (50%)	15 (48%)	31 (53%)	16 (44%)	0.700	14 (50%)	48 (49%)	0.900	39 (45%)	23 (59%)	0.160
Memory impariment	65 (53%)	17 (55%)	29 (50%)	19 (53%)	0.900	17 (61%)	48 (49%)	0.300	45 (52%)	20 (51%)	0.900
n	125	32	58	36		28	97		86	39	

3M: three months; 6M: six months; 12M: 12 months; ICU: Intensive Care unit

status for those admitted to the ICU, for which the majority was independent [96% (n = 27) *vs* 73% (n = 75), *p*-value = 0.02]. Comorbidities were similar between groups, with the exception of heart failure, which was more prevalent in the non-ICU group [7% (n = 2) *vs* 26% (n = 25), *p*-value = 0.03] [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Both admission diagnosis and SARS-CoV-2 severity were different between the two groups: all patients admitted in the ICU had COVID-19 disease [100% (n = 28) *vs* 70% (n = 68), *p*-value < 0.001] and critical condition was the most frequent in this group (82%, n = 23, *p*-value < 0.001). LOS (both total and SARS-CoV-2) was also higher in the ICU group (27 ± 18 *vs* 16 ± 16, *p*-value = 0.02; 21 ± 12 *vs* 12 ± 8, *p*-value < 0.001) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

From the 28 patients admitted to the ICU, 82% (n = 23) required IMV and five patients alone NIMV. A total of eight patients underwent non-invasive ventilation in the ICU compared to the COVID-19 ward [29% (n = 8) *vs* 3% (n = 3), *p*-value < 0.01]. There was a higher prevalence of nosocomial infections in the ICU group (32% *vs* 13%, *p*-value = 0.02) [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Regarding COVID-19 fog symptoms, the results were similar between the two groups, with the exception of mood changes [54% (n = 15) *vs* 23% (n = 22), *p*-value = 0.02] and attention disturbances [61% (n = 17) *vs* 32% (n = 31), *p*-value = 0.006], which were higher in the ICU group (Table 1).

As for the QoL, it didn't seem affected by ICU admission, since the index, VAS and difference were similar in both groups (Table 2).

Considering the statistically significant difference in admission diagnosis between ICU and ward patients, a subanalysis was performed, including only patients admitted due to COVID-19 disease [Appendix 2, Tables 1 and 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15045)]. COVID-19 fog symptoms showed the same distribution, with a statistically significant higher prevalence of mood changes [54% (n = 15) *vs* 22% (n = 15), *p*-value = 0.002] and attention disturbances [61% (n = 17) *vs* 56% (n = 22), *p*-value = 0.01]. QoL remained unchanged with index, VAS and difference alike.

Elderly subgroup analysis

The elderly (over 65 years old) consisted of 69% (n = 86) of our sample. They were overall similar in relation to gender and ethnicity, but they were more dependent in ADL [27% (n = 23) *vs* 0%, *p*-value < 0.001]. Both the elderly and the young had a similar distribution of comorbidities, with the exception of heart failure, which was more frequent in the elderly [28% (n = 24) *vs* 8% (n = 3), *p*-value = 0.01], and post solid organ transplantation status which was less frequent in this group [2% (n = 2) *vs* 13% (n = 5), *p*-value = 0.02] [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Hospital admission for COVID-19 disease [81% (n = 70) *vs* 67% (n = 26), *p*-value = 0.007] was more prevalent in the elderly, but disease severity and severity markers were much the same between the two groups [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18784/15043)].

Considering the COVID-19 fog symptoms, their distribution was comparable between groups, except fatigue, which was higher in the elderly [63% (n = 54) *vs* 44% (n = 17), *p*-value = 0.0045] (Table 1).

Regarding QoL, the only statistically significant difference between the two groups was on the index following SARS-CoV-2 infection, which was lower in the elderly (0.69 ± 0.3 *vs* 0.8 ± 0.2, *p*-value = 0.01). QoL was also lower according to VAS and index and VAS difference, but not statistically significant (Table 2).

Table 2 – Quality of life (index, VAS and difference): total and by subgroup analysis

EQ-5D-5L	Total	*p*-value	3M	6M	12M	*p*-value	ICU	Ward	*p*-value	Elderly	Young	*p*-value
Index before SARS-CoV-2	0.81 ± 0.26		0.80 ± 0.20	0.78 ± 0.30	0.80 ± 0.24	0.700	0.85 ± 0.20	0.79 ± 0.26	0.380	0.78 ± 0.20	0.86 ± 0.23	0.100
Index after SARS-CoV-2	0.73 ± 0.30	< 0.001	0.70 ± 0.30	0.70 ± 0.30	0.75 ± 0.28	0.800	0.76 ± 0.20	0.72 ± 0.29	0.590	0.69 ± 0.30	0.80 ± 0.20	0.010
Index difference	-0.082 ± 0.20		-0.10 ± 0.10	-0.07 ± 0.20	-0.07 ± 0.2	0.770	-0.08 ± 0.16	-0.08±0.2	0.900	-0.10 ± 0.20	-0.03 ± 0.20	0.100
VAS before SARS-CoV-2	72 ± 20		76 ± 15	68 ± 21	76 ± 21	0.090	73 ± 20	72 ± 20	0.700	70 ± 19	76 ± 21	0.100
VAS after SARS-CoV-2	64 ± 22	< 0.001	69 ± 20	58 ± 22	67 ± 20	0.039	65 ± 22	64 ± 22	0.800	62 ± 20	68 ± 23	0.100
VAS difference	-8.74 ± 19.00		-6.00 ± 19.00	-10.00 ± 16.00	-8.00 ± 21.00	0.600	-8.90 ± 22.00	-8.70 ± 18.00	0.900	-10.00 ± 18.00	-5.60 ± 19.00	0.200
n	125		32	58	36		28	97		86	39	

3M: three months; 6M: six months; 12M: 12 months; ICU: Intensive Care unit; VAS: Visual Analogue Score

DISCUSSION

This study's sample included 125 participants, with a response rate of about 30%. Its demographics followed the admission in a ward for SARS-CoV-2 infection as shown in other studies. We reported two different LOS (total and SARS-CoV-2) due to the heterogeneity of patient reasons for admission (admitted due to COVID-19 disease and those who were admitted due to other clinical conditions and tested positive for SARS-Cov-2 at hospital admission, and those who contracted nosocomial SARS-CoV-2 infection) and destination following discharge (those who required physical therapy following infection but still needed isolation). LOS was higher in the latter. In fact, resolution of SARS-CoV-2 infection evolved faster than these other aforementioned- conditions and patients who were stable and able to ensure isolation at home were discharged earlier.

Concerning the COVID-19 fog persistent symptoms, the prevalence in our sample was similar to what is described in previous studies considering fatigue, but it was slightly higher for memory impairment, attention disturbances and insomnia.[3]

Also consistent with other studies, we found a reduction in QoL following SARS-CoV-2 infection, both in Index and VAS. While QoL index correlated both with patient characteristics (age, COPD, asthma, and heart failure) and persistent symptoms, VAS only correlated with some persistent symptoms (fatigue, mood changes, difficulty concentrating and memory loss). Even though worsening of QoL with age had already been suggested,[6] we did not find correlation with other factors described in our study, such as gender and severity markers.[7] Considering the comorbidities, which were correlated with a QoL worsening, we hypothesize that it might be related to a deterioration/decline in the baseline health status.

On the 3-time point subgroup analysis, we observed different SARS-CoV-2-related LOS, which relates to the different definitions of disease duration over the period of our study. Initially, patients required a double negative swab to be considered as cured, and more recently, patients with mild disease were considered cured at seven days, or 20

for severe disease or immunocompromised patients, according to the national guidelines.

We also found different levels of disease severity at admission over the three time points. This resulted from hospital admissions in the 12M group period that were made for monitoring patients with risk factors for severe disease, despite low severity at admission, and patients unable to quarantine. In contrast with an increase of disease severity at admission, severity markers, such as ICU admission and mechanical ventilation, decreased over time, which suggests a positive preventive effect of COVID-19 vaccination.

COVID-19 fog persistent symptoms were similar throughout the three time-points. Nevertheless, headache is confounded by both gender and the disease severity, and therefore those results are not reliable. Despite that, all other persistent symptoms show consistency

Regarding QoL, the results were consistently low through the time period of our analysis. However, there were no differences between the three time points, when considering the index value, even after adjusting for confounding factors (gender and disease severity), showing consistency through time. Even though VAS is affected by gender, which has been reported,[19] its variation is not, which suggests that the change in QoL assessed by VAS is stable over time.

These results suggest that the effects of the disease on QoL and on COVID-19 fog symptoms occur at an early stage and its effects last for up to 12 months.

The ICU group analysis had baseline differences, related to the different populations which were assessed (COVID-19 ward *versus* ICU), which resulted from patient selection for ICU admission regarding their age, comorbidities, and functional status. Furthermore, patients were heterogeneous regarding reason for hospital admission, and all patients admitted to the ICU had COVID-19 disease. Despite the previously described worsening of QoL in patients with ICU admission,[6] our cohort showed no differences between the COVID-19 ward and ICU group, both in index and VAS. Moreover, QoL worsened after hospital admission from SARS-CoV-2 in both groups. Therefore, besides our small subpopulation of ICU admitted patients, we hypothesize that ICU admission might not worsen the already existing deterioration of QoL from SARS-CoV-2, which was not assessed in previous studies, as they only focused on ICU patients. This is consistent with the findings of Garrigues *et al*, in which there was no difference in QoL between COVID-19 ward and ICU patients.[3] Of course, one must not exclude other factors, such as recall bias or the effect of intensive physical therapy and rehabilitation following ICU admission. Conversely, COVID-19 fog persistent symptoms of mood changes and attention disturbances were higher in ICU admitted patients, in contrast with the results of Garrigues *et al*.[3]

Due to heterogeneity of reasons for hospital admission, which could impact our results, we performed a subanalysis only with patients admitted for COVID-19 disease. Still, there was no change between ward and ICU patients in QoL as assessed by EQ-5D-5L index and VAS, contributing to the notion that ICU admission does not increase the QoL worsening from COVID-19. We still observed a higher frequency of COVID-19 fog persistence symptoms (mood changes and attention disturbances) in the ICU admitted patients.

Our elderly subgroup analysis was innovative, as there is lack of data regarding hospital admitted older patients with SARS-CoV-2, and also because there are no previously described correlations of decreasing QoL with age. Both older and young populations were comparable, with the exception of a higher degree of dependency in ADL and a higher prevalence of heart failure in the former. Out of the COVID-19 fog persistent symptoms, only fatigue was higher in the elderly.

Overall, QoL in the elderly was lower compared to the younger population, both in pre- SARS-CoV-2 and after-SARS-CoV-2 situations, but statistical significance was only found in the latter. The two groups differed in the decrease of QoL, both in index (-0.1 *vs* -0.03) and VAS (-10 *vs* -5.6), but it was not significant. The lack of significance can be due to the small size of our sample, but also to the lower QoL at baseline of the elderly group. These are comparable to the findings of Walle-Hansen *et al*, another study performed in the elderly, which showed a decrease in QoL, but no difference between the elderly and the young.[20]

This study has many issues. Firstly, our response rate was only of 30% which, even if expected, decreased our sample size, with particular impact in the subgroup analysis. Secondly, despite its validation, the retrospective method still raises some issues, namely the recall bias. However, this bias will always remain an issue, since its unlikely to have data of QoL of patients prior to their hospital admission. Thirdly, the self-administration component of the questionnaire may have led to missing data, and even some confusion in filling in. Filling in by phone or face-to-face interview could have overcome some of these issues. Fourthly, our sample included all patients with SARS-CoV-2 infection, including those with asymptomatic infection, admitted for other conditions. Although this heterogeneity reduces the strength of our conclusions, this was intentional, because we wanted to have a representative sample. Furthermore, we had issues specific to our sub-analysis. Primarily, our analysis by time-points, being a cross-sectional study, did not evaluate the same patients through time, but different patients at different times following SARS-CoV-2 infection. This could have been overcome if the different

samples had comparable baseline characteristics, which was not the case, with differences in the distribution of gender and disease severity. Therefore, confounder adjustment was performed through logistic regression, improving the robustness of our findings and conclusions. Finally, in the ICU group, the issue with the heterogeneity of the diagnosis (already addressed above) becomes more relevant, because only patients with COVID-19 were admitted. Hence, a sub-analysis was performed and included only patients admitted due to COVID-19 disease.

Nevertheless, we believe that our study has brought some light into some questions regarding long-term effects of SARS-CoV-2 in hospitalized patients, particularly in the elderly group.

CONCLUSION

SARS-CoV-2 infection has a significant impact in QoL, often associated with chronic conditions, and more severe in the elderly. The absence of variation throughout the different time points suggests a long-standing effect, which should be addressed in future studies. Similarly, the persistent symptoms associated with COVID-19 fog have high prevalence and can persist up to one year.

AUTHORS CONTRIBUTION

IF: Study design; data collection; data analysis; draft of the manuscript.

JBF, SD: Data collection; draft of the manuscript.

DDB, JF: Data collection.

VB, HG: Study design; critical review of the manuscript.

AP: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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A Prospective Study of Patients with Persistent Symptoms After SARS-CoV-2 Infection Referred to Physical Medicine and Rehabilitation

Um Estudo Prospetivo de Doentes com Sintomas Persistentes Após Infeção por SARS-CoV-2 Referenciados à Medicina Física e Reabilitação

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ABSTRACT

Introduction: New evidence and extrapolated data from other coronaviruses suggest that symptoms and consequences of COVID-19 may persist beyond the cure. The aims of this study were to evaluate persistent symptoms after SARS-CoV-2 infection and its impact on physical condition, activities of daily living, and quality-of-life; establish whether symptom persistence is associated with higher disability; and document the evolution of the multiple domains after a home exercise program.

Methods: Prospective study with patients referred to a Physical and Rehabilitation Medicine clinic, after SARS-CoV-2 infection. Patient evaluations, including a symptom questionnaire, the 1-Min Sit-to-stand test (1-MSTS), the EQ-5D questionnaire and the London Chest Activity Daily Living (LCA-DL) questionnaire, were performed before and after a home exercise program.

Results: Seventy-four patients were included. The majority (n = 71) had been hospitalized (mean stay 19.66 ± 13.35 days), 51% required intensive care. At first evaluation, 54 days after symptom onset, a mean of 18.6 repetitions in the 1-MSTS were performed. The percentage of LCA-DL was above 28% in 23% of the patients. Impairments on EQ-5D were present in 44% for mobility and 44% for anxiety/depression. Mean EQ-5D VAS was 66.5 out of 100. Fifty-one (70%) had at least one persistent symptom (Symptomatic Group), while 22 (30%) were asymptomatic (Asymptomatic Group). The Symptomatic Group had statistically significantly worse mean results on 1-MSTS (16.8 *vs* 22.9; $p < 0.001$), % LCA-DL score, EQ-D5 (7.8 *vs* 5.7; $p < 0.001$) and EQ-D5-VAS. No patient characteristic, clinical background, comorbidity, or hospitalization characteristics was significantly different between groups. Every patient was given a home exercise program; 47 patients joined an additional rehabilitation program or were clinically discharged and were therefore excluded from the second evaluation. Twenty-seven patients participated in a second evaluation. In the matched analysis, mean 1-MSTS improved by 3.4 repetitions. Mean LCA-DL, mean EQ-5D score (7.1 to 6.6) and EQ-VAS score changed favourably and significantly.

Conclusion: Two months after infection by SARS-CoV-2, persistent symptoms were frequent in patients referred to a Physical Medicine and Rehabilitation clinic. Additionally, the SARS-CoV-2 infection, as well as the persistence of symptoms, had a negative impact in the physical condition and functionality in ADL and quality-of-life. With a home exercise program in place, a statistically significant improvement was observed. Referral of patients with persistent symptoms to Physical and Rehabilitation Medicine may be warranted.

Keywords: Activities of Daily Living; Physical and Rehabilitation Medicine; Portugal; Post-Acute COVID-19 Syndrome; Quality of Life

RESUMO

Introdução: Nova evidência e dados extrapolados de outros coronavírus sugerem que os sintomas e consequências da COVID-19 podem persistir para além da cura. Os objetivos deste estudo foram: avaliar a persistência de sintomas após infeção por SARS-CoV-2 e o seu impacto no condicionamento ao esforço, atividades da vida diária e qualidade-de-vida; estabelecer se a persistência de sintomas condiciona maior incapacidade; e documentar evolução dos vários domínios, após um programa de exercícios domiciliário.

Métodos: Estudo prospetivo, de doentes referenciados à consulta de Medicina Física e de Reabilitação, após infeção por SARS-CoV-2. Foram realizadas avaliações clínicas com questionário de sintomas, o teste 1-Minuto Sentar-e-Levantar (1-MSTS), o questionário EQ-5D e o questionário *London Chest Activity Daily Living* (LCA-DL), antes e após um programa de exercício domiciliário.

Resultados: Setenta e quatro pacientes foram incluídos. A maioria (n = 71) foi hospitalizada (média de 19,7 ± 13,4 dias), 51% necessitaram de cuidados intensivos. Na primeira avaliação, realizada 54 dias após instalação de sintomas, a média de repetições no 1-MSL foi de 18,6. A percentagem de LCA-DL foi superior a 28% em 23% dos pacientes. Alterações no EQ-5D estavam presentes em 44% na mobilidade e 44% para ansiedade/depressão. O EQ-5D VAS médio foi de 66,5 de 100. Cinquenta e um (70%) tinham pelo menos um sintoma persistente (Grupo Sintomático), enquanto 22 (30%) eram assintomáticos (Grupo Assintomático). O Grupo Sintomático teve piores resultados médios no 1-MSL (16,8 *vs* 22,9; $p < 0,001$), % pontuação LCA-DL, EQ-D5 (7,8 *vs* 5,7; $p < 0,001$) e EQ-D5-VAS. Nenhuma das características de paciente, antecedente clínico, característica da doença ou da hospitalização foi significativamente diferente entre os grupos. Todos os pacientes receberam um programa de exercício domiciliário; 47 pacientes integraram um programa de reabilitação adicional ou tiveram alta clínica, pelo que foram excluídos da segunda avaliação. Vinte e sete pacientes foram submetidos a uma segunda avaliação. Na análise emparelhada, o 1-MSL melhorou em 3,4 repetições. O LCA-DL médio, a pontuação média no EQ-5D (7,1 para 6,6) e o EQ-VAS evoluíram favorável e significativamente.

Conclusão: Dois meses após a infeção por SARS-CoV-2, os sintomas persistentes foram frequentes em doentes referenciados para Medicina Física e de Reabilitação. Adicionalmente, a infeção por infeção por SARS-CoV-2, bem como a persistência de sintomas, tiveram impacto negativo na condição física e funcionalidade nas atividades da vida diária e qualidade de vida. Com um plano de exercícios domiciliários implementado, observou-se uma melhoria estatisticamente significativa. O seguimento em Medicina Física e de Reabilitação dos doentes com sintomatologia persistente poderá ser vantajoso.

Palavras-chave: Atividades da Vida Diária; Medicina Física e de Reabilitação; Portugal; Qualidade de Vida; Síndrome Pós COVID-19 Aguda

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INTRODUCTION

The estimated time for COVID-19 recovery is two weeks for moderate disease and six weeks for severe cases.[1] However, new evidence and data from other coronaviruses suggest that symptoms and consequences of COVID-19 may persist beyond the cure.[2,3] The so called 'long COVID', or 'post COVID syndrome' includes a large spectrum of symptoms that linger for two months or more after acute infection, with impact to the patient's life, and that are not explained by an alternative diagnosis.[4,5]

The most consistently reported persisted symptoms are fatigue (35% - 72%) and dyspnoea (29% - 66%). Cough, arthralgia and myalgia are among the others in variable percentages.[3,6-8]

Advanced age, need for hospitalization or Intensive Care (ICU) stay and a high number of comorbidities are considered possible risk factors for slower recovery or symptom persistence.[3,8-13] Nevertheless, it is still undetermined who is at risk of long-term symptoms. Even patients with mild acute disease, with no need for hospitalization, frequently report symptom persistence.[2,11,14]

Like with acute manifestations of COVID-19, long term impact seems to be multisystemic, but the consequences of symptom persistence, or up to what point sequalae are debilitating, are not yet clear.[15,16]

Even in functionally independent patients, persistent symptoms may be limiting and inhibit physical activity, affecting activities of daily living (ADL) and even delaying return to work.[6,8,9,12] These aspects motivate referral to Physical and Rehabilitation Medicine (PRM).

The aim of this study was to evaluate what are the persistent symptoms after SARS-CoV-2 infection and the impact of SARS-CoV-2 in physical condition, ADL, and quality-of-life (QoL), in patients referred to the PRM clinic after SARS-CoV-2 infection.

A second aim was to compare, at the time of the first appointment, both symptomatic and asymptomatic patient groups, in order to perceive if the persistence of symptoms increases restrictions in the physical condition, ADL and QoL. Additionally, characteristics of the symptom-persistent population that may represent risk factors for 'long COVID' will be identified.

The last aim was to evaluate physical capacity, ADL and QoL, in a second appointment, after prescribing of a home-based exercise program, and compare results with the baseline evaluation.

METHODS

Study, design and participants

This prospective study included all COVID-19 patients referred to the Physical and Rehabilitation Medicine clinic, at Hospital Pedro Hispano, Porto, Portugal, with a first appointment between December 2020 and February 2021, after SARS-CoV-2 infection. All patients who were previously autonomous or with modified autonomy were included.

The study was approved by the Ethics Committee for Health of Unidade Local de Saúde de Matosinhos (N.º 12/CES/JAS). All the participants were asked to carefully read and sign an informed consent form. Researchers ensured the confidentiality of study participants and the data collected. The study was conducted according to the criteria set by the Declaration of Helsinki, with pertinent National and International regulatory requirements.

Data collection and clinical evaluation

Demographic data, clinically relevant background and disease related data were extracted from the hospital digital information system. All patients had laboratory confirmation of SARS-CoV-2 infection by real-time PCR methods.

The clinical evaluation included a symptom survey, the 1-Minute Sit-to-Stand test (1-MSTS), to evaluate response to effort, and the application of two clinical surveys – the EuroQol five-dimension questionnaire (EQ-5D), related to QoL, and the London Chest Activity Daily Living questionnaire (LCA-DL), related to dyspnoea during ADL performance.

Symptom survey

Our symptom survey included dyspnoea, cough, fatigue, perceived muscular weakness, myalgia, and arthralgia, among others. It alluded to the most commonly reported symptoms at the time.

Physical condition

The 1-MSTS correlates with inferior limb strength and exercise capacity, and has been applied to different diseases [including chronic obstructive pulmonary disease (COPD)] mainly in the elderly. The exercise consists in getting up from a chair and sitting back, and performing repetitions as fast as possible, within one minute. Sitting and standing from a chair is also an important activity of daily living, and therefore the test also reflects functional status. Values of sit-to-stand capacity are normalized by age and geographic region. And an increase in 3 sit-to-stands represents a minimum clinically meaningful benefit after a rehabilitation program. The test is a validated measure of the functional outcome in COPD patients.[17,18]

Activities of daily living

The London Chest Activity Daily Living questionnaire contains 15 ADL items divided into Personal Care (4 items), Domestic (6 items) Physical (2 items) and Leisure (3 items) sections. The patients report how dyspnoea interferes in

ADL, from 0 - 5, for each activity: 0 (I would not do it anyway), 1 (I have no shortness of breath doing this), 2 (I have a slight shortness of breath), 3 (I have a significant shortness of breath), 4 (I no longer do this) and, 5 (I need help in doing this or someone to do it for me). LCA-DL was recorded as a categorical variable, and the percent LCA-DL score was calculated (with the sum of the patient result divided by the total maximum LCA-DL). LCA-DL categories were considered affected if > 2 points for Physical Activity and > 4 for Personal Care. A score above 28% reflects patients with the worst functional condition.[19] The LCA-DL has a Portuguese validated version for CDOP, which was applied in this study.[20]

Quality-of-life

Health-related quality-of-life was assessed using the EuroQol five-dimension questionnaire (EQ-5D). This is a self-evaluation of QoL based on five sections: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each section is rated from 0 - 3: 0 (no problems), 1 (slight problems), 2 (moderate problems), 3 (extreme problems/unable to perform). Changes in the EQ-5D were considered if the score was > 1, representing a moderate-to-severe attainment. The visual analogue scale (EQ-VAS) is a quantitative measure that estimates the patient self-perception of general health, and the score ranges from 0 (the worst health you can imagine) to 100 points (the best health you can imagine). We applied the EQ-5D Portuguese validated version.[21]

Home exercise program and follow-up

All patients received counselling and a home exercise program (Fig. 1). Patients without any other guided intervention (such as a hospital rehabilitation program) and without clinical criteria for discharge were revaluated in a second appointment, with repetition of the previously described process.

Statistical analysis

Statistical analysis of the collected data was done through the IBM SPSS statistics software version 26.0. Continuous variables were presented as mean (standard deviation) and categorical variables as frequency rates (percentages). A descriptive and comparative statistical

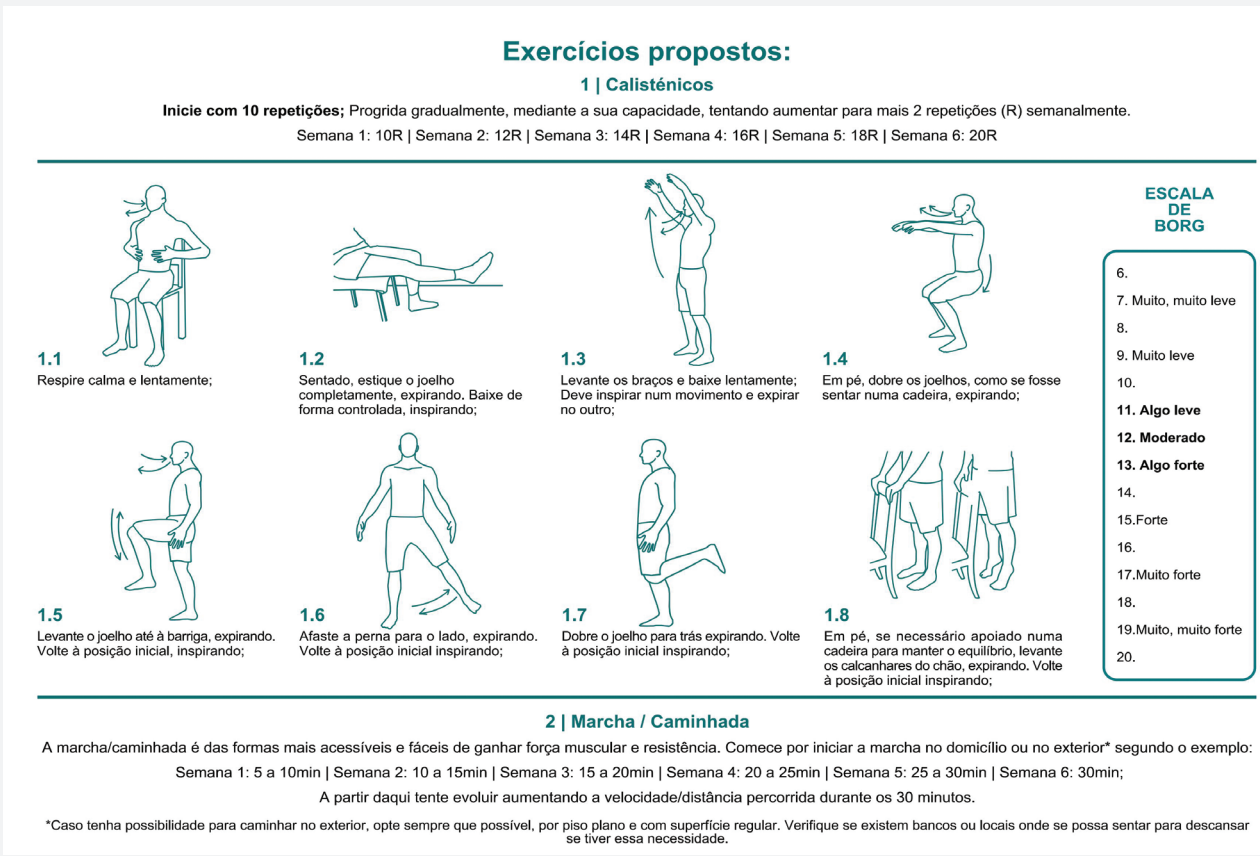

Figure 1 – Home exercise program: "Re-education to effort/Rehabilitation after COVID-19"

analysis was established, between symptomatic and asymptomatic patients, during the first appointment, using the Mann-Whitney-U test for discrete variables, and the chi-square test for categorical variables. Results were also compared between the first and the second appointment by means of the Wilcoxon test, for matched in-patient analysis. *p*-values < 0.05 were considered statistically significant.

RESULTS

First evaluation

Seventy-four patients were included in the study, 66% males, averaging 61.5 ± 13.8 years of age, where 46% were obese. The majority (n = 71) had been hospitalized for a mean duration of 19.7 ± 13.4 days, with 51% needing Intensive Care and 32% requiring invasive mechanical ventilation (IMV) (for an average of 12.0 ± 8.9 days); 42% of patients underwent physiotherapy during the hospitalization period (Table 1).

The first evaluation took place approximately 54 days after symptom onset. From the 74 patients, 52 (70%) had at least one persistent symptom (Symptomatic Group), while 22 (30%) were asymptomatic (Asymptomatic Group).

Fatigue was the most frequently reported symptom, being reported by 54% of patients, followed by cough in 30%, dyspnea in 22%, myalgia in 20% and perceived weakness, thoracalgia and arthralgia in lower percentages (1% to 8%). In the 1-MSTS, an average of 18.61 repetitions were performed, mean oxygen saturation level during physical

Table 1 – Demographic and clinical characteristics of patients referred to the PRM appointment after COVID-19

Demographic and clinical characteristics	**Total n = 74**
Men, n (%)	49 (66%)
Age (years), mean ± SD	61.5 ± 13.8
Relevant clinical background	
Obesity, n (%)	34 (46%)
Diabetes mellitus, n (%)	19 (26%)
Smoker/ex-smoker, n (%)	12 (18%)
Previous pulmonary disease, n (%)	9 (12%)
Previous cardiac disease, n (%)	10 (14%)
Others	
Autoimmune, n (%)	2 (3%)
Neoplasic, n (%)	4 (5%)
	Hospitalized patients n = 71
Time from symptoms to hospitalization (days), mean ± SD	8.3 ± 5.2
In-hospital stay duration (days), mean ± SD	19.7 ± 13.4
Intensive Care, n (%)	51 (72%)
Days in ICU**,** mean ± SD	12.8 ± 11.9
Mechanic ventilation, n (%)	23 (32%)
Days of IMV**,** mean ± SD	12.0 ± 8.9
Lung CT, n (%) (n = 67)	
Typical COVID pattern, NE	6 (9%)
[25, 50[%	21 (33%)
[50, 75[%	27 (40%)
≥ 75%	12 (18%)
Relevant complications, n (%)	
Bacterial infection	17 (24%)
Pulmonary embolism	3 (4%)
Others	7 (10%)
In-hospital physiotherapy (n = 69)	29 (42%)
Time from discharge to 1st evaluation (days), mean ± SD	24.8 ± 15.4

Results were presented as n, (%) or mean ± SD (standard deviation).
ICU: Intensive Care Unit; IMV: invasive mechanical ventilation; CT: computerized tomography.

activity was 94.7 ± 3.2, with a mean modified Borg score of 1.52 and a mean Borg score of 12.36. The average percentage of LCA-DL was 24.9 ± 7.4%. The LCA-DL score was above 28% in 23% of patients. Nineteen patients (31%) reported changes in the LCA-DL Personal Care domain, and 34 (59%) in the Physical Activity domain. The average total score of the EQ-5D survey was 7.14 ± 2.09. Changes in the EQ-5D were present in 44% of patients for Mobility, 30% for Self-care, 41% for Usual Activities, 26% for Pain/Discomfort and 44% for Anxiety/Depression. The average EQ-5D VAS score was 66.5 out of 100.

Symptomatic versus asymptomatic at first evaluation

A comparison between the symptomatic and the asymptomatic groups was then performed on physical condition, ADL, and QoL (Table 2). The Symptomatic Group had the worst results in the 1-MSTS, with 16.8 repetitions, with 22.9 repetitions in the Asymptomatic Group ($p < 0.001$). The score in the LCA-DL was also significantly higher in the Symptomatic Group, 26.4% *vs* 20.9% ($p = 0.034$). Similarly, results for the EQ-D5 and EQ-D5 VAS were substantially worse when persistent symptoms were present, with a score of 7.8 and 63.3 out of 100, respectively in the Symptomatic Group, against 5.7 and 85.1 out of 100 in the Asymptomatic Group ($p < 0.001$).

Table 3 shows the comparison made between the two groups for the study of risk factors in persistent symptoms. The Symptomatic Group showed an average age of 62.3 years and the Asymptomatic Group 59.8 years, with no statistically significant differences. No differences were found in gender distribution. Regarding clinical background, in the Symptomatic Group a larger prevalence rate of obesity, diabetes mellitus, smokers/ex-smokers, previous lung disease and cardiac disease was observed, when compared with the Asymptomatic Group. Regarding hospitalization, 73% of the Symptomatic Group required ICU hospitalization, against 64% in the Asymptomatic Group. However, the differences between the groups were not found to be

Table 2 – Test results and comparison of the symptomatic and asymptomatic groups at 1st appointment

	Symptomatic (n = 51)	**Asymptomatic** (n = 22)	***p*-value**
1-MSTS	16.8 ± 4.9	22.9 ± 5.6	< 0.001
% LCA-DL score	26.4 ± 8.1	20.9 ± 1.5	0.034
EQ-D5	7.8 ± 2.1	5.7 ± 1.3	< 0.001
EQ-D5-VAS	63.3 ± 16.2	85.1 ± 9.3	< 0.001

Results were presented as mean ± SD (standard deviation); the Mann Whitney U test was applied. Note: one patient was excluded from analysis for lack of symptom information. 1-MSTS: 1Minute Sit-to-Stand; LCA-DL London Chest Activity Daily Living; EQ-D5 EuroQol Five-Dimension Questionnaire; EQ-D5-VAS EuroQol Five-Dimension Questionnaire Visual Analogue Scale.

Table 3 – Comparison between the symptomatic and asymptomatic groups for possible risk factors

	Symptomatic n = 51 n (%)	**Asymptomatic** n = 22 n (%)	***p*-value**
Female	19 (37%)	5 (23%)	0.225
Age (years), mean ± SD	62.3 ± 14.1	59.8 ± 13.5	0.340
Age > 50	40 (80%)	15 (68%)	0.277
Obesity	24 (47%)	9 (41%)	0.628
DM	15 (29%)	3 (14%)	0.151
Smoker (active/ex)	10 (20%)	3 (14%)	0.541
Previous pulmonary disease	7 (14%)	2 (9%)	0.580
Previous cardiac disease	7 (14%)	3 (14%)	0.992
Hospitalization duration (days), mean ± SD	18.9 ± 12.6	19.6 ± 15.9	0.567
ICU	37 (73%)	14 (64%)	0.446
ICU stay (days), mean ± SD	8.7 ± 11.5	9.6 ± 12.0	0.765
IMV	18 (35%)	5 (23%)	0.289
IMV duration (days), mean ± SD	3.9 ± 7.6	3.6 ± 7.4	0.507
Lung CT ≥ 50%	26 (60%)	13 (68%)	0.484
Hospitalization complications	22 (43%)	4 (19%)	0.053

Results were presented as n (%) or mean ± SD (standard deviation); the Mann Whitney U test or chi-square test were applied. Note: one patient was excluded from analysis for lack of symptom information. DM: diabetes mellitus; ICU: Intensive Care Unit; IMV: invasive mechanical ventilation; CT: computerized tomography

statistically significant. The duration of hospitalization, duration of stay in ICU and IMV period duration were also not statistically significant in the Symptomatic Group. Lastly, clinically significant complications during hospitalization, such as bacterial superinfection and pulmonary embolism, occurred in 43% of the Symptomatic Group, against 19% in the Asymptomatic Group ($p = 0.053$).

Re-evaluation

At the first evaluation, every patient was given a home exercise program that was adequate to their functional level, with instructions for exercise intensity progression. Twenty-three patients participated in an additional rehabilitation program and 24 were clinically discharged and were therefore excluded from the second evaluation.

Twenty-seven patients were re-evaluated in a second appointment, approximately one month later.

Sixty percent of patients remained symptomatic; once more, fatigue, cough and myalgias were the most frequently reported symptoms (43%, 21% and 18%, respectively). Considering the comparison between the first and the second appointment, the 1-MSTS average improved 3.4 repetitions ($p < 0.001$). The LCA-DL score varied favorably with a 2.02 points ($p = 0.002$) drop. The average result of the EQ-5D survey also had a drop of 0.5 points from 7.1 to 6.6 ($p = 0.002$) and the EQ-D5 VAS improved 5.1 points ($p = 0.001$; the average EQ-VAS score at the second appointment was 74.4). All these variations were considered statistically significant (Table 4).

DISCUSSION

After infection by SARS-CoV-2 about 70% of patients referred to the PRM clinic showed symptom persistence, which is in line with the previously reported values of 60% to 87% from the literature.[2,3]

This study also found a relevant impact that was not so discussed in previous papers, regarding the capacity for physical activity, dyspnea during ADL performance and QoL post SARS-CoV-2 infection. Considering the present population sample, an average of 18.6 repetitions/min was found in the 1-MSTS, when the average level for the elderly is 27 to 30 repetitions/min.[17] Regarding dyspnea's impact in ADL, close to one-quarter of the patients (23%) scored above 28% in the LCA-DL, a cutoff that differentiates patients with a worse functional condition.[19] In both the LCA-DL and the EQ-5D, about one third of patients reported an impact in the Personal Care domain, with an even higher percentage showing changes in Mobility and Physical Activity. Considering the previous literature, these are similar results to those already reported by Halpin *et al*,[8] and higher rates than those reported by Fernandes *et al*,[22] for the Portuguese post-COVID-19 population.

When comparing the Symptomatic and Asymptomatic groups, it was possible to confirm that the persistence of symptoms was associated with a worse physical condition, dyspnoea in ADL and QoL. No patient characteristics, clinical background, characteristic of the disease or the hospitalization analysed in this study help in the differentiation of symptomatic or asymptomatic patients. In contrast with what was previously reported, factors such as sex, old age, obesity or previous pulmonary disease were not risk factors for persistent disease in our population.[11,23,24] Comorbidities such as hypertension, asthma or psychiatric disease, previously highlighted as possible risk factors for long COVID, were not analysed, which is a limitation of this study.[11,23,24]

The relationship between severe COVID-19 and persistent symptoms is poorly established, even though it has been previously reported.[9-13] Other previously studied

Table 4 – Matched comparison of patients' tests results between first and second appointment

n = 27	First appointment	Second appointment	*p*-value
1-Minute Sit-to-Stand			
Mean nr. of repetitions	18.6 ± 5.9	22.0 ± 6.9	< 0.001
Mean 1-MSTS change		**> 3.4**	
LCA-DL			
Mean LCA-DL total score	14.3 ± 6.1	12.1 ± 3.7	0.002
Mean LCA-DL change		**< 2.02**	
% total score LCA-DL (n = 16)	24.9 ± 7.37	23.2 ± 3.56	
EQ-5D			
Mean EQ-5D total score	7.1 ± 2.1	6.6 ± 1.7	0.002
Perceived health [EQ-5D VAS scale]	69.3 ± 17.6	74.4 ± 15.6	0.001
Mean EQ-5D VAS change		**> 5.1**	

Results were presented as mean ± SD (standard deviation); the Wilcoxon test was applied.
1-MSTS: 1-Minute Sit-to-Stand; LCA-DL London Chest Activity Daily Living; EQ-D5 EuroQol Five-Dimension Questionnaire; EQ-D5-VAS EuroQol Five-Dimension Questionnaire Visual Analogue Scale.

factors included ICU admission or need for IMV, these being representative of the severity of the acute disease. In our study, these factors did not seem to influence symptom persistence in the studied population. Therefore, attention should be granted to the possibility of long COVID syndrome, even in the absence of indicators of acute severity in hospitalized patients.

With counselling and a home exercise plan, statistically significant improvements were ascertained in patients with long-term low-to-moderate attainment in every domain. A post-rehabilitation improvement of at least three repetitions in the 1-MSTS and a decrease of around 0.03 in the EQ-D5 score are outlined as minimum clinically meaningful differences.[18,25] As such, the average improvements in physical condition and quality-of-life presented here can be considered clinically relevant.

The main limitations of this study are the reduced size of the study sample, and a selection bias due to the selection channel – only patients referred to the PRM clinic were studied – possibly leading to an underestimation of asymptomatic patients and to a higher representation of hospitalized patients during the acute COVID phase. Moreover, the non-supervision or lack of adhesion surveillance of the home exercise program limits the conclusions of the effect of physical activity in these patients. This might, however, reflect the reality of exercise practice after medical counselling. Another addition is the application of surveys commonly used in chronic obstructive pulmonary disease, but not developed specifically for COVID-19, given the lack of more appropriate tools, even though the 1-MSTS is already widely used in COVID studies.[26]

Predicting which patients could suffer from long-term symptoms remains a challenge. Clinicians should be aware of the possibility of long COVID following acute infection in all patients, regardless of comorbidities or severity of disease. Timely referral to a PRM clinic is pertinent, considering the positive patient evolution in the various domains after counselling with a home exercise program and given the role of the specialty in functionality optimization, exercise prescribing and physical reconditioning.

CONCLUSION

Two months after infection by SARS-CoV-2, persistent symptoms were frequent in patients referred to a Physical Medicine and Rehabilitation clinic. Additionally, the SARS-CoV-2 infection, as well as the persistence of symptoms, had a negative impact in the physical condition and functionality in ADL and quality-of-life.

PREVIOUS PRESENTATIONS AND AWARDS

Presented at the XXI National Congress of Physical Medicine and Rehabilitation, which took place from October 13 to 15, 2021.

AUTHOR CONTRIBUTIONS

JR: Contribution to the design and draft of the work. Analysis and interpretation of data. Draft of the paper. Critical review and final approval of the version to be published.

DD, PA: Contribution to the design and draft of the work. Data collection. Critical review and final approval of the version to be published.

JA, PR: Analysis and interpretation of data. Draft of the paper. Critical review and final approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Predictors of Long-COVID-19 and its Impact on Quality of Life: Longitudinal Analysis at 3, 6 and 9 Months After Discharge from a Portuguese Centre

Preditores da COVID-19 Longa e o seu Impacto na Qualidade de Vida: Análise Longitudinal aos 3, 6 e 9 Meses Após a Alta de um Centro Português

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ABSTRACT

Introduction: Long-COVID-19 impacts health-related quality of life (HR-QoL) but data is scarce. The aim of this study was to describe and prospectively assess the prevalence and risk factors for long-COVID-19 after hospital discharge, and to evaluate its impact on patient HR-QoL.

Methods: Single-centre longitudinal study including all COVID-19 patients discharged between December 2020 and February 2021. Patients were contacted remotely at three, six and nine months. Data were collected as follows: 1) Long-COVID-19 symptoms were self-reported; 2) HR-QoL were assessed using the 3-level EuroQoL-5D (EQ-5D-3L) questionnaire. Pregnant women, demented, bedridden, and non-Portuguese-speaking patients were excluded.

Results: The three-, six- and nine-month assessments were completed by 152, 117 and 110 patients (median age: 61 years; male sex: 56.6%). Long-COVID-19 (≥ 1 symptom) was reported by 66.5%, 62.4% and 53.6% of patients and HR-QoL assessment showed impairment of at least some domain in 65.8%, 69.2% and 55.4% of patients at three, six and nine months, respectively. Fatigue was the most common long-COVID-19 symptom. Anxiety/depression domain was the most frequently affected in all three time-points, peaking at six months (39%), followed by pain/discomfort and mobility domains. Long-COVID-19 was associated with the impairment of all EQ-5D-3L domains except for self-care domain at each time-point. Neither intensive care unit admission nor disease severity were associated with long-COVID-19 nor with impairment of any EQ-5D-3L domain. After adjusting for sex, age, frailty status, and comorbid conditions, long-COVID-19 remained significantly associated with HR-QoL impairment at three (OR 4.27, 95% CI 1.92 – 9.52, $p < 0.001$), six (OR 3.46, 95% CI 1.40 – 8.57, $p = 0.007$) and nine months (OR 4.13, 95% CI 1.62 – 10.55, $p = 0.003$) after hospital discharge. In a longitudinal analysis, patients reporting long-COVID-19 at three months had an EQ-5D-3L index value decreased by 0.14 per visit ($p < 0.001$) compared to those without long-COVID-19 and both groups had a non-significant change in mean EQ-5D-3L index over the nine-month period (time-point assessment, Z = 0.91, $p = 0.364$).

Conclusion: Clinical sequelae associated with long-COVID-19 can persist for at least nine months after hospital discharge in most patients and can impair long-term HR-QoL in more than half of patients regardless of disease severity, and clinicodemographic characteristics.

Keywords: COVID-19; Portugal; Post-Acute COVID-19 Syndrome; Quality of Life

RESUMO

Introdução: Os dados referentes ao efeito da COVID-19 longa na qualidade de vida relacionada com a saúde (QV-RS) são escassos. O objetivo deste estudo foi descrever prospectivamente a prevalência e os fatores de risco associados à COVID-19 longa após a alta hospitalar e avaliar o seu impacto na QV-RS.

Métodos: Estudo longitudinal unicêntrico incluindo todos os doentes com COVID-19 com alta hospitalar entre dezembro de 2020 e fevereiro de 2021. Os doentes foram contactados telefonicamente aos três, seis e nove meses. Os dados foram colhidos da seguinte forma: 1) autorrelato dos sintomas associados à COVID-19 longa; 2) avaliação da QV-RS através do questionário de três níveis EuroQoL-5D (EQ-5D-3L). Excluímos grávidas, doentes dementes, acamados e não-falantes de português.

Resultados: Cento e cinquenta e dois, 117 e 110 doentes foram avaliados aos três, seis e nove meses (idade mediana: 61 anos; homens: 56,6%). A COVID-19 longa (≥ 1 sintoma) estava presente em 66,5%, 62,4% e 53,6% dos doentes, e 65,8%, 69,2% e 55,4% descreveram compromisso da QV-RS (≥ 1 domínio) aos três, seis e nove meses, respetivamente. O sintoma persistente mais comum foi a fadiga. O domínio ansiedade/depressão foi o mais afetado nos três momentos, com pico aos seis meses (39%), seguido pelos domínios dor/desconforto e mobilidade. A COVID-19 longa associou-se ao compromisso de todos os domínios da EQ-5D-3L, exceto ao do autocuidado. Nem a admissão nos cuidados intensivos nem a gravidade da doença se associou à COVID-19 longa nem ao compromisso de qualquer domínio da EQ-5D-3L. A COVID-19 longa permaneceu significativamente associado à diminuição da QV-RS aos três (OR 4,27, IC 95% 1,92 – 9,52, $p < 0,001$), seis (OR 3,46, IC 95% 1,40 – 8,57, $p = 0,007$) e nove meses (OR 4,13, IC 95% 1,62 – 10,55, $p = 0,003$) após ajuste para o sexo, idade, grau de autonomia e comorbilidades. Na análise longitudinal, o índice EQ-5D-3L estava diminuído em 0,14/visita ($p < 0,001$) nos doentes com COVID-19 longa aos três meses em comparação com os assintomáticos, e ambos os grupos mostraram uma variação não significativa do índice EQ-5D-3L durante os nove meses do estudo (Z = 0,91, $p = 0,364$).

Conclusão: As sequelas clínicas associadas à COVID-19 longa podem persistir por pelo menos nove meses após a alta hospitalar e podem comprometer a QV-RS a longo prazo em mais da metade dos doentes, independentemente da gravidade da doença e das características clinicodemográficas.

Palavras-chave: COVID-19; Portugal; Qualidade de Vida; Síndrome Pós-COVID-19

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INTRODUCTION

The COVID-19 pandemic remains a public health concern with an unparalleled health and socioeconomic burden. The short-term outcomes of COVID-19 are still an area of active research and many studies have investigated the clinical characteristics, risk factors, and potential new treatments.[1] Another less studied, albeit equally worrying, aspect of the disease are the long-term consequences following the acute infection, also known as long-COVID-19. The Portuguese Directorate General of Health defines long-COVID-19 as the presence of persistent signs and/or symptoms occurring three months after the acute SARS-CoV-2 infection, lasting for at least two months, and not otherwise explained by alternative causes.[2]

The number of people affected by long-COVID-19 remains uncertain as data regarding its prevalence varies greatly between studies. A recent meta-analysis estimates that the global prevalence of long-COVID-19 is 43%, with regional differences (Asia, 51%; Europe, 44%; and North-America, 31%).[3] There is no published data on the prevalence of long-COVID-19 in Portugal.

The growing body of evidence suggests that long-COVID-19 is a multisystemic condition: prolonged fatigue, dyspnea, cognitive impairment, sleep disturbances, and chronic pain reflect multiorgan involvement.[4] It is well recognized that survivors of severe acute respiratory syndrome (SARS) and middle east respiratory syndrome suffer from long-term physical and psychological consequences leading to decreased health-related quality of life (HR-QoL).[5–9] The effect of COVID-19 on the general health, physical function, and productivity of patients is starting to be clarified and, very recently, a group of investigators from China reported that COVID-19 survivors had not returned to the same health status two years after the acute infection.[10] Nevertheless, little is known about its pathophysiology and the specific impact of persisting COVID-19 symptoms on HR-QoL after the acute infection.

The aim of this study was to describe and prospectively assess the prevalence and risk factors for long-COVID-19 up to nine months after hospital discharge, and to evaluate its impact on patients' HR-QoL.

METHODS

Study design and participants

This longitudinal study was conducted in two phases and included all COVID-19 patients (aged over 18 years old) admitted to a COVID-19 dedicated ward at Hospital Santa Maria, Centro Hospitalar Universitário Lisboa Norte, between December 1st, 2020, and February 28th, 2021. All patients had a positive nasopharyngeal swab test for SARS-CoV-2 by reverse-transcriptase polymerase chain reaction. Asymptomatic SARS-CoV-2 positive patients who had been hospitalized for other reasons and pregnant women were not included. As we aimed to explore the persistence of COVID-19 symptoms and its impact on HR-QoL through a questionnaire (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15050), we did not include those unable to answer independently, non-Portuguese speaking as well as bedridden, demented and mentally impaired patients. There was no readmission during the recruitment period and all patients were unvaccinated against SARS-CoV-2.

The study was approved by the Hospital Santa Maria's ethics committee (Nº132/21) in accordance with the Helsinki Declaration statements. The requirement for written informed consent was waived due to sanitary reasons, but all patients agreed to participate in the study in a verbal, explicit and informed way.

Phase 1: Clinical characterization

Demographics, comorbidities, and clinical data were assessed retrospectively during March 2021. As all authors were actively involved in the medical care of patients, all data were either self-reported by patients and/or extracted from existing clinical records. Data were stored according to the applicable legislation and the anonymity of patients was warranted.

Phase 2: Persisting symptoms and quality of life assessment

We created a telephone questionnaire to collect the post-discharge data regarding the symptoms' persistence and to assess the HR-QoL (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15050). Patients were contacted by trained physicians at three, six and nine months (+/- 2 weeks) after hospital discharge.

Initially, patients were asked if they had been experiencing symptoms attributable to COVID-19 and if so, to shortly describe them. Then, we asked the patients whether they had returned to their previous functional status. HR-QoL was assessed using the Portuguese version of the 3-level EuroQoL-5D (EQ-5D-3L) questionnaire and EuroQoL-Visual Analogue Scale (EQ-VAS).[11] In the EQ-5D-3L, patients had to rate their health state from 1 ("no problem") to 3 ("severe impairment/unable") in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-index was calculated for each patient using the Portuguese EQ-5D-3L value set.[11] As for the EQ-VAS, patients were asked to rate their overall health from 0 ("the worst possible health") to 100 ("the best possible health") at that moment. Patients were asked the same questions in each time-point regardless of their previous

answer and no answer was changed in respect to the previous or a later response.

Definitions

COVID-19 severity was classified using the World Health Organization clinical progression scale.[12] We also classified as severe disease the composite score of intensive care unit (ICU) admission and/or any type of ventilatory support (invasive or non-invasive). The terms "persisting COVID-19 symptoms" and "long-COVID-19" will be used interchangeably. See Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15051) for a detailed description of comorbid conditions and other definitions.

Statistical approach

We used STATA® (version 16) for statistical analysis. Continuous and categorical variables are presented as median [interquartile range (IQR)] and number (%), respectively. Continuous variables were compared using the Student's *t*-test or Mann-Whitney U test after checking for normality, and categorical variables using the chi-square (χ^2) test or the Fisher's exact test when appropriate. We used univariable logistic regression models to explore risk factors associated with long-COVID-19 and with HR-QoL impairment. To investigate the association between long-COVID-19 and HR-QoL, we performed multivariable logistic regression adjusting for demographic characteristics, comorbidities, and severity outcomes. Variables were eligible for multivariable analysis considering their clinical/biologic significance and/or their statistically significant between-group differences and were selected using a stepwise method. Only comorbidities that were present in at least 10% of the cohort were included in the model, hence enhancing the robustness of the effect estimates. A longitudinal analysis was performed to address the changes in the EQ-5D-3L index between patients with and without long-COVID-19 at the first assessment. Patients were censored if they were lost to follow-up. Significance was set as a two-sided α of less than 0.05.

RESULTS

During the study period, 546 patients were admitted to our unit. Of those, 169 (30.9%) died during hospitalization or in the following three months. After excluding demented/bedridden (n = 86), unreachable (n = 108), non-Portuguese speaking patients (n = 4) and those declining to participate (n = 27), 152 patients answered the first telephone questionnaire. During the following three months, 35 patients were lost to follow-up, and later another seven more patients [Appendix 3, Fig 1 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. At the end of the study, 110 patients completed the three time-point questionnaires.

Patient characteristics

The demographic, clinical and laboratory characteristics of all participants are shown in the Appendix 3, Table 1 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052). The median age was 61 (IQR 73 – 52) years, and the majority were men (n = 86, 56.6%). The most common comorbidity was high blood pressure (n = 88, 57.9%), followed by dyslipidaemia (n = 70, 46.1%), obesity (n = 57, 37.8%), and diabetes *mellitus* (n = 50, 32.9%). Depression and/or anxiety was present in 19.7% of patients. The median duration of hospital stay was 12 (IQR 18.5 – 8) days. Fever (75.3%), cough (70.3%), dyspnea (62.4%) and fatigue (52.5%) were the most common presenting symptoms. Only 17 patients (11.2%) did not receive any type of oxygen therapy. Of the remaining, 55 patients (n = 55/135, 40.7%; 36.2% of all patients) required at least one type of ventilatory support, the most frequent being high flow nasal cannula (n = 41, 26.9%). Thirty-six patients (23.7%) were admitted to the ICU with a median stay of 8.5 (IQR 13 – 5.5) days. Most patients (84.9%) were in a good health status before hospitalization [clinical frailty scale (CFS) ≤ 3]. After hospital discharge, the proportion of patients returning to their prior health status increased over time (three months, 69.1%; six months, 72.7%, nine months, 77.3%).

Persisting symptoms

At least one persisting symptom was reported by 66.5%, 62.4% and 53.6% of patients at three, six and nine months after hospital discharge (Fig. 1A).

At three months, the most common persisting symptoms were fatigue (59.2%) and cough/dyspnea (13.8%), both with decreasing prevalence over the follow-up period. The prevalence of pain/discomfort and cognitive disturbances peaked at six months (both 13.7%) but only the latter showed a significant increase from its previous value ($p = 0.008$). At the end of follow-up, more than half of patients still reported at least one symptom, the most frequent being fatigue (42.7%).

Patients were categorized into two groups according to whether they had persistent symptoms or not. Risk factors for long-COVID-19 for each time-point were assessed (Table 1). Neither sex, age, nor CFS were associated with the presence of persisting symptoms. Patients who returned to their pre-hospitalization functional status were consistently less symptomatic at the third [odds ratio (OR) 0.24, 95% confidence interval (CI) 0.10 – 0.59, $p = 0.002$], sixth (OR 0.29, 95% CI 0.11 – 0.76, $p = 0.013$) and ninth (OR 0.21, 95% CI 0.07 – 0.62, $p = 0.004$) month of follow-up. Except for chronic kidney disease (CKD), which was associated

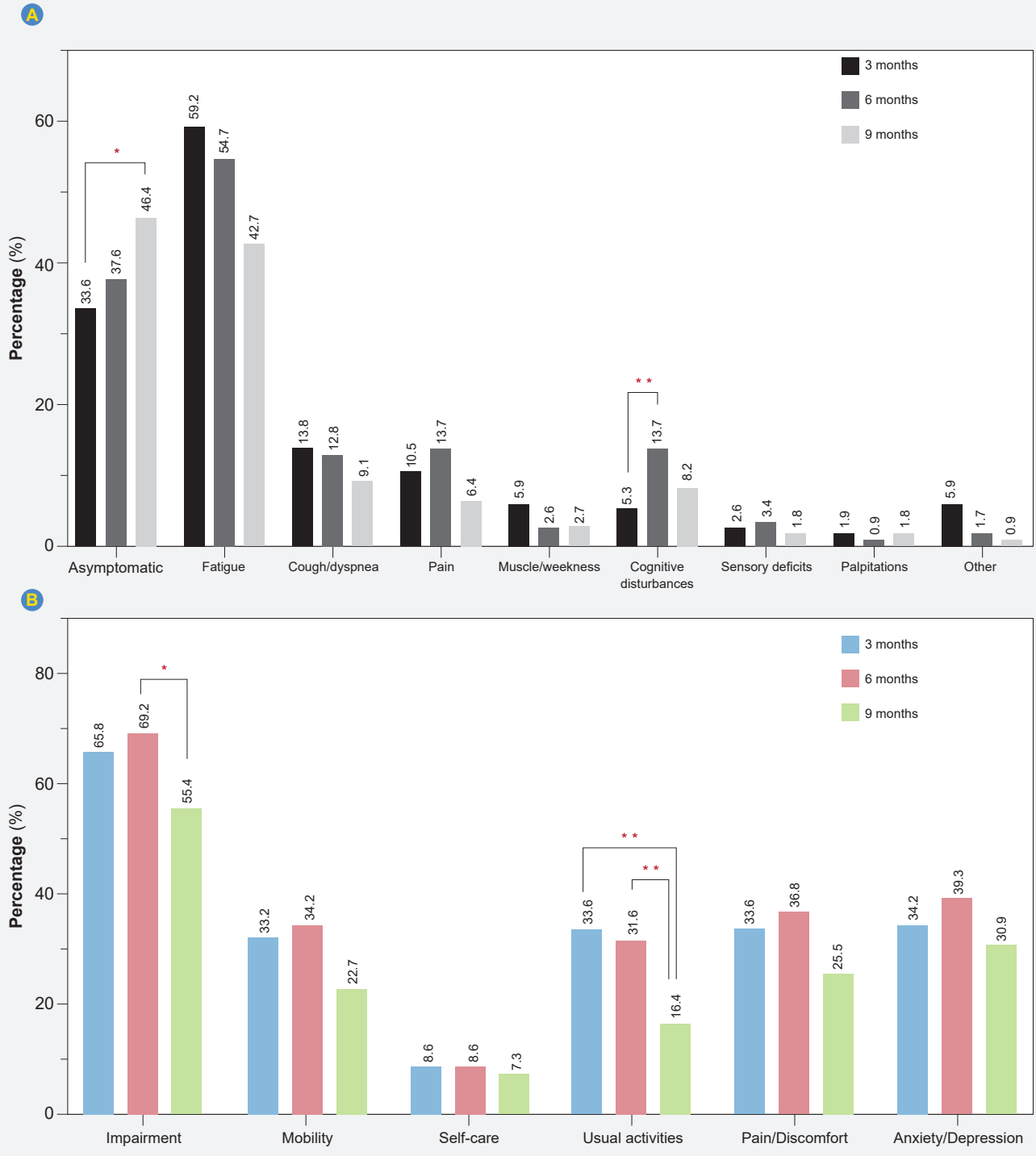

Figure 1 – Proportion of patients reporting (A) persisting symptoms and its specification at three, six and nine months after hospital discharge. Cognitive impairment included foggy brain, memory lapses, concentration difficulty. Sensory deficits included both taste and/or smell disturbances. Other symptoms included all the following: dizziness, postural imbalance, cold extremities/limb paresthesia, wheezing, hair loss; and (B) some degree of impairment in the EQ-5D-3L questionnaire at three, six and nine months after hospital discharge.

*$p < 0.05$; **$p < 0.010$

with a decreased probability of having persisting symptoms, none of the remaining pre-existing comorbidities were associated with long-COVID-19 at the three time-points. Neither the ICU nor in-hospital length of stay was associated with long-COVID-19. Severe disease was not associated with long-COVID-19 throughout the study. This is echoed by the WHO clinical progression scale, whose median value (5, IQR 5 – 5) did not differ between symptomatic and asymptomatic patients at the three time-points. See Appendix 3, Table 2 (Appendix 3: https://www.actamedicaportuguesa.

Table 1 – Univariate logistic regression for persisting symptoms at three, six and nine months after hospital discharge (section 1 of 2)

	Three months		Six months		Nine months	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographics						
Male sex	0.53 (0.26 – 1.07)	0.076	0.53 (0.24 – 1.13)	0.101	0.50 (0.23 – 1.08)	0.076
Age[a]	0.99 (0.97 – 1.02)	0.718	1.00 (0.97 – 1.02)	0.971	1.00 (0.97 – 1.03)	0.883
CFS[a]	0.89 (0.62 – 1.28)	0.518	0.87 (0.58 – 1.31)	0.505	0.83 (0.55 – 1.26)	0.390
Return do previous CFS	0.24 (0.10 – 0.59)	**0.002**	0.29 (0.11 – 0.76)	**0.013**	0.21 (0.07 – 0.62)	**0.004**
Comorbid conditions						
Cardiovascular disease	1.26 (0.63 – 2.49)	0.512	0.90 (0.42 – 1.94)	0.793	0.75 (0.35 – 1.62)	0.469
High blood pressure	1.07 (0.54 – 2.11)	0.855	0.81 (0.38 – 1.73)	0.581	0.76 (0.36 – 1.64)	0.489
Heart failure	0.51 (0.19 – 1.36)	0.178	0.33 (0.10 – 1.09)	0.068	0.14 (0.03 – 0.69)	**0.016**
Ischaemic heart disease	1.01 (0.33 – 3.12)	0.985	0.74 (0.19 – 2.89)	0.660	0.67 (0.17 – 2.64)	0.566
Dyslipidemia	0.94 (0.48 – 1.85)	0.860	1.15 (0.54 – 2.44)	0.721	0.89 (0.42 – 1.88)	0.753
Cerebrovascular disease	0.74 (0.20 – 2.76)	0.656	1.54 (0.29 – 8.32)	0.613	1.16 (0.25 – 5.46)	0.848
Obesity	1.03 (0.51 – 2.07)	0.929	0.78 (0.37 – 1.66)	0.524	0.99 (0.47 – 2.13)	0.997
Diabetes mellitus	0.65 (0.32 – 1.33)	0.240	0.58 (0.27 – 1.28)	0.179	0.68 (0.31 – 1.50)	0.339
Lung disease	1.46 (0.66 – 3.24)	0.346	1.47 (0.62 – 3.48)	0.385	1.86 (0.79 – 4.40)	0.154
Depression /anxiety	1.23 (0.52 – 2.92)	0.646	0.88 (0.36 – 2.17)	0.781	0.83 (0.33 – 2.12)	0.702
Chronic kidney disease	0.39 (0.16 – 0.94)	**0.036**	0.22 (0.07 – 0.67)	**0.009**	0.26 (0.08 – 0.89)	**0.032**
Osteoarthritis	1.63 (0.60 – 4.39)	0.337	1.25 (0.43 – 3.60)	0.684	1.88 (0.60 – 5.91)	0.281
Hypothyroidism	5.49 (0.68 – 44.17)	0.109	2.58 (0.52 – 12.77)	0.244	7.84 (0.95 – 65.03)	0.056
Chronic liver disease	1.82 (0.37 – 9.12)	0.464	4.56 (0.54 – 38.38)	0.163	1.48 (0.34 – 6.53)	0.603
Autoimmune disease	3.72 (0.45 – 31.12)	0.225	3.16 (0.36 – 27.99)	0.301	4.63 (0.52 – 41.0)	0.169
Active solid cancer	0.36 (0.08 – 1.67)	0.192	0.59 (0.08 – 4.36)	0.606	1.75 (0.15 – 19.93)	0.650
Active hematologic cancer	1.28 (0.24 – 6.82)	0.776	1.54 (0.29 – 8.32)	0.613	2.27 (0.42 – 12.23)	0.341

Table 1 – Univariate logistic regression for persisting symptoms at three, six and nine months after hospital discharge (section 2 of 2)

	Three months		Six months		Nine months	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Clinical manifestations						
Fever	1.66 (0.80 – 3.44)	0.175	2.07 (0.92 – 4.68)	0.079	1.75 (0.76 – 4.02)	0.185
Cough	1.94 (0.97 – 3.90)	0.062	1.65 (0.76 – 3.58)	0.204	1.73 (0.78 – 3.82)	0.176
Dyspnea	1.47 (0.75 – 2.91)	0.265	1.09 (0.50 – 2.40)	0.816	1.59 (0.73 – 3.50)	0.245
Fatigue	1.46 (0.74 – 2.87)	0.278	1.23 (0.58 – 2.61)	0.584	0.80 (0.38 – 1.70)	0.566
Myalgia/arthralgia	1.90 (0.94 – 3.87)	0.075	1.53 (0.71 – 3.29)	0.281	1.13 (0.53 – 2.40)	0.760
Chest pain	1.30 (0.55 – 3.07)	0.551	0.67 (0.26 – 1.71)	0.401	1.07 (0.40 – 2.83)	0.892
Diarrhea	0.84 (0.37 – 1.94)	0.687	1.37 (0.51 – 3.67)	0.535	1.52 (0.57 – 4.02)	0.400
Headache	1.55 (0.61 – 3.96)	0.357	1.25 (0.46 – 3.40)	0.656	1.37 (0.51 – 3.68)	0.529
Nausea/vomiting	1.01 (0.36 – 2.87)	0.983	0.58 (0.14 – 2.45)	0.458	0.49 (0.11 – 2.17)	0.350
Dysgeusia	0.58 (0.17 – 2.00)	0.390	0.79 (0.17 – 3.72)	0.768	0.86 (0.16 – 4.45)	0.854
Anorexia	0.13 (0.03 – 0.64)	0.012	0.38 (0.06 – 2.40)	0.307	0.20 (0.02 – 1.87)	0.160
Anosmia	0.36 (0.08 – 1.67)	0.192	0.90 (0.14 – 5.61)	0.910	1.31 (0.21 – 8.18)	0.771
Odynophagia	1.01 (0.18 – 5.71)	0.991	1.21 0.11 – 13.76	0.877	1.75 (0.15 – 19.93)	0.650
Hospitalization and outcomes						
Time since disease onset and hospital admission (days)	1.11 (1.01 – 1.21)	**0.037**	1.09 (0.99 – 1.21)	0.087	1.09 (0.99 – 1.21)	0.079
Hospital length of stay (days)	1.01 (0.98 – 1.05)	0.518	1.03 (0.99 – 1.07)	0.212	1.01 (0.98 – 1.05)	0.509
ICU admission	1.42 (0.62 – 3.24)	0.402	1.70 (0.67 – 4.27)	0.261	1.66 (0.68 – 4.05)	0.266
ICU length of stay (days)	1.06 (0.93 – 1.20)	0.414	1.06 (0.92 – 1.23)	0.427	1.03 (0.90 – 1.17)	0.684
High flow nasal cannula	2.16 (0.94 – 4.98)	0.069	2.34 (0.95 – 5.80)	0.065	1.67 (0.72 – 3.87)	0.234
Non-invasive ventilation	1.12 (0.37 – 3.43)	0.837	1.24 (0.39 – 3.89)	0.715	2.40 (0.70 – 8.18)	0.162
Endotracheal intubation	1.89 (0.59 – 6.07)	0.284	2.17 (0.56 – 8.36)	0.260	1.84 (0.52 – 6.52)	0.343
Ventilatory support	1.81 (0.87 – 3.76)	0.114	2.08 (0.93 – 4.67)	0.076	2.03 (0.92 – 4.46)	0.080
Severe disease[b]	1.71 (0.83 – 5.51)	0.145	1.97 (0.89 – 4.36)	0.095	1.98 (0.90 – 4.32)	0.088
WHO ordinal scale	1.30 (0.83 – 2.04)	0.254	1.48 (0.85 – 2.59)	0.168	1.37 (0.83 – 2.24)	0.216

Data are shown as odds ratio (OR) and 95% confidence interval (CI).
[a] Per one-unite increase OR.
[b] Severe disease was defined as ICU admission rate and/or need for any kind of ventilatory support (invasive or non-invasive) during the in-hospital stay.
See Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15051) for further detail on comorbid conditions and outcomes' definitions.
CFS: clinical frailty scale; HIV: human immunodeficiency virus; ICU: intensive care unit; WHO: World Health Organization.

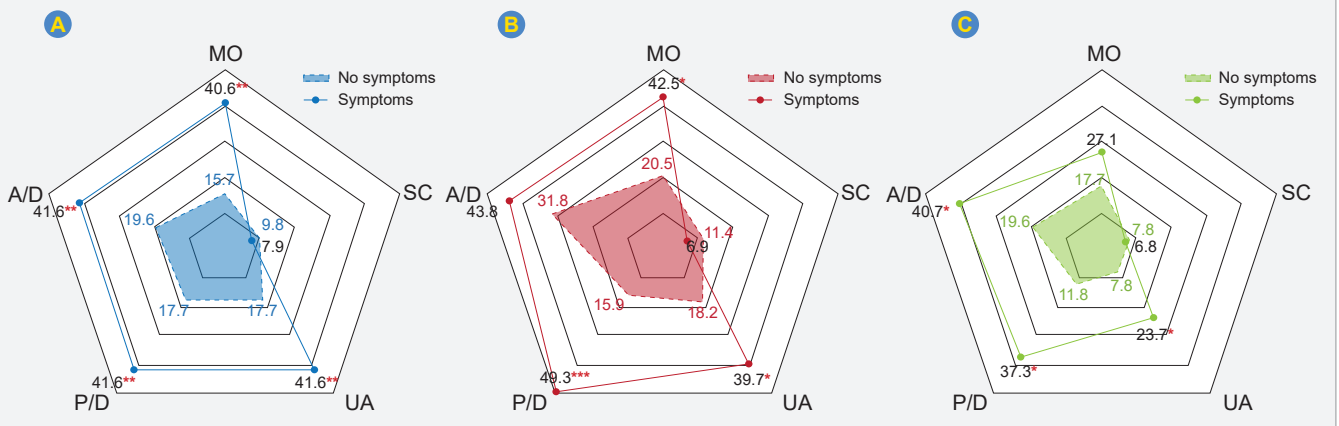

Figure 2 – Distribution and comparison of the proportion of patients reporting EQ-5D-3L domain impairment between patients who did and did not report persisting symptoms at three (A), six (B) and nine (C) months after hospital discharge.
A/D: anxiety/depression; MO: mobility; P/D: pain/discomfort; SC: self-care; UA: usual activities.
*$p < 0.050$; **$p < 0.010$; ***$p < 0.001$

com/revista/index.php/amp/article/view/19047/15052) for detailed comparison between the designated groups.

Quality of life assessment

At three months, 65.8% had at least some impairment (level ≥ 1: moderate or severe impairment) in some EQ-5D-3L domain. This proportion slightly increased at six months (69.2%) but then suffered a significant reduction ($p = 0.032$) towards the end of the study (55.4%) (Fig. 1B).

Impairment on the anxiety/depression domain was the most frequently reported in all three time-points, peaking at six months (39.3%). We observed the same trend in the pain/discomfort and mobility domains. The impairment of all these domains showed a decreased frequency at the end of the follow-up, even though the difference was not statistically significant. Only the proportion of impairment of usual activities, reported by nearly one third (33.6%) of patients in the initial assessment, showed a significant decrease between successive time-point assessments.

Three months after hospital discharge (Fig. 2A), the proportion of patients reporting mobility, usual activities, pain/discomfort, and anxiety/depression impairment was significantly higher among patients with long-COVID-19 compared to asymptomatic patients (all $p < 0.010$). This pattern stayed approximately stable over time as the differences in the proportion of each EQ-5D-3L domain impairment (except for mobility) remained statistically significant between patients with and without long-COVID-19 (Fig. 2C), except for the anxiety/depression domain whose difference was lost at six months due to an increase in the proportion of impairment among asymptomatic patients. Self-care impairment was similarly reported between groups throughout the study.

In an univariable logistic regression model (Table 2) the presence of long-COVID-19 at each time-point was significantly associated with the impairment of all EQ-5D-3L domains throughout the study [OR (95% CI) ranging from 2.81 (1.18 – 6.67), $p = 0.019$ for anxiety/depression domain at nine months; and 5.14 (2.03 – 13.02), $p = 0.001$ for pain/discomfort domain at six months] except for the self-care domain. Being male was associated with lower odds of impairment of all EQ-5D-3L domains, but only reached statistical significance in the mobility domain at three months ($p = 0.047$), pain/discomfort at six months ($p = 0.002$) and anxiety/depression at three ($p = 0.011$) and six ($p = 0.004$) months. Increasing age was associated with compromised mobility at all three time-points and with pain/discomfort at six (per one-unit increase OR 1.03, 95% CI 1.00 – 1.06, $p = 0.041$) and nine months (per one-unit increase OR 1.06, 95% CI 1.02 – 1.10, $p = 0.002$), and it showed a non-significant positive correlation with all other domains throughout the follow-up period. Increasing CFS was associated with mobility impairment at all time-points and with self-care disability at six and nine months after discharge. Noteworthy, patients who returned to their previous health status had consistent and statistically significant decreased odds of impairment in all EQ-5D-3L domains at all time-points.

Regarding previous comorbidities, osteoarthritis and lung disease were the ones that most frequently showed statistically significant between group differences in all EQ-5D-3L domains [Appendix 3, Tables 3 to 7 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. The presence of osteoarthritis was associated with mobility, self-care and pain/discomfort domains, and lung disease with mobility, usual activities, and anxiety/depression domains impairment

Table 2 – Univariate logistic regression for all EQ-5D-3L domains impairment (moderate to severe) at three, six and nine months after hospital discharge

	M	Long-COVID-19[a]	Male sex	Age	CFS	Return to previous CFS
MO	3	3.67 (1.57 – 8.62)**	0.49 (0.25 – 0.99)*	1.05 (1.02 – 1.08)**	2.17 (1.44–3.29)***	0.15 (0.07 – 0.31)***
	6	2.87 (1.21 – 6.83)*	0.68 (0.32 – 1.46)	1.04 (1.01 – 1.08)**	2.00 (1.26 – 3.16)**	0.12 (0.05 – 0.30)***
	9	1.74 (0.69 – 4.36)	0.92 (0.38 – 2.24)	1.05 (1.01 – 1.09)*	2.26 (1.33 – 3.82)**	0.32 (0.12 – 0.85)*
SC	3	0.79 (0.25 – 2.55)	1.25 (0.39 – 4.02)	1.08 (1.02 – 1.14)**	1.53 (0.84 – 2.78)	0.11 (0.03 – 0.42)**
	6	0.57 (0.16 – 2.11)	0.84 (0.23 – 3.09)	1.03 (0.98 – 1.09)	2.60 (1.24 – 5.45)*	0.13 (0.03 – 0.54)**
	9	0.85 (0.20 – 3.61)	1.48 (0.34 – 6.53)	1.03 (0.98 – 1.09)	2.88 (1.27 – 6.52)*	0.15 (0.03 – 0.66)*
UA	3	3.32 (1.46 – 7.55)**	0.63 (0.32 – 1.24)	1.01 (0.96 – 1.04)	1.81 (1.22 – 2.67)**	0.22 (0.11 – 0.46)***
	6	2.97 (1.21 – 7.28)*	0.45 (0.21 – 1.01)	1.02 (0.99 – 1.05)	1.48 (0.96 – 2.28)	0.08 (0.03 – 0.20)***
	9	3.66 (1.12 – 11.94)*	0.84 (0.31 – 2.31)	1.01 (0.98 – 1.05)	1.42 (0.82 – 2.44)	0.11 (0.04 – 0.34)***
P/D	3	3.32 (1.46 – 7.55)**	0.56 (0.28 – 1.10)	1.02 (0.99 – 1.04)	1.17 (0.81 – 1.68)	0.43 (0.21 – 0.89)*
	6	5.14 (2.03 – 13.02)**	0.29 (0.13 – 0.64)**	1.03 (1.00 – 1.06)*	1.23 (0.82 – 1.87)	0.27 (0.12 – 0.63)**
	9	4.46 (1.64 – 12.15)**	0.46 (0.19 – 1.10)	1.06 (1.02 – 1.10)**	1.43 (0.89 – 2.28)	0.09 (0.03 – 0.26)***
A/D	3	2.92 (1.32 – 6.47)**	0.41 (0.21 – 0.82)*	1.00 (0.98 – 1.03)	0.96 (0.67 – 1.39)	0.30 (0.15 – 0.63)**
	6	1.67 (0.76 – 3.67)	0.32 (0.15 – 0.69)**	1.01 (0.98 – 1.04)	1.24 (0.83 – 1.88)	1.34 (0.57 – 3.12)
	9	2.81 (1.18 – 6.67)*	0.57 (0.25 – 1.29)	1.02 (0.99 – 1.05)	0.95 (0.61 – 1.49)	0.30 (0.12 – 0.77)*

Data are shown as odds ratio (OR) and 95% confidence interval (CI). Age and CFS was taken as continuous variables (per one-unit increase OR).
[a] Long-COVID-19 symptoms (at least one persisting symptom) at each time-point.
[b] Severe disease was defined as ICU admission rate and/or need for any kind of ventilatory support (invasive or non-invasive) during the in-hospital stay.
See Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15051) for further detail on comorbid conditions and definitions of outcomes .
A/D: anxiety/depression; CFS: clinical frailty scale; HIV: human immunodeficiency virus; ICU: intensive care unit; MO: mobility; M: months; P/D: pain/discomfort; SC: self-care; UA: usual activities; WHO: World Health Organization.
*$p < 0.050$; **$p < 0.010$; ***$p < 0.001$

(Table 2). The presence of pre-existing depression was only associated with anxiety/depression impairment later during follow-up (nine months, $p < 0.010$).

Neither ICU admission nor severe disease were associated with impairment of any EQ-5D-3L domain. While ICU length of stay was significantly higher among patients reporting mobility (12, IQR 19 – 7 days *vs* 6.5, IQR 9 – 4 days, $p = 0.025$) [Appendix 3, Table 3 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)] and impairment of usual activities (12, IQR 19 – 8 days *vs* 6.5, IQR 9 – 4 days, $p = 0.015$) [Appendix 3, Table 5 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)] at three months compared to those who did not, the total length

Cardiovascular disease	Lung disease	Osteoarthritis	Depression	ICU	Severe disease[b]
2.0 (0.97 – 4.19)	2.14 (1.01 – 4.52)*	3.02 (1.24 – 7.36)*	1.28 (0.55 – 2.95)	1.47 (0.68 – 3.21)	1.58 (0.79 – 3.17)
1.94 (0.86 – 4.38)	1.22 (0.52 – 2.85)	9.83 (2.97 – 32.56)***	1.71 (0.69 – 4.21)	1.09 (0.45 – 2.66)	1.04 (0.48 – 2.28)
3.56 (1.22 – 10.35)*	2.55 (1.00 – 6.51)*	3.74 (1.20 – 11.67)*	2.39 (0.86 – 6.60)	0.72 (0.24 – 2.14)	1.00 (0.40 – 2.48)
2.32 (0.61 – 8.79)	1.86 (0.57 – 6.05)	3.95 (1.17 – 13.34)*	0.32 (0.04 – 2.53)	0.56 (0.12 – 2.66)	0.72 (0.21 – 2.46)
2.90 (0.59 – 14.33)	1.88 (0.49 – 7.16)	4.43 (1.11 – 17.68)*	1.66 (0.40 – 6.93)	0.78 (0.16 – 3.90)	1.03 (0.27 – 3.88)
5.31 (0.63 – 44.76)	4.87 (1.09 – 21.81)*	8.27 (1.81 – 37.85)**	2.62 (0.56 – 11.93)	0.42 (0.05 – 3.56)	0.48 (0.09 – 2.47)
1.48 (0.73 – 2.99)	1.70 (0.80 – 3.57)	2.28 (0.94 – 5.53)	1.19 (0.52 – 2.73)	1.36 (0.63 – 2.95)	1.26 (0.63 – 2.52)
1.93 (0.84 – 4.44)	2.53 (1.08 – 5.89)*	3.33 (1.19 – 9.33)*	1.29 (0.51 – 3.26)	0.78 (0.16 – 3.90)	1.49 (0.68 – 3.30)
1.11 (0.39 – 3.11)	4.23 (1.48 – 12.07)**	3.15 (0.93 – 10.71)	1.17 (0.35 – 3.99)	0.42 (0.05 – 3.56)	1.24 (0.45 – 3.45)
1.93 (0.94 – 3.98)	0.94 (0.43 – 2.02)	2.28 (0.94 – 5.53)	0.67 (0.27 – 1.63)	0.84 (0.37 – 1.87)	1.26 (0.63 – 2.52)
2.76 (1.21 – 6.28)*	2.15 (0.94 – 4.93)	4.39 (1.51 – 12.77)**	2.24 (0.91 – 5.49)	1.70 (0.72 – 4.04)	1.01 (0.47 – 2.19)
1.65 (0.67 – 4.08)	1.03 (0.40 – 2.66)	4.29 (1.39 – 13.24)*	2.51 (0.93 – 6.77)	0.79 (0.28 – 2.22)	0.78 (0.32 – 1.91)
0.66 (0.33 – 1.30)	1.41 (0.67 – 2.97)	1.19 (0.48 – 2.93)	1.14 (0.50 – 2.63)	1.31 (0.60 – 2.83)	1.97 (0.99 – 3.91)
0.93 (0.43 – 1.97)	1.08 (0.47 – 2.47)	1.68 (0.61 – 4.60)	2.39 (0.97 – 5.86)	0.25 (0.09 – 0.73)*	0.73 (0.34 – 1.57)
1.17 (0.51 – 2.69)	2.43 (1.02 – 5.80)*	3.03 (0.99 – 9.20)	3.60 (1.37 – 9.48)**	0.73 (0.27 – 1.93)	1.52 (0.67 – 3.46)

of hospital stay did not differ between groups in all EQ-5D-3L domains throughout the study. See Appendix 3, Tables 3 to 7 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052) for full details on summary statistics regarding patient demographics, comorbid and clinical characteristics for each EQ-5D-3L domain.

We performed a multivariable logistic regression analysis to investigate the association between long-COVID-19 and HR-QoL compromise (impairment of at least one EQ-5D-3L domain) at each time-point (Table 3). After adjusting for sex, age, CFS and comorbidities, the presence of long-COVID-19 remained associated with HR-QoL deterioration at three (OR 4.27, 95% CI 1.92 – 9.52, $p < 0.001$), six (OR 3.46, 95% CI 1.40 – 8.57, $p = 0.007$ and nine months (OR 4.13, 95% CI 1.62 – 10.55, $p = 0.003$) after hospital discharge.

EQ-5D-3L index

Patients were categorized according to whether they had persisting COVID-19 symptoms at the first assessment aiming to describe changes in the EQ-5D-3L index over the nine months of follow-up and to determine whether the patterns of change differed between patients with and without

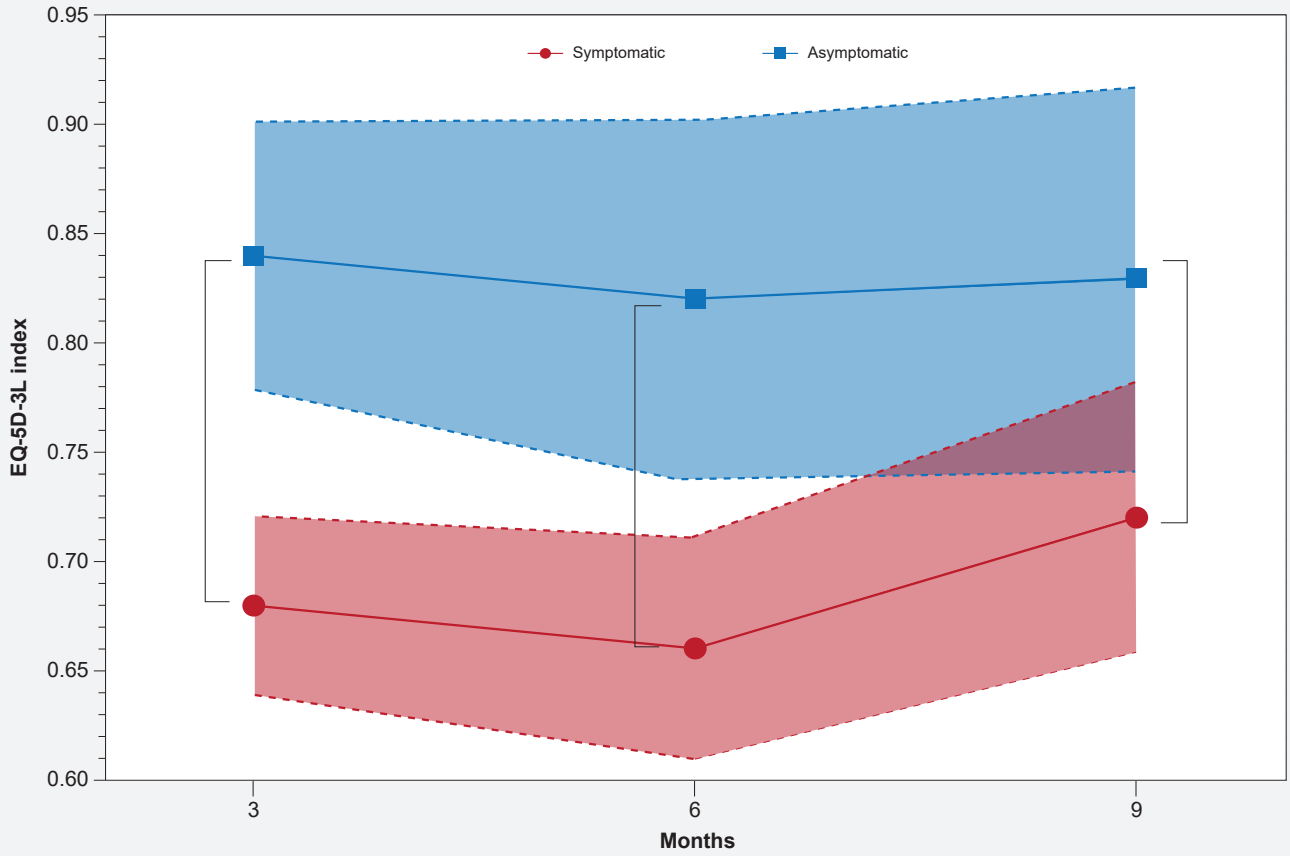

Figure 3 – Comparison of the EQ-5D-3L index (mean value and 95% confidence interval) at three, six and nine months after hospital discharge between patients with (red) and without (blue) long-COVID-19 symptoms at the first assessment.
*$p < 0.050$; **$p < 0.010$; ***$p < 0.001$

long-COVID-19 (Fig. 3).

Three months after hospital discharge, patients with long-COVID-19 had a decreased EQ-5D-3L index by approximately 0.14 per visit ($p < 0.001$) [Appendix 3, Table 8 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. Both groups had a non-significant change in the mean EQ-5D-3L index throughout the study (time-point assessment, Z = 0.91, $p = 0.364$). Therefore, although patients reporting long-COVID-19 at the first assessment had poorer HR-QoL, this disparity did not change significantly over the 9 months of follow-up, even though we observed an increasing trend over time in those with long-COVID-19 symptoms and even after adjusting for sex, age, CFS and comorbidities [multivariate estimated regression coefficients (95% CI): -0.10 (-0.15 – -0.05), $p < 0.001$]. [Appendix 3, Table 9 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)].

DISCUSSION

We carried out a longitudinal follow-up study of Portuguese COVID-19 patients who were systematically assessed at three, six and nine months after hospitalization for COVID-19. In this study, we reported a detailed characterization of the prevalence and risk factors associated with long-COVID-19 and found an unequivocal correlation between those symptoms and a sustained deterioration in HR-QoL over time.

Long-COVID-19 has been increasingly recognized and is now a matter of great interest as the sequelae of COVID-19 can persist for up to two years after acute infection. A Spanish multicentre study reported that more than one-third of hospitalized patients showed persisting symptoms 12 months after discharge.[13] Another single-centre longitudinal study from China, including 1192 hospital discharged patients, showed that 55% still have at least one sequelae symptom after two years of follow-up.[10]

Studies assessing patients prospectively and systematically at specific time-points after hospital discharge remain

scarce.[10,14–16] We show that more than 65% of patients report at least one symptom three months after discharge. Carvalho-Schneider *et al*[17] also found persisting symptoms in more than two-thirds of non-critical hospitalized COVID-19 patients assessed 60 days after discharge. Approximately three months after hospital admission, 74% of patients reported at least one ongoing symptom in a British study,[18] although a lower prevalence rate (50%) has been described.[19] With a median follow-up time after symptoms onset of 186 (IQR 175 – 199) days, a large Chinese cohort study including 1733 face-to-face interviews, found at least one persisting symptom in 76% of patients.[20] Nine months after disease onset, the prevalence of persistent symptoms may range from 20%[21] to more than 70%.[15] In our study, more than half of patients were still symptomatic nine months after hospital discharge regardless of demographic and clinical characteristics.

The high heterogeneity regarding the methodology of follow-up studies might justify the differences regarding the prevalence of long-COVID-19 and highlights the importance of using standardized tools to evaluate these patients in the future. Despite this, our results agree with the known decreasing tendency in the prevalence of long-COVID-19 symptoms over time. We observed that the proportion of COVID-19 survivors reporting at least one persistent symptom decreased significantly from 66.4% to 53.4% over a nine month period, and very similar results were reported by others.[16] The observed reduction of fatigue and dyspnea, the two most frequently reported long-COVID-19 symptoms, is in line with published data.[21]

Risk factors for symptom persistence have not been consistently reported. The female sex has been associated with a greater risk of long-COVID-19,[16,22,23] especially regarding mental health impairment,[13,16] while other authors describe no influence of sex.[10] We also did not find a higher risk of long-COVID-19 among women, even though we saw a non-significant trend toward a protective effect in male subjects throughout the study (Table 1). Advanced age is associated with a more severe COVID-19 phenotype and is one of the main prognostic determinants.[24,25] A frailer phenotype leads to a prolonged hospital stay and increased mortality during the COVID-19 acute phase.[24,26] Therefore, greater long-term persistence of symptoms would be expected in older and frailer patients.[16] One could also assume that severe disease, commonly associated with ICU admission, mechanical ventilation and longer hospital stay, would lead to lasting symptoms. Longer hospitalization is associated with physical and cognitive deconditioning, as well as longer recovery time after discharge.[27] In our study, neither age, frailty status, nor disease severity were risk factors for long-COVID-19. Although we report a similar median age compared to most published studies,[10,16,22] our results should be carefully interpreted since we have not included severely disabled, and hence frailer patients.

Consistent with others,[4,15,16,22] nearly 43% of our patients reported fatigue nine months after discharge. This is not surprising since some authors observed a higher prevalence of fatigue up to four years during the recovery phase of SARS[28] and recent data on COVID-19 already showed persisting fatigue up to two years.[10] Although the pathogenesis of long-lasting fatigue after COVID-19 is unclear, it probably arises from a combination of lung diffusion capacity impairment, cytokine disturbance, physical and psychological distress, as described after SARS pandemic.[28,29]

We were surprised to find that CKD was associated with a decreased odds of long-COVID-19 since it is a known risk factor for poor outcomes during the acute phase of the disease.[25,30] While most studies did not mention the effect of CKD on persisting COVID-19 symptoms, Xue-Zhang *et al*[22] reported that CKD was not associated with long-COVID-19. This unexpected finding deserves further investigation.

Knowledge about the relationship between COVID-19 severity, development of long-COVID-19 and decreasing HR-QoL is scarce. Halpin *et al*[31] found that COVID-19 severity is associated with a worse HR-QoL, while another study found no differences between ICU and ward patients.[32] Moderate to extreme problems in at least one dimension of the five-level EQ-5D questionnaire were described in around 64% of COVID-19 patients with a median time of 55 days after ICU discharge in a tertiary centre in Northern Portugal.[33] In our study, more than two-thirds of patients had at least some impairment in QoL at three months, and more than 55% at nine months after discharge. Notably, we also did not observe any positive association between disease severity, whether as a composite score (ICU admission and/or any kind of ventilatory support) or as ICU admission alone, and impairment of each QoL domain individually throughout the study (Table 2).

As others have shown,[10,32–34] the self-care domain was the least affected in our sample. Considering that nearly 85% of our patients were in good health status prior to hospitalization (CFS ≤ 3), and that self-care impairment usually reflects a severe disability, our results were expected. On the other hand, usual activities, anxiety/depression, and pain/discomfort are among the most frequently impaired domains,[10,32,33] as shown in our study. Fluctuations and relapses of long-COVID-19 symptoms have been described, but the underlying mechanism remains unclear.[10] We saw that the prevalence of impairment in the pain/discomfort and anxiety/depression domains increased at six months, being reported by almost 40% of patients. Curiously, up to 30% of patients that recovered from acute COVID-19 may fulfill criteria for fibromyalgia,[35] which has a similar pattern of changes in HR-QoL as we see in long-COVID-19.[36] This

could also explain why we observe a simultaneous increase in the prevalence of cognitive symptoms at six months (Fig. 1A), as memory impairment, foggy brain and problems with attention, are recognized consequences of depressive and/or anxious states[37] and chronic pain.[38]

The impact of baseline characteristics, including age and CFS, and the persistence of long-COVID-19 on HR-QoL, was also investigated. Righi *et al*[21] reported that a status of excellent physical health, present in 90% of patients prior to SARS-CoV-2 infection declined to 24% at disease onset and then increased to 82% at nine-months of follow-up. In our study, we also saw this trend as patients progressively achieved their previous health status over the study period, and this was associated with a significant reduction in the odds of reporting impairment in all EQ-5D-3L domains throughout the study (Table 2). Despite observing a negative effect of older age and higher CFS on mobility and self-care domains, these variables do not influence the global HR-QoL (Table 3).

One of our main goals was to explore the impact of long-COVID-19 on HR-QoL. Post-COVID-19 syndrome has been associated with long-term HR-QoL impairment[4] and our results emphasize this: the presence of long-COVID-19 at each time-point remained associated with HR-QoL impairment throughout the study after multivariate adjustment. More importantly, regardless of sex, age, health status and previous comorbid conditions, we found that the QoL, measured by the mean ED-5D-3L index, was significantly and persistently decreased over the 9 months of follow-up in patients reporting at least one persisting COVID-19 symptom three months after hospital discharge compared to those who did not [Fig. 3; Appendix 3, Table 9 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19047/15052)]. We found this of clinical value as the identification of predictors for prolonged impaired HR-QoL after hospital discharge could help clinicians to identify patients at risk and to minimize the disease burden at an early stage. To the best of our knowledge, this has never been shown before and future studies should validate our findings.

Different SARS-CoV-2 variants may induce different long-COVID phenotypes.[39,40] Moreover, a recent systematic review suggests, although with a low level of evidence, that vaccination before SARS-CoV-2 infection could be associated with a lower risk of subsequent long-COVID-19.[41] We should reinforce that all our patients were unvaccinated, and the recruitment period occurred when the Alpha variant was the predominant variant in Portugal.[42] Thus, our findings could differ from current reality and should be interpreted carefully.

Despite our small sample size, our results confirm that long-COVID-19 is a matter of public health concern among COVID-19 survivors in our country. National health services should prioritize follow-up guidelines and algorithms concerning the management of patients with persistent symptoms. The Directorate-General of Health in Portugal published a guideline with diagnostic criteria and clinical approach to long-COVID patients. It suggests that patients at higher risk should be reevaluated four to six weeks after the acute illness. The role of primary care is well defined as

Table 3 – Multivariate logistic regression aiming to investigate the association between long-COVID-19 and the impairment of at least one EQ-5D-3L domain

	Three months		Six months		Nine months	
	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*
Long-COVID-19	4.27 (1.92 – 9.52)	**< 0.001**	3.46 (1.40 – 8.57)	**0.007**	4.13 (1.62 – 10.55)	**0.003**
Male sex	0.48 (0.22 – 1.05)	0.067	0.30 (0.12 – 0.78)	**0.013**	0.53 (0.22 – 1.30)	0.166
Age[a]	1.01 (0.97 – 1.04)	0.484	1.01 (0.97 – 1.04)	0.713	1.03 (0.99 – 1.07)	0.105
CFS[a]	1.28 (0.78 – 2.10)	0.332	1.21 (0.69 – 2.14)	0.506	1.03 (0.58 – 1.84)	0.919
Return to previous CFS	0.27 (0.09 – 0.77)	**0.014**	0.51 (0.16 – 1.66)	0.262	1.63 (0.54 – 4.90)	0.386
Lung disease	0.89 (0.37 – 2.14)	0.786	1.83 (0.63 – 5.29)	0.266	3.27 (1.13 – 9.48)	**0.029**
Osteoarthritis[b]	0.99 (0.30 – 3.35)	0.995	-	-	3.22 (0.65 – 15.99)	0.145

Data are shown as odds ratio (OR) and 95% confidence interval (CI).
[a] Per one-unit increase OR.
[b] All patients with osteoarthritis had impairment in at least one EQ-5D-3L domains at six months, and were therefore excluded from the analysis.
CFS: clinical frailty scale.

well as the criteria for hospital referral.[43] Identifying patients at higher risk of disease burden is essential to reduce the collateral impact in the activities of daily life, improve clinical outcomes and reduce health-related costs.

The strength of our study is the well-defined longitudinal design with a long follow-up period where patients were all assessed at specific time-points, making it easier to draw conclusions. Our study has several limitations. First, being a single centre study with a relatively small number of patients, generalizability is compromised. Second, persistent symptoms were self-reported, without any objective assessment, which could represent an information bias. Third, no control group was considered, which hampers the possibility to assess whether the observed symptoms were due to COVID-19. Fourth, we did not collect other variables that might impact QoL (e.g.: education level, marital and socioeconomic status). Lastly, we did not have a baseline QoL assessment (e.g.: at admission; at discharge) to which our results could be compared.

CONCLUSION

Long-COVID-19 persists for at least nine-months after hospital discharge in most hospitalized patients and is unequivocally associated with impaired HR-QoL in more than half of patients regardless of disease severity and demographics. Identifying patients at higher risk of disease burden is crucial to improve outcomes and health-related costs. Follow-up guidelines for discharged COVID-19 patients should be carefully drawn and taken as a priority in a post-pandemic world.

AWARDS AND PRESENTATIONS

Preliminary results of the current study were presented at the National Congress of Internal Medicine (2021) as oral communications ("Health-Related Quality of Life Of COVID-19 Patients Three Months After Hospital Discharge" and "Persistent Symptoms in Patients With COVID-19 After Hospitalization"). The final results were presented at the National Congress of Internal Medicine (2022) ("Prevalence and Risk Factors for Long-COVID-19: Longitudinal Analysis after Hospital Discharge") and was recognized as one of the five best oral presentations in the clinical research category.

AUTHOR CONTRIBUTIONS

PG, MD: Conception of the study, data acquisition, drafting, critical review and supervision of the manuscript.

IP, HDG, FP, VM, HAB, CC, LD: Data acquisition, critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Impact of Lifting Mask Mandates on COVID-19 Incidence and Mortality in Portugal: An Ecological Study

Impacto do Fim da Obrigatoriedade do Uso de Máscara em Portugal na Incidência e Mortalidade de COVID-19: Um Estudo Ecológico

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ABSTRACT

Introduction: The use of face masks in public was one of several COVID-19 non-pharmaceutical interventions adopted to mitigate the pandemic in Portugal. The aim of this study was to evaluate the impact of lifting the mask mandate on the April 22, 2022 on COVID-19 incidence and mortality in mainland Portugal and in the Azores. As a secondary objective, we aimed to evaluate the evolution of COVID-19 cases in a setting without a mask mandate (Azores islands) and in a setting with a mask mandate (Madeira islands).

Methods: Surveillance data on laboratory-confirmed COVID-19 cases and COVID-19 deaths were used to conduct an interrupted time series analysis to estimate changes in daily incidence and deaths during a mask mandate period (28th March – 21st April 2022) and during a post-mask mandate period (22nd April – 15th May 2022), in mainland Portugal and Azores. In a second phase, for each archipelago, we fitted a negative binomial regression model, with daily COVID-19 incident cases as the primary outcome of interest, and relative frequency of Omicron BA.5 lineage as explanatory variable.

Results: Significant changes in trends were observed for the overall incidence rate and COVID-19 deaths; increasing trends were observed for COVID-19 incidence and deaths in the post mandate period [5.3% per day; incidence rate ratio (IRR): 1.053; 95% confidence interval (CI): 1.029 - 1.078] and [3.2% per day; mortality rate ratio (MRR): 1.032; 95% CI: 1.003 - 1.062], respectively. For every unit increase in the percentage of Omicron BA.5 lineage there was a 1.5% increase per day (IRR: 1.015; 95% CI: 1.006 - 1.024) in COVID-19 incidence rate in the Azores islands, while for Madeira islands an increase of 0.05% COVID-19 cases per day was observed (IRR: 1.005; 95% CI: 1.000 - 1.010).

Conclusion: Lifting the mask mandate in Portugal was associated with an increase in COVID-19 incidence and deaths, thus highlighting the positive effect of face mask policies in preventing respiratory virus transmission and saving lives.

Keywords: COVID-19; Masks; Pandemics; Portugal; SARS-CoV-2

RESUMO

Introdução: O uso de máscara em público foi uma das várias intervenções não farmacêuticas adotadas para mitigar a pandemia de COVID-19 em Portugal. Pretendeu-se com este estudo avaliar o impacto do levantamento da obrigatoriedade do uso de máscara, a 22 de abril de 2022, na incidência e mortalidade por COVID-19, em Portugal Continental e nos Açores. Como objetivo secundário, pretendeu-se avaliar a evolução de casos de COVID-19 numa região sem obrigatoriedade de uso de máscara (Região Autónoma dos Açores) e numa região com obrigatoriedade de uso de máscara (Região Autónoma da Madeira).

Métodos: O número de casos de COVID-19 confirmados laboratorialmente e de mortes específicas por COVID-19 foram utilizados para realizar uma análise de séries temporais interrompidas, de modo a estimar mudanças na incidência diária e óbitos, durante um período com obrigatoriedade de uso de máscara (28 de março a 21 de abril de 2022) e durante um período após o fim da obrigatoriedade de uso de máscara (22 de abril a 15 de maio de 2022), em Portugal Continental e nos Açores. Numa segunda fase, para cada região autónoma, ajustou-se um modelo de regressão binomial negativa, tendo como variável de interesse os casos diários de COVID-19 e como variável explicativa a frequência relativa da linhagem Omicron BA.5.

Resultados: Foi observada uma alteração significativa nas tendências relativas à taxa de incidência e mortes por COVID-19; foi observada uma tendência crescente quer para a incidência, quer para as mortes por COVID-19 no período pós-obrigatoriedade de uso de máscara [5,3% por dia; razão da taxa de incidência (IRR): 1,053; intervalo de confiança (IC) a 95%: 1,029 - 1,078] e [3,2% por dia; razão da taxa de mortalidade (MRR): 1,032; IC 95%: 1,003 - 1,062], respetivamente. Para cada aumento de 1% na linhagem BA.5 da variante Omicron estimou-se um aumento de 1,5% por dia (IRR: 1,015; IC 95%: 1,006 - 1,024) na taxa de incidência de COVID-19 na região autónoma dos Açores, enquanto que para a região autónoma da Madeira se observou um aumento de 0,05% nos casos de COVID-19 diários (IRR: 1,005; IC 95%: 1,000 - 1,010).

Conclusão: O fim da obrigatoriedade do uso de máscara em Portugal esteve associado a um aumento na incidência e mortes por COVID-19, destacando-se assim o efeito positivo desta medida de saúde pública na prevenção da transmissão de vírus respiratórios e na redução da mortalidade.

Palavras-chave: COVID-19; Máscaras; Pandemia; Portugal; SARS-CoV-2

INTRODUCTION

The use of face masks was one of several COVID-19 non-pharmaceutical interventions (NPIs) adopted to mitigate the pandemic in Portugal. This intervention was part of a multi-layered approach that emphasized vaccination, included restrictions enforced by the government with different stringency levels and duration periods, and recommended preventive actions at all times, such as respiratory etiquette, physical distancing, and hand hygiene. Mask use,

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closure of nightclubs, limits to public gatherings, and the requirement to present a COVID-19 digital certificate to access restaurants, were some of the compulsory restrictions implemented during longer time periods in Portugal.[1]

However, as the pandemic moved into the next phase, with high vaccination coverage rates as well as anti-viral treatments becoming available, and much lower rates of severe illness, several mandatory restrictions started to be lifted one step at a time. Apart from the requirement, which is no longer in place, for people who test positive for COVID-19 to self-isolate, mask use required in all indoor public spaces in the mainland Portugal since the 30th April 2020, was one of the last restrictions to be lifted. On the 22nd April 2022, mask use was no longer compulsory in indoor spaces, except in public transportation, access to healthcare services, and long-term care facilities.[2] This NPI was also lifted in the Azores islands but continued in place in Madeira islands until the 15th May 2022. Between April 22, 2022 and April 17, 2023, mask use was only required in healthcare institutions and long-term care facilities.[3]

Other European countries, such as Denmark, Norway, and the UK had already abolished the mandatory use of face masks in indoor public areas, between February and April 2022, at the peak of COVID-19 epidemic waves. Moreover, although a high number of cases was registered at the time, the epidemic continued its descending trajectory.[4,5] Opposite results, however, had been observed in some American states in 2021, where after mask mandates were lifted increasing trends of the epidemic were observed.[6]

There is a large body of evidence supporting the efficacy of public mask wearing in controlling COVID-19 transmission and as a consequence, in preventing COVID-19 cases and deaths.[7–8] A study on the effectiveness of COVID-19 NPIs during Europe's second wave found that wearing masks in public led to a reduction in the COVID-19 reproduction number of around 12%.[9] Another modelling study analysing COVID-19 mortality rates across 44 countries, including Portugal, showed that face mask mandates were associated with lower COVID-19 death rates.[10] Nevertheless, most studies examined the impact of mask mandates, and very few focused on the impact of lifting this NPI.[11]

We intended to address this gap by evaluating the impact of lifting the mask mandate on COVID-19 incidence and mortality in Portugal. First, we evaluated changes in COVID-19 cases and mortality trends pre- and post-lifting of the mask mandate in mainland Portugal and in the Autonomous Region of the Azores. As the lifting of mask mandates coincided with the evolution of the Omicron BA.5 lineage in Portugal, in a second phase we aimed to evaluate the evolution of COVID-19 cases in a setting without a mask mandate (Azores islands) and in a setting with a mask mandate in place (Madeira islands).

METHODS

Study design and population

An ecological study was performed using an interrupted time series analysis to estimate the impact of lifting mask mandates, on the 22nd April 2022, on the development of COVID-19 infections and deaths. For the main analysis the target population comprised residents of mainland Portugal (North, Center, Lisbon and Tagus Valley, Alentejo and Algarve) and the autonomous region of Azores. We excluded Madeira islands from the main analysis as this autonomous region only lifted the mask mandate on the 15th May 2022.

The Omicron BA.5 lineage was detected for the first time in the week 13/2022 (28th March – 3rd April 2022) and became dominant in Portugal (estimated relative frequency of 78.7%, as of May 23, 2022).[12] As the growth rate of COVID-19 variants is time-dependent it prevented us from adjusting our interrupted time series regression for the relative frequency of the Omicron BA.5 lineage. Consequently, in a second phase, we used a quasi-experimental research design to evaluate the evolution of COVID-19 cases, using the relative frequency of the Omicron BA.5 lineage as explanatory variable, in a setting without a mask mandate (Azores islands) and in a setting with a mask mandate (Madeira Islands). We purposely chose these two regions because they are similar in terms of population size and, since they are geographically isolated, Omicron BA.5 lineage circulation was delayed compared to mainland Portugal, giving us a unique opportunity to evaluate if a mask mandate could have mitigated the impact of the pandemic even in the presence of a highly transmissible variant.

Outcome variables

We used national surveillance data concerning the daily number of SARS-CoV-2 laboratory-confirmed infections and COVID-19 deaths in Portugal provided by the Directorate General of Health (DGS).[13] The provided dataset also included the date of symptom onset, date of diagnosis and date of confirmation/notification for each case. Imputation methods, described in previous studies, were used to estimate missing dates of disease onset.[14,15] Daily counts of COVID-19 cases by date of symptom onset were used to perform all statistical analyses regarding incidence, while for the analysis regarding mortality, date of death was considered.

The most recent resident population counts, extracted from Statistics Portugal, were used as denominators to compute incidence and mortality rates.[16]

Covariates

The weekly relative frequency of Omicron BA.5 lineage, by specimen collection date, in Portugal was made available by the National Health Institute Doutor Ricardo Jorge.[17] The

daily relative frequency of Omicron BA.5 lineage was computed using linear interpolation.

Lag periods

The evidence suggests there is a three day median lag time between SARS-CoV-2 Omicron variant transmission and symptom onset.[18] Furthermore, a symptom-onset-to-death delay was estimated through analysis of the lag distribution between COVID-19 onset of symptoms and death. This resulted in a potential lag of three days between the end of the mask mandate and associated COVID-19 incidence and an overall likely lag of 13 days between the end of the mask mandate and associated COVID-19 mortality. These durations underpin a choice of 3- and 13-day lags, respectively, for modelling the impact of lifting the mask mandate on COVID-19 incidence and mortality and for the decision to use a 10-day extension in the mortality analysis study period.

Study period

To control for the effects of simultaneously occurring interventions, the beginning of the observation period in our analysis was chosen considering the first confirmed case of the Omicron BA.5 lineage in Portugal, while the ending was chosen considering the administration of the second booster dose of COVID-19 vaccine for the population over 80 years old.[12,19]

Therefore, to assess the change in trend in COVID-19 incidence in mainland Portugal and Azores islands before and after lifting the mask mandate, we compared two periods (Fig. 1): (i) a mask mandate period from March 28, 2022 to April 21, 2022; (ii) a post-mask mandate period from April 22, 2022 until May 15, 2022.

To assess the change in trend of COVID-19 deaths in mainland Portugal and the Azores before and after lifting the mask mandate, we compared two periods (Fig. 1): (i) a mask mandate period starting on March 28, 2022 until April 21, 2022; (ii) a post-mask mandate period starting on April 22, 2022 until May 25, 2022 (considering a 10-day delay between the onset of disease and death).

As a secondary objective, we evaluated the evolution of COVID-19 cases, using the relative frequency of Omicron BA.5 lineage as an explanatory variable, in a setting without a mask mandate (Azores islands) and in a setting with a mask mandate (Madeira islands). To accomplish this goal, we took into consideration not only the timings of mask mandates in both archipelagos but also periods with equivalent Omicron BA.5 lineage evolution in both settings. Therefore, we used 18th April – 8th May 2022 as the Azores islands observation period (no mask mandate in place) and

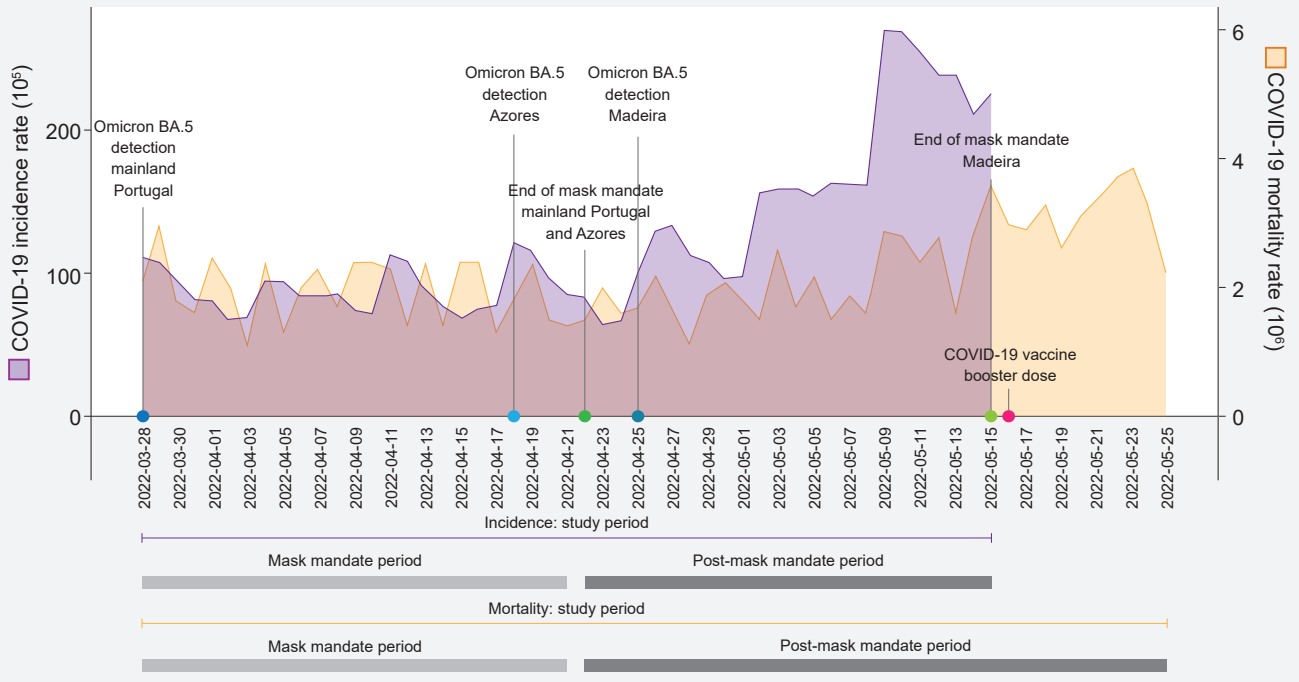

Figure 1 – COVID-19 daily incidence rates[a], COVID-19 mortality rates[b] and timeline of mask mandate lifting, Portugal, 28th March 2022 – 25th May 2022

COVID-19: coronavirus disease; [a]: Per 100 000 population; [b]: Per 1 000 000 population.

Time interval regarding the study period for assessing the impact of lifting the mask mandate in incidence is depicted in purple. The time interval regarding the study period for assessing the impact of lifting the mask mandate in mortality is depicted in orange.

25th April – 15th May 2022 as the observation period for the Madeira islands (mask mandate in place) (Fig. 1).

Statistical analysis

To estimate changes in COVID-19 daily incidence and mortality before and after lifting the mask mandate we used an interrupted time series analysis, fitting separate models for each outcome.

A negative binomial regression model was adjusted, with daily COVID-19 incident cases as the primary outcome of interest, whereas for COVID-19 deaths a Poisson regression model was used. Explanatory factors included the linear effect of time (slope) and change in trend after lifting the mask mandate (change in slope). The population was included in models as an offset variable.

Due to the SARS-CoV-2 Omicron variant, median incubation period of three days, for the incidence regression model, we included a lag of three days in explanatory variables.[17] For the regression model applied to COVID-19 deaths, we included a lag of 13 days in explanatory variables.

The statistical models used in the main analysis, for COVID-19 cases and deaths, were given as follows:

(cases) $logE(C_t) = \beta_0 + \beta_1 Time_t + \beta_2 Time_t \times Mask_{t-3} + log(Pop_t)$

(deaths) $logE(D_t) = \alpha_0 + \alpha_1 Time_t + \alpha_2 Time_t \times Mask_{t-13} + log(Pop_t)$

where C_t and D_t are daily counts of COVID-19 cases and deaths by the time of symptom onset or date of death (t), respectively; exp(β_0) and exp(α_0) are the incidence and mortality rate at Time = 0; $Time_t$ is time in days since the start

Table 1 – Daily trends in the COVID-19 incidence rate before and after lifting mask mandate, March 18 – May 15, 2022 (n = 607 760) and daily trends in the COVID-19 mortality rate before and after lifting mask mandate, March 28 – May 25, 2022 (n = 1 302), mainland Portugal and Azores islands

	Mask mandate		Post-mask mandate		Change in trend	95% CI	*p* value[a]
	28th Mar – 21st April 2022		22nd April – 15th May 2022				
COVID-19 incidence rate	**IRR**	**95% CI**	**IRR**	**95% CI**			
	1.005	0.997 - 1.013	1.053	1.029 - 1.078	1.048	1.032 - 1.064	< 0.001
	28th Mar – 21st April 2022		22nd April – 25th May 2022				
COVID-19 mortality rate	**MRR**	**95% CI**	**MRR**	**95% CI**			
	0.999	0.989 - 1.009	1.032	1.003 - 1.062	1.033	1.014 - 1.053	< 0.001

CI: confidence interval; COVID-19: coronavirus disease; IRR: incidence rate ratio; MRR: mortality rate ratio

[a]: Two-sided Wald test *p* values were obtained from negative binomial regression models. A *p*-value < 0.05 was considered evidence of statistical significance.

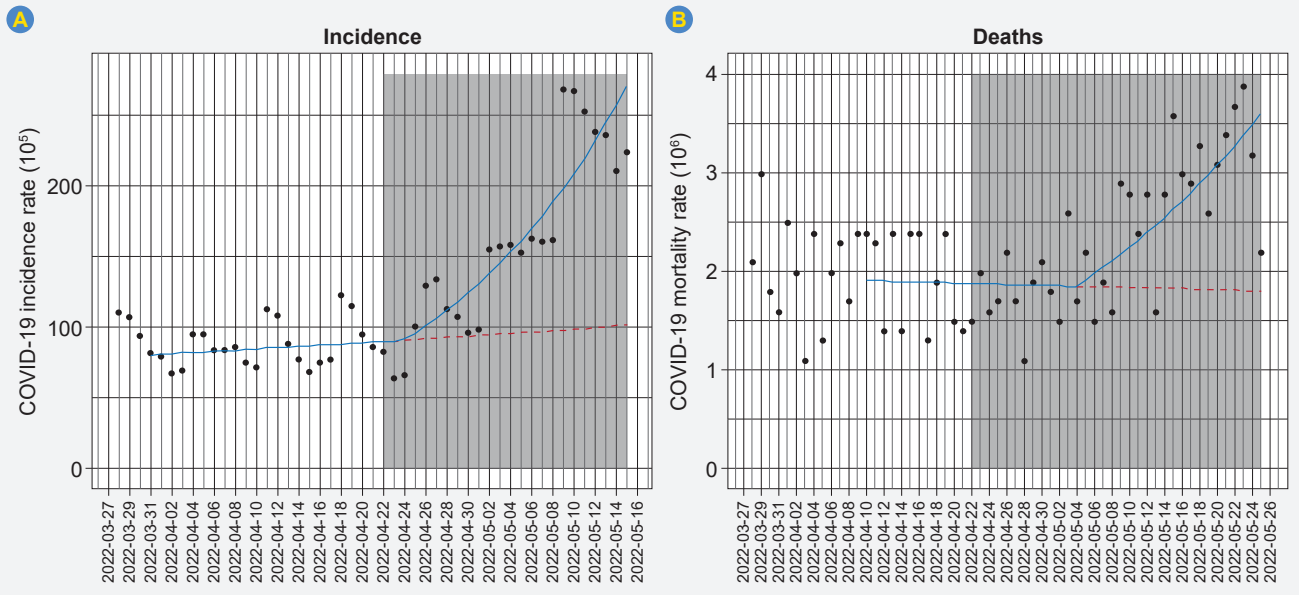

Figure 2 – COVID-19 daily incidence rates. (A) 28th March – 15th May 2022 (n = 607 760) and COVID-19 daily mortality rates; (B) 28th March – 25th May 2022 (n = 1 302) before and after lifting mask mandate, mainland Portugal and Azores islands

COVID-19: coronavirus disease; [a]: Per 100 000 population; [b]: Per 1 000 000 population.

The shaded grey area represents the period after lifting the mask mandate. Blue solid lines represent the fitted incidence and mortality rates before and after lifting mask mandate, respectively. The red dashed line represents the predicted incidence and mortality rate in a counterfactual scenario, i.e. if the mask mandate had not ended.

of the study period; $Mask_{t-3}$ and $Mask_{t-13}$ are dummy variables representing, the end of mask mandate (0 in mask mandate period, 1 otherwise); exp(β_1) and exp(α_1) are the slope of the outcome variable until the end of the mask mandate; exp(β_2) and exp(α_2) are the change in slope after lifting of the mask mandate; Pop_t represents the population at time *t*.

The daily percentage change of COVID-19 incidence and mortality in the post-mask mandate periods was calculated as 100% [incidence rate ratio (IRR)−1] and 100% [mortality rate ratio (MRR)−1], respectively, where IRR and MRR were estimated as exp($\beta_1+\beta_2$) and exp($\alpha_1+\alpha_2$), respectively.

As a secondary objective, for each group of islands, we fitted a negative binomial regression model, with daily COVID-19 incident cases as the primary outcome of interest, and relative frequency of Omicron BA.5 lineage as explanatory variable, as follows:

(BA.5 lineage) $logE(C_t) = \beta_0 + \beta_1 BA5_t + log(Pop_t)$

where C_t is a daily count of COVID-19 cases by time of symptom onset (t); exp(β_1) is the percent change in the incident rate of COVID-19 for every unit increase in BA5; $BA5$ is the relative frequency of Omicron BA.5 lineage; Pop_t represents the population at time t.

The level of significance was set at 5% for all tests. Model goodness-of-fit was assessed by graphical analyses of residuals and Pearson's chi-squared test. R version 3.5.1[20] was used to perform statistical analyses.

The aggregated data used within this study were anonymised and collected in the scope of epidemiological surveillance and therefore submission to an ethics committee was not required.

RESULTS

Trends in COVID-19 incidence and death rates

In the mask mandate period (28th March – 21st April 2022) a stable trend was observed for the COVID-19 incidence rate (IRR: 1.005; 95% CI: 0.997 - 1.013). In the post-mask mandate period (22nd April – 15th May 2022), a statistically significant change in trend was observed for the incidence rate. A significant increasing trend was observed in mainland Portugal (5.3% per day; IRR: 1.053; 95% CI: 1.029 - 1.078) (Table 1 and Fig. 2).

A stable trend was observed during the mask mandate period (28th March – 21st April 2022) for the COVID-19 mortality rate (MRR: 0.999; 95% CI: 0.989 - 1.009). In the post-mask mandate period (22nd April – 25th May 2022), a statistically significant change in trend was observed for the mortality rate. A statistically significant increasing trend was observed (3.2% per day; MRR: 1.032; 95% CI: 1.003 - 1.062) (Table 1 and Fig. 2).

Evolution of COVID-19 incidence in settings without (Azores) and with (Madeira) mask mandates

The Omicron BA.5 lineage was detected in week 13 of 2022 in mainland Portugal. However, the first confirmed samples of Omicron BA.5 lineage in the Azores and Madeira islands were only detected in week 16 of 2022 and week 17 of 2022, respectively. An increasing trend in the relative frequency of the Omicron BA.5 lineage was observed in the Azores islands from the 18th April to the 8th May 2022 and in the Madeira islands from the 25th April to the 15th May 2022. For these observation periods, the maximum estimates in each region were 26.7% in week 18 of 2022 for the Azores islands and 34.4% in week 19 of 2022 for the Madeira islands (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18974/15137).

For every unit increase in the percentage of Omicron BA.5 lineage there was a 1.5% increase per day (IRR: 1.015; 95% CI: 1.006 - 1.024) in COVID-19 incidence rate in the Azores islands, while for the Madeira islands an increase of 0.05% COVID-19 cases per day was observed (IRR: 1.005; 95% CI: 1.000 - 1.010) (Fig. 3 and Table 2).

DISCUSSION

Our findings suggest that lifting the mask mandate was associated with an increase of the number of COVID-19 cases in mainland Portugal and Azores. These results are in line with a study from the United States which found an increase of 12 per 100 000 daily new COVID-19 cases after state and county level mask mandates were lifted in January 2021.[6] Additionally, as the efficacy of public mask wearing in preventing the spread of COVID-19 is largely supported by epidemiological and ecological data, as well as models, this adds to the body of evidence that lifting mask mandates should have an impact on the COVID-19 transmission.[7–9] However, the impact of mask mandates may go beyond the direct impact on COVID-19 incidence and may be an indirect consequence of changes in mobility or altered risk perception. A study evaluating the effects of NPIs and population mobility on daily COVID-19 cases in Ontario, Canada, found that the implementation of mask mandates in indoor settings was correlated with reductions in social mobility.[21] In Portugal, mobility trends for retail and recreation, parks, and public transport hubs such as subway, bus, and train stations, increased after mask mandates were lifted [compared to the period with mask mandates (28th March – 21st April 2022)], which suggests that lifting the mask mandate may also have an indirect impact on increasing the number of daily cases through population behavioural changes.[22] Additionally, a Portuguese study suggested that risk perception may be associated with restrictions imposed to mitigate the pandemic, which corroborates the hypothesis that the population may reduce their preventive behaviours with

Figure 3 – COVID-19 daily incidence rates and weekly relative frequency of BA.5 Omicron lineage, in the Azores islands (April 18 - May 8, 2022) (n = 8 751 COVID-19 cases; n = 173 sequenced COVID-19 samples) and the Madeira islands (April 25 – May 15, 2022) (n = 4 192; n = 105 sequenced COVID-19 samples)
COVID-19: coronavirus disease, [a]: Per 100 000 population.

Table 2 – Daily trends in the COVID-19 incidence rate before and after lifting the mask mandate, in Azores islands (April 18 - May 8, 2022) (n = 8 751) and Madeira islands (April 25 - May 15, 2022) (n = 4 192)

Area	Change in IRR	95% CI	*p* value[a]
Azores islands (18 April - 8 May, 2022)	1.015	1.006 - 1.024	<0.001
Madeira islands (25 April - 15 May, 2022)	1.005	1.000 - 1.010	0.042

COVID-19: coronavirus disease; CI: confidence interval; IRR: incidence rate ratio.
[a]: Two-sided Wald test *p* values were obtained from negative binomial regression models. A *p* value < 0.05 was considered evidence of statistical significance.

the end of mask mandates.[23] We also note that restrictions on mass gatherings had already been lifted before mask mandates were abolished in Portugal. Therefore, infections arising from settings with substantial population mixing may have been amplified with the end of mask mandates, as a Japanese study on COVID-19 risk assessment in professional baseball and football games found that the infection risk increased as the face-mask-wearing proportion

decreased in those settings.[24]

Even though other European countries, such as Denmark, Norway, and the UK, did not register an increase in COVID-19 incidence after the end of mask mandates, we note that NPI were lifted at the peak of COVID-19 epidemic waves with outstanding numbers of cases and, thus, those populations may have benefited from increased immunity after a COVID-19 infection.[4,5] The Portuguese population, however, was at risk of waning immunity as approximately three months had passed since the last epidemic wave in Portugal (December 2021 – February 2022) and a first booster dose of COVID-19 vaccine had been administered in the early winter months.[25] In addition, apart from South Africa, Portugal was one of the first countries where the Omicron BA.5 lineage was detected.[26] Recent findings indicated an increase of the Omicron BA.5 lineage relative to other variants in its capacity to infect, and be transmitted from, previously infected and vaccinated individuals.[26,27] In fact, the transmission advantage of the Omicron BA.5 lineage seems to stem from its capacity to infect individuals who were immune, not only to other COVID-19 variants, but also to earlier forms of Omicron.[28] This leverage may have contributed to the rise of the Omicron BA.5 lineage in Portugal and could be a possible explanation for its growth advantage relative to other variants in circulation at the time.

Our results suggest that the end of the mask mandate was associated with an increase in COVID-19 deaths in mainland Portugal and the Azores islands. A study conducted in the United States found no statistically significant effect on deaths associated with lifting mask mandates between January and March 2021. Nevertheless, the authors note this could be due to limited data from the recent states which lifted mask mandates.[6] On the other hand, a modelling study on COVID-19 scenarios for the United States projected that universal mask use could save an additional 129 574 lives between September 22, 2020 and the end of February 2021, thus providing supporting evidence that the end of mask mandates can have a potential impact on COVID-19 mortality.[29] Similar results were found in another modelling study analysing COVID-19 mortality across 44 countries, including Portugal: countries without face mask mandates had an average daily increase of 0.0533 deaths per million, compared with the average daily increase of 0.0360 deaths per million for countries with face mask mandates.[10] We note, nonetheless, that after the end of the mask mandate, the incidence of COVID-19 in Portugal experienced a high increase in age groups over 60 years old, which can explain the increased mortality rates observed.[25]

As mask mandates were lifted at different time points in the Portuguese autonomous regions, we took advantage of this difference to compare trends in COVID-19 infections in a setting without a mask mandate (Azores islands) and in a setting with a mask mandate in place (Madeira islands), using the relative frequency of Omicron BA.5 lineage as explanatory variable. Compared with a setting with a mask mandate, we found that without a mask mandate in place, a higher growth rate of COVID-19 cases was observed with the increase of the Omicron BA.5 lineage. This suggests that mask mandates appear to have mitigated COVID-19 transmission in Madeira islands even in the presence of a more transmissible COVID-19 variant. Such results are broadly in line with findings from studies that, taking advantage of the asynchronous mask mandates across Germany, created artificial controls and then estimated that face masks reduced the daily growth rate of COVID-19 infections by around 47%.

Our study has some limitations. It is plausible that the waning immunity of the Portuguese population is an important factor which we did not account for in our analysis. Nonetheless, waning immunity, in addition to high transmissibility of the Omicron BA.5 lineage and limited vaccine effectiveness against Omicron infection, suggest there is added value to wearing masks, particularly to prevent COVID-19 morbidity and mortality.[26,27,31]

We accounted for a lag between infection and disease onset in our regression models, and this may be considered a strength of our study, as it provides us a more precise interpretation of the impact of lifting the mask mandate in Portugal. However, there is limited information on the Omicron BA.5 lineage and, consequently, we assumed an incubation period similar to that of the Omicron BA.1 lineage.[18] We point out though, that we do not expect the incubation period to differ significantly between these two lineages as they derived from a common ancestor and, therefore, are genetically closely related.

Another limitation of our study is the increase of the Omicron BA.5 lineage during our study period. As the relative frequency of the Omicron BA.5 lineage is time-dependent we did not control for confounding in our interrupted time series analysis. Yet, by using a quasi-experimental design in addition to the main analysis we added evidence that mask mandates may mitigate the spread of the Omicron BA.5 lineage, which can be more robust than merely presenting estimates in a “before – after” manner with no use of a strict control group approach.

Finally, the ecological approach of this study requires some caution in the interpretation of its results, as it cannot be inferred that lifting the use of mask at a population level, will necessarily increase the risk of COVID-19 disease at individual level (‘ecological fallacy’). It was not possible to control adequately for confounders, effect modifiers and mediators at the individual level and therefore the present study has potential susceptibility to aggregation bias and unknown sources of confounding.[32] Nonetheless, to some

extent, the aggregation of data was unavoidable since the main predictor of interest, lifting the mask use, was measured at the population level and, hence, is an ecological variable.

CONCLUSION

Lifting the mask mandate in Portugal was associated with an increase in COVID-19 incidence and deaths, which highlights the positive effect of face mask policies in preventing respiratory virus transmission and saving lives. These results may, therefore, aid public health authorities in choosing appropriate mitigation measures for future pandemics.

AUTHORS CONTRIBUTION

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Recent Developments in the Treatment of Pancreatic Cancer

Desenvolvimentos Recentes no Tratamento do Cancro do Pâncreas

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ABSTRACT

Pancreatic duct adenocarcinoma is currently the sixth-leading cause of cancer death worldwide and the fourth in Europe, with a continuous increase in annual lethality in Portugal during the last two decades. Surgical *en-bloc* resection of the tumor with microscopic-negative margins and an adequate lymphadenectomy is the only possibility of long-term survival. As this type of cancer is a systemic disease, there is a high rate of recurrence even after curative resection, turning systemic therapy the core of its management, mostly based on chemotherapy. Neoadjuvant strategies for nonmetastatic disease showed significant improvement in overall survival compared with upfront surgery, namely in borderline resectable disease. Moreover, these strategies provided downstaging in several situations allowing R0 resections. Under these new oncologic strategies, several recent surgical issues were introduced, namely more aggressive vascular resections and even tumor resections in oligometastatic disease. This review revisits the state-of-the-art of surgical and oncological interventions in pancreatic duct adenocarcinoma and highlights recent advances in the field aiming to achieve higher survival rates.
Keywords: Carcinoma, Pancreatic Ductal/drug therapy; Carcinoma, Pancreatic Ductal/surgery; Carcinoma, Pancreatic Ductal/therapy; Pancreatic Neoplasms/drug therapy; Pancreatic Neoplasms/surgery; Pancreatic Neoplasms/therapy

RESUMO

O adenocarcinoma ductal é atualmente a sexta causa de morte oncológica a nível mundial, e a quarta na Europa, com um aumento contínuo da letalidade anual em Portugal nas duas últimas décadas. A ressecção cirúrgica em bloco do tumor com margens microscopicamente negativas e com uma linfadenectomia adequada é a única possibilidade de sobrevida a longo prazo. Como o adenocarcinoma ductal é uma doença sistémica tem uma alta taxa de recidiva, mesmo depois de uma ressecção curativa, tornando a terapêutica sistémica o centro da sua abordagem, baseada sobretudo em quimioterapia. As estratégias neoadjuvantes para a doença não metastizada demonstraram uma melhoria significativa na sobrevida global em comparação com a cirurgia direta, nomeadamente em doença tangencialmente ressecável. Além disso, estas estratégias possibilitaram um re-estadiamento inferior em várias situações, permitindo ressecções R0. Sob essas novas estratégias oncológicas, foram introduzidas várias modalidades cirúrgicas recentes, nomeadamente ressecções vasculares mais agressivas e mesmo ressecções tumorais na doença oligometastática. Esta revisão aborda o estado da arte das intervenções cirúrgicas e oncológicas no adenocarcinoma ductal pancreático e destaca os avanços recentes na área visando alcançar maiores taxas de sobrevida.
Palavras-chave: Carcinoma Ductal Pancreático/cirurgia; Carcinoma Ductal Pancreático /tratamento; Carcinoma Ductal Pancreático/tratamento farmacológico; Neoplasias Pancreáticas/cirurgia; Neoplasias Pancreáticas/tratamento; Neoplasias Pancreáticas/tratamento farmacológico

INTRODUCTION

Despite its much lower incidence than other malignancies such as lung, breast, colorectal, or prostate, pancreatic ductal adenocarcinoma (PDAC) is the sixth-leading cause of cancer death worldwide and the fourth in Europe and in the United States.[1,2]

In Portugal, PDAC-associated deaths doubled from 1991 to 2015, reflecting a mean annual increase of around 3%, predicting a 51% increase in annual deaths during the next two decades: generating more awareness concerning PDAC is highly pertinent in the near future.[3]

Pancreatic cancer primarily consists of adenocarcinomas originating from the exocrine portion of the pancreas. However, a smaller proportion comprises neuroendocrine tumors derived from the endocrine pancreas. In most cases, PDAC develops through a series of cumulative genetic alterations starting from precursor lesions known as pancreatic intraepithelial neoplasia (PanIN). These PanIN lesions are microscopic in size (< 5 mm) and arise from the pancreatic ducts. Low grade PanIN represents ductal cells with mucinous differentiation and minimal atypia, while high grade PanIN corresponds to carcinoma in situ, indicating a more advanced stage. The average time between the progression from low to high grade PanIN1 is estimated to be approximately 11.7 years.[4,5]

Epidemiological studies have identified several modifiable risk factors associated with PDAC. These factors include overweight and obesity,[6,7] physical inactivity,[8] smoking,[9,10] alcohol consumption[11] and diabetes mellitus.[12] Additionally, there are non-modifiable risk factors such as age,[13] chronic pancreatitis,[11] and genetic factors/family history of PDAC.[14]

Pancreatic duct adenocarcinoma is usually diagnosed at advanced stages, with 53% of the patients having metastasis at the time of diagnosis. The prognosis remains very poor, with a 5-year survival rate of 2.9% for metastatic disease and just 20% for resectable disease.[1] Therefore,

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identifying high-risk individuals for early detection is a rising strategy, using new diagnostic and therapeutic tools.

About 10% of PDAC cases harbor inherited factors or associated germline pathogenic variants, and a smaller number of these will have a therapeutically actionable gene change. Among these, one of the most common molecular abnormalities are mutations in the breast cancer susceptibility genes (BRCA 1/2), making these cells particularly sensitive to platinum-based chemotherapy and olaparib as maintenance therapy.[15,16]

The only potentially curative treatment is surgical resection with negative margins (R0), and this statement has remained accurate for more than 20 years.[17,18] Local radicality (R0) in oncological pancreatic surgery includes *en-bloc* resection of the tumor with clear margins in combination with an adequate extent of lymphadenectomy, which follows the same principles of any digestive cancer.[19]

Local radicality is more difficult to achieve in PDAC compared to other gastrointestinal cancers, due to the pancreatic anatomical relationships (with the major visceral blood vessels), and to PDAC biology (with its predisposition for perineural invasion and growth towards these main structures).

Radicality is defined by the resection margin (R−) status and by the distance to it.[20]

The R-status has considerable impact on survival outcomes if all relevant margins (including transection and circumferential) are thoroughly evaluated according to current standards. If a pancreatic head cancer was resected with a minimum safety margin of 1 mm, this is associated with a median survival of 42 months and a 38% five-year survival rate. For left-sided pancreatic cancers the median survival and five-year survival associated with a minimum safety margin of 1 mm are even more favorable, with 62 months and 53%, respectively.

Surgical resection will remain the cornerstone of treatment for localized PDAC, and its indication will even be extended.[21] Despite more active systemic therapy combinations for PDAC, cure remains elusive and is feasible only with localized, operable disease.[22]

Based on whether a distant organ is involved, PDAC is divided into metastatic or nonmetastatic diseases. In surgical terms, resectability status for the nonmetastatic group is defined by the probability of obtaining a negative margin, assessing circumferential degrees of contact between the tumor and the arterial (superior mesenteric artery, SMA, celiac axis, CA, and common hepatic artery, CHA) and venous (portal vein, PV, or superior mesenteric vein, SMV) structures: the so-called vascular margins. For nonmetastatic disease, that status can further be classified as resectable (RPC), borderline resectable (BRPC) and unresectable/locally advanced (LAPC) disease.[23] The concept of resectability itself is currently a point of debate, considering the context of neoadjuvant therapy (treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery). Beyond anatomical factors, biological and conditional host-related factors should be evaluated before considering surgery.[24] New criteria are being proposed, including inflammatory response, liquid biopsy markers, and genomic mutations.[25]

Surgical options in the treatment of PDAC

There has been a continuous effort in order to achieve a R0 resection: surgical options aim for local radicality and should be guided towards the mesenteric and celiac arteries and at the mesenteric and portal veins.

All the techniques of PDAC surgery must be based on two closely related factors: efficacy and safety. The main parameters of safety are perioperative (90-day or in-hospital) morbidity and mortality, both mostly determined by the rate of postoperative pancreatic fistula. The efficacy of surgery is defined by two main outcome parameters: median survival time and five-year survival rates.

The efficacy is mainly determined by local radicality of the resection while its safety is mainly determined by the reconstruction.

Perioperative morbidity, especially pancreatic fistula and other septic complications have considerable impact on the possible delay in the administration of adjuvant therapy, which in turn is closely associated with survival. On the opposite, increase in local radicality (extended lymph node dissection, vascular/multivisceral resections, and total pancreatectomy) increases the risk of morbidity.[26]

Resection phase: efficacy issues

Lymphadenectomy

Pancreatic duct adenocarcinoma spreads rapidly to the regional lymph nodes with a high number of metastatic lymph nodes found even in early cancers, which is considered an important prognostic factor. Recent data highlights the importance of peripancreatic lymphatics in the progression and metastases and their potential as a predictor of patient outcomes and a therapeutic target.[27,28]

Due to the prognostic importance of lymph node involvement, lymphadenectomy is considered an essential step of any resection technique, and should be removed with the specimen whenever possible. Standard lymphadenectomy is a guide for surgeons when operating on patients with resectable tumors, and according to literature, extended lymphadenectomy does not benefit long-term survival and might lead to higher levels of morbidity.[29]

Comparable to the setting of pancreatic head resection, more extended lymphadenectomy is not recommended in distal resections, as this is associated with increased

morbidity without proven oncological benefit.

The volume of lymph node dissection in total pancreatectomy comprises standard lymph- adenectomy in pancreaticoduodenectomy and distal pancreatectomy.[30]

Artery-first approaches

The rates of R1 resection (removal of all macroscopic disease, but microscopic margins are positive for tumor) remain high with most patients, who develop recurrence either locally (mainly along the SMA margin) or liver metastases within the first two years.

The increasing use of neoadjuvant therapy for BRPC and LAPC has created the added challenge of local staging predominantly along the SMA. Starting surgical resection by the dissection of the SMA (artery-first approach) has a potential role allowing trial dissection and frozen sections along the SMA at an earlier stage of pancreatoduodenectomy before irreversible steps are taken to identify tumor regression along this margin.[31]

Recent studies suggest that there is only a marginal improvement in R0 resection status with an artery-first approach, and that therefore evidence is lacking to support its routine use.[32]

Oligometastatic PDAC

It defines an intermediate stage between limited and metastatic disease, being characterized by the presence of fewer than five metastases.[33] These include para-aortic lymph-nodes, liver, and pulmonary metastases.

According to currently valid guidelines, local resection procedures are not recommended in the metastatic stage of PDAC.[34]

There is increasing data suggesting that there may be subgroups within stage IV patients that might benefit from primary tumor and metastatic resection, especially in the setting of modern multimodal therapy regimens. No data are currently available so far, and therefore the oncological benefit cannot be assessed beyond individual experiences and individual case reports.

Vascular resections

Experience with vein resections has increased and is now accepted as a standard approach for selected patients in most institutions.[35] The need to perform a venous resection must be considered whenever required to get negative resection margins.

Surgical outcomes show that pancreatectomy with venous resection requires longer operative time and increases blood loss compared to standard resections, even if postoperative morbidity is similar.[36]

Based on the lower R0 rates and more positive lymph nodes, overall survival rates can be lower,[37] even though this remains controversial as a recent analysis showed similar survival in pancreaticoduodenectomy with venous resection compared to standard pancreaticoduodenectomy after adjustment for baseline characteristics.[38]

In contrast with the wide acceptance of vein resection in treating PDAC, performing pancreatectomy with artery resection remains debatable, since there are only a few publications that show favorable long-term survival results.

Traditional resectability criteria are currently challenged by the development of new and more powerful systemic treatments. In fact, recent literature has demonstrated that there are survival advantages associated with arterial resections compared to palliative procedures.[39]

There is evidence that overall prognosis and survival outcomes are more associated with the biological characteristics of the tumor rather than the vessels involved. Therefore, factors such as the aggressiveness of tumor development and its response to systemic therapy should be taken into consideration prior to performing surgical treatment.[40]

There are three main modalities of radical pancreatectomies with arterial resection that are described in the literature:

- Pancreaticoduodenectomy with superior mesenteric artery resection[41];
- Distal pancreatectomy with *en-bloc* celiac axis resection (modified Appleby Operation)[42];
- Pancreatoduodenectomy with common hepatic artery resection and reconstruction.[43]

These complex arterial resections should be reserved for high volume centers as they require experience beyond pancreatic surgery and entail skills in vascular and transplant surgery.

Minimally invasive (laparoscopically and robotic) surgery

As pancreatic surgery implies intricate dissections and complex sutured anastomoses, open surgery remains standard practice. Minimally invasive surgery practice among pancreatic surgeons is significantly lower than in other surgical specialties, largely due to a considerable learning curve for laparoscopic pancreaticoduodenectomy (PD). The LEOPARD-2 trial comparing laparoscopic versus open PD was terminated early due to a higher mortality directly related to the laparoscopic group of patients.[44]

As robotic pancreatic surgery is a new technology, there is still an absence of robust and established evidence to justify its use despite the perceived advantages.[45]

Reconstruction phase: safety issues

Post-operative pancreatic fistula and hemorrhage

Post-operative pancreatic fistula (POPF) is a serious

complication and a major cause of morbidity and mortality in pancreatic surgery. It is the main complication after cephalic pancreaticoduodenectomy, a procedure with a constantly high morbidity (30% - 50%) for the last 20 years.[46]

Post-operative pancreatic fistula are responsible for and/or associated with 70% of deaths due to septic and/or hemorrhagic complications.

The diagnosis of POPF has been based on the definition of the International Study Group for Pancreatic Fistula, namely a level of amylase in drained fluid greater than three times the upper limit of blood amylase from D3 postoperatively, associated with a significant change in postoperative course or management.[47]

According to the classification, post-operative hemorrhage is divided by time of onset:

- Early (within the first 24 hours after operation),
- Delayed (beyond 24 hours).

Based on the intensity, events of bleeding are classified into:

- Mild (hemoglobin decrease less than 3 g/dL and no need for surgical or interventional angiographic procedures),
- Severe (hemoglobin decrease more than 3 g/dL, life-threatening, invasive procedures are necessary).

Grade A consists of all episodes of early mild bleeding and Grade C of all late severe events. Grade B contains the early severe and late mild bleeding occurrences.

The most common bleeding sources are the stump of the gastroduodenal artery, followed by the common and proper hepatic artery, superior mesenteric artery, and other bleeding sites.[48,49]

Since 2003, it has been shown that radiological interventions, mainly for intraabdominal fluid collections due to undrained postoperative pancreatic fistulas but also for control of post pancreatectomy hemorrhage, can prevent the need for re-operation in a high proportion of patients postoperatively and reduce associated morbidity/mortality.[50]

Delayed gastric emptying

Delayed gastric emptying (DGE) is a frequent complication of pancreaticoduodenectomy, accounting for 14% - 30% of patients post-operatively. Delayed gastric emptying, or gastroparesis, occurs due to the impaired motor function of the stomach to empty its contents.

The International Study Group on Pancreatic Surgery (ISGPS) suggested as definition “the inability to progress to a standard diet by the end of the first post-operative week” and includes prolonged nasogastric intubation.[51]

It is possible that there is an association with several risk factors such as sepsis, intra-abdominal collections, POPF and respiratory complications. Management of these complications is mandatory. The type of digestive anastomosis makes no difference in the incidence of DGE.[52]

Patience from the surgeon is crucial. Reoperation is not indicated in the absence of any mechanical obstruction and can aggravate the problem.

Adjuvant therapy

Adjuvant therapy is the additional treatment given after the primary treatment to lower the risk that the cancer will come back.

After diagnosis, only 10% to 20% of cases are resectable.[18] Pancreatic duct adenocarcinoma is a systemic disease, with a 70% - 80% recurrence rate, even after curative resection, turning systemic therapy the mainstay of its management, largely based on cytotoxic agents.[53] It has been demonstrated that there are epithelial to mesenchymal transition (EMT) cells in mouse models seeding the liver at pancreatic intraepithelial neoplasia (PanIN) stage.[54] Circulating tumor cells (CTC) have been found in all stages of PDAC even in precursor lesions.[55] This is probably the reason why surgery alone does not enable long-term survival in these patients, with median survival times of around eight to 10 months and early tumor relapse in most of them.[56,57] Adjuvant chemotherapy has thus been developed during the last decades with improvement in overall survival (OS).

The ESPAC-1 trial showed for the first time that a fluorouracil-based adjuvant chemotherapy significantly increased survival, compared to surgery alone (median OS: 20.1 *vs* 15.5 months, respectively). A detrimental effect on survival by using concomitant chemoradiotherapy compared to chemotherapy was also shown.[58]

The CONKO-001 trial compared adjuvant gemcitabine in monotherapy versus observation in resectable PDAC, with a statistically significant improvement in disease-free survival (DFS) (13.4 *vs* 6.9 months, respectively), and an OS comparable between the gemcitabine and the control group (22.1 *vs* 20.2 months, respectively).[59]

The ESPAC-3 trial compared the two regimens fluorouracil and gemcitabine-based chemotherapy used in the ESPAC-1 and in CONKO-001 trials and showed no significant differences between the two (median OS 23.0 *vs* 23.6 months respectively) with a more acceptable safety profile in the gemcitabine arm (grade 3 - 4 toxicities: 7.5% *vs* 14.0% in the fluorouracil arm).[60]

In 2017, the ESPAC-4 trial demonstrated a superior OS of gemcitabine plus capecitabine *versus* gemcitabine alone in patients with R0 resection, of 28 months to the experimental arm and 25.5 months for the control arm (gemcitabine alone). No relapse free survival (RFS) was seen.[61]

The PRODIGE 24 trial (2018), compared modified mFOLFIRINOX (5-FU+irinotecan+oxalplatin) and gemcitabine: the toxicity was higher in the experimental arm

with grade 3 - 4 toxicities of 75.5% *vs* 51.1%.[62]

According to current guidelines, FOLFIRINOX (5-FU+irinotecan+oxalplatin) is now the first choice for fit selected patients.

New strategies are being implemented like the addition of immunotherapy -algenpantucel-L to standard adjuvant therapy, with a 12-month DFS of 62% and OS of 86%. A multi-institutional phase 3 trial is ongoing.[63]

At the American Society of Clinical Oncology (ASCO) in 2022 a phase I trial of adjuvant autogene cevumeran, an mRNA neoantigen vaccine identified from resected PDAC, concomitant with atezolizumab and FOLFIRINOX, was presented. The vaccine induced neoantigen-specific immunity with responders performing a long RFS versus non responders (median not reached versus 13.7 months). Further clinical trials are necessary.[64]

The role of radiotherapy in the adjuvant setting has contradictory data, as shown in the ESPAC1 and EORTC trials with no benefit, even in R1 resected patients. However, more recent studies with data reported from two different cancer database registries, showed potential benefit, particularly in node positive and R1 resection.[57,65-67]

Neoadjuvant therapy

Neoadjuvant/induction strategies (treatment given as a first step to shrink a tumor before the main treatment, usually surgery) result from the evidence of many trials with different entities (LAPC, BRPC, even RPC).

A meta-analysis of neoadjuvant versus upfront surgery, using six prospective randomized trials for RPC and BRPC, with 850 patients, significantly improved OS in an intention to treat approach for neoadjuvant treatment. All neoadjuvant chemotherapy were gemcitabine based, and none used associations with Nab-paclitaxel nor FOLFIRINOX.[68]

Neoadjuvant therapy seems consensual, but the best regimen to use is not well established.

The intention to treat results from a meta-analysis of 20 studies, representing 283 patients with BRPC who received neoadjuvant FOLFIRINOX, showed an OS of 22.2 months, 67.8% underwent a curative resection with a R0 rate of 89.1%. Toxicity with severe adverse events was more frequent with neutropenia 17.5%, diarrhea 11.1% and fatigue 10.8%.[69]

Similar results have been reported in a meta-analysis published in 2017 including eleven non-randomized studies (315 patients) with LAPC with a median PFS of 15 months and an OS of 24.2 months, which is identical to that reported in the ESPAC- 3 trial (patients in stage I-II that underwent resection followed by adjuvant therapy with gemcitabine).[70]

Gemcitabine and Nab-paclitaxel have been tested prospectively in this setting, and two phase II trials should be mentioned. The Italian GAP trial tested gemcitabine plus Nab-paclitaxel versus gemcitabine alone, with a reduction of 20% in distant spread after three cycles of the combination and an advantage in PFS, of seven versus four months, OS, 12.7 *vs* 10.6 months and a response rate of 27% *vs* 5%, respectively, in the combination arm and in the gemcitabine alone arm.[71]

LAPACT was a phase II single arm trial that tested induction with Nab-paclitaxel plus gemcitabine. The trial validated the activity of Nab-paclitaxel plus gemcitabine in LAPC and the potential to convert unresectable into resectable disease.[72]

In a time of more effective chemotherapy regimens, the role of chemoradiotherapy in the treatment of LAPC and even RPC remains poorly understood.

In LAP07, a phase III randomized trial, 449 patients with LAPC were enrolled between 2008 and 2011. This trial reported no differences in OS between groups, including chemoradiotherapy *versus* CT and GEM alone or GEM/erlotinib as maintenance therapy. However, the chemoradiotherapy group experienced a decrease in local progression (32% *vs* 46%, $p = 0.03$).[73]

The SCALOP multicenter phase II study was designed to evaluate the safety and efficacy of GEM-based and CAP-based chemoradiation in 74 patients with locally advanced PDAC. The initial results suggested that the CAP-based regimen would be better than the GEM-based regimen after the induction phase, and better tolerated. However, the difference in the nine-month PFS (primary endpoint) was not statistically significant. Long-term results of the SCALOP study revealed that the CAP-based chemoradiation was superior regarding OS and PFS.[74]

The AGEO-FRENCH Group published a retrospective non-randomized study in 2019 including 203 patients with BRPC or LAPC. This study evaluated the effect of the addition of neoadjuvant chemoradiotherapy to a FOLFIRINOX induction regimen and showed an OS and DFS of 45.4 months and 16.2 months, respectively. Patients with additional CRT had higher R0 resection rate (89.2% *vs* 76.3%), ypN0 rate (no residual tumor after chemo(radio)therapy in the lymph nodes) (76.2% *vs* 48.5%), and a higher rate of pathologic major response (tumor shrinkage) (33.3% *vs* 12.9%). In the FOLFIRINOX+CRT group, patients had a lower rate of locoregional relapse (28.3% *vs* 50.7%). Patients with additional CRT had longer OS than those receiving FOLFIRINOX alone (57.8 *vs* 35.5 months), suggesting that additional chemoradiotherapy may be beneficial in the neoadjuvant setting.[75]

The ALLIANCE A021501 study randomized patients with BRPC to either mFOLFIRINOX or preoperative mFOLFIRINOX, followed by stereotactic body radiation therapy (SBRT). The results demonstrated that neoadjuvant mFOLFIRINOX was associated with favorable OS.

Moreover, mFOLFIRINOX with hypo fractionated radiation therapy (RT) did not improve OS compared with the historical data.[76]

The PREOPANC-1 was a multicenter, phase III trial, where patients with RPC and BRPC were randomly assigned (1:1) to neoadjuvant chemoradiotherapy or upfront surgery. Neoadjuvant chemoradiotherapy consisted of three cycles of gemcitabine combined with 36 Gy radiotherapy in 15 fractions during the second cycle. After restaging, patients underwent surgery followed by adjuvant gemcitabine. Patients in the upfront surgery group underwent surgery followed by adjuvant gemcitabine. The primary outcome was OS by intention-to-treat.

Two hundred and forty-six patients were enrolled between 2013 and 2017. The long-term results showed a better OS for the chemoradiotherapy arm compared with the surgery upfront arm, 15.7 months *vs* 4.3 months, the five-year OS rate was 20.5% (95% CI, 14.2 to 29.8) with neoadjuvant chemoradiotherapy and 6.5% (95% CI, 3.1 to 13.7) with upfront surgery.[77]

ESPAC-5F was a prospective four arm phase II trial with the aim of determining the feasibility and efficacy of a comparison of immediate surgery versus neoadjuvant GEMCAP or FOLFIRINOX or CRT. The resection rate was 62% for immediate surgery and 55% for neoadjuvant therapy. The R0 resection rate in resected patients was 15% and 23%, respectively. The one-year survival rate was 40% for immediate surgery and 77% for neoadjuvant therapy. Albeit there was no difference in resection rate between arms, neoadjuvant therapy had a significant survival benefit compared with immediate surgery.[78]

In conclusion, both FOLFIRINOX and GEM/nab-P could be suggested as induction therapy to patients with LAPC and in the neoadjuvant setting for RPC or BRPC cases. Chemoradiotherapy in the neoadjuvant setting seems to decrease the rate of local recurrence, improve R0 resection and, in some studies, is associated with a survival benefit.

Many trials are ongoing, that could improve our understanding about the best strategy to follow in the years to come.

CONCLUSION

Pancreatic duct adenocarcinoma has become a leading cause of cancer death worldwide, presently the fourth in Europe and in the United States. In Portugal, a significant increase of PDAC-associated deaths in the last two decades predicts its continuous rise, justifying the need to raise awareness of this disease.

Its only potentially curative treatment is *en-bloc* surgical resection with negative margins (R0), in combination with an adequate extent of lymphadenectomy, according to staging (represented in Fig. 1).

This is a systemic disease, with a high recurrence rate, even after curative resection, turning systemic therapy the mainstay of its management, largely based on adjuvant cytotoxic agents developed during the last few decades with improvement in OS.

In the continuous effort to achieve an R0 resection aiming for local radicality and oriented at the mesenteric and celiac vessels, surgery for PDAC has been changing and

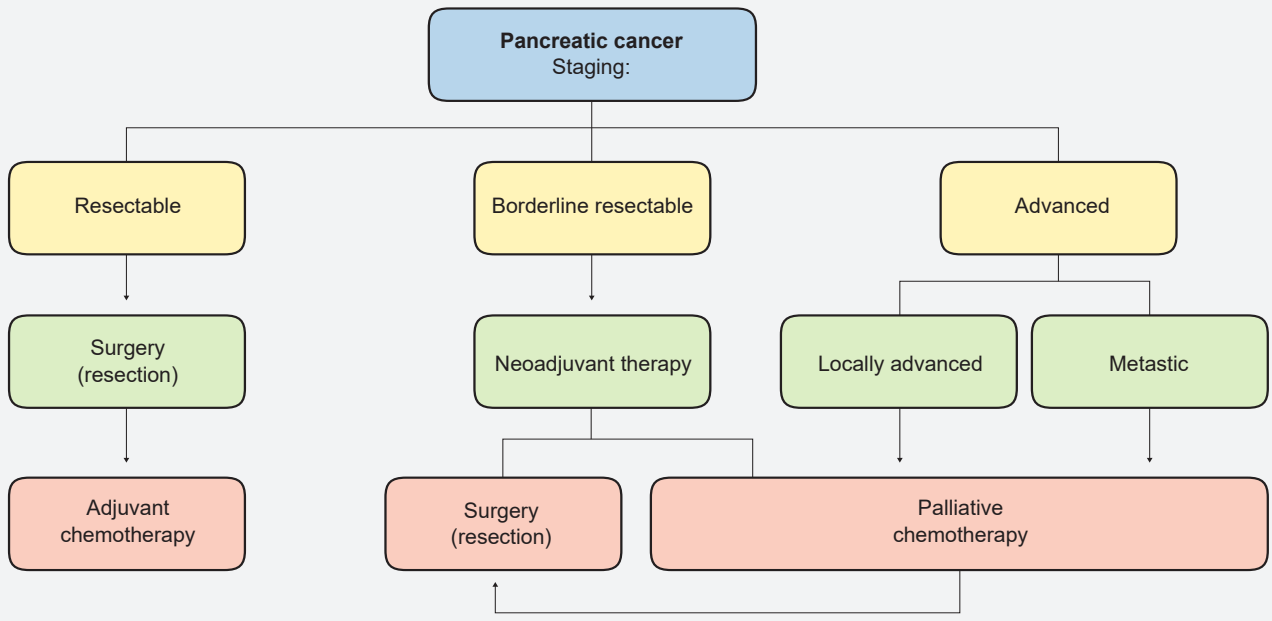

Figure 1 – Treatment algorithms for pancreatic cancer after staging

developing rapidly with specific technical approaches, including issues of efficacy and safety.

Neoadjuvant/induction strategies seem consensual, even though the best regimen is still not well established. Many trials that considered most different entities together, such as LAPC, BRPC and even RPC, showed significantly improved in OS in an intention to treat approach: there is an emerging emphasis in these strategies, to maximize R0 resections and early identification or failures.

There are several opportunities for progress through increased financial investment in fundamental research and the integration of data from diverse platforms of multi-omics (such as genome, proteome, transcriptome, epigenome, and microbiome combined analysis). The concept of using multi-omics as a valuable tool to subtype tumors and provide prognostic information is captivating, although its implementation in routine medical practice is still distant. Nevertheless, the use of these high-throughput technologies in the search for novel biomarkers and identification of therapeutic prospects holds tremendous potential. This approach can establish a framework wherein the data integration of multi-omics can yield valuable biomarkers with clinical usefulness. Moreover, understanding the influence of the stroma and its impact on tumor progression could represent a remarkable advancement in enhancing therapeutic efficacy. Investment should also prioritize the development of guidelines for early detection in high-risk groups, including those with genetic predisposition, individuals with family history of pancreatic cancer, smokers, alcohol consumers, patients with type 2 diabetes, patients with chronic pancreatitis, and individuals with obesity. Additionally, the implementation of national public health plans and raising awareness within the medical community and the public are crucial. These strategies have proven successful in other cancer types and are urgently needed to combat pancreatic cancer.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Surgical Management of Bilateral Limbal Stem Cell Deficiency

Abordagem Cirúrgica da Deficiência de Células Límbicas Bilateral

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ABSTRACT

At the age of 43 years-old, a man was left with bilateral limbal stem cell deficiency after an ocular alkaline burn with lime, which resulted in corneal opacification. After multiple unsuccessful surgical attempts to restore vision, including penetrating keratoplasties and Boston keratoprosthesis, visual acuity was counting fingers in the left eye. At 73 years of age, the patient underwent another surgery in his left eye. Cauterization of neovessels and removal of the vascular pannus were followed by partial excision of Tenon's capsule. Penetrating keratoplasty was followed by an intrastromal injection of anti-VEGF (vascular endothelial growth factor), and the ocular surface was covered with amniotic membrane. Postoperatively, the graft was clear with no signs of inflammation; vision improved to 20/50 and remained stable throughout the following two years. Herein we describe some adjunctive procedures that might have delayed failure and rejection of the corneal graft. This case demonstrates the difficulties in treating bilateral limbal stem cell deficiency in a tertiary eye care center with no capacity to perform stem cell therapy.
Keywords: Corneal Diseases/surgery; Epithelium, Corneal; Eye Burns/complications; Limbus Corneae; Ophthalmologic Surgical Procedures; Prosthesis Implantation; Stem Cells

RESUMO

Um doente do sexo masculino foi vítima de uma queimadura ocular com cal aos 43 anos, da qual resultou opacificação corneana bilateral e acuidade visual de perceção luminosa à direita e conta-dedos à esquerda. Foram feitas múltiplas tentativas para restaurar a visão, incluindo queratoplastias penetrantes e queratoprótese de Boston. Aos 73 anos, uma das abordagens cirúrgicas ao olho esquerdo do doente incluiu cauterização dos neovasos e remoção do *pannus* vascular, peritomia e excisão parcial da cápsula de Tenon. Seguidamente fez-se queratoplastia penetrante e injeção intraestromal de anti-VEGF (*vascular endothelial growth factor*), e a superfície ocular foi recoberta com membrana amniótica. No pós-operatório, o enxerto do olho esquerdo apresentava-se transparente, sem sinais de inflamação e a visão melhorou para 20/50, mantendo-se estável ao longo dos dois anos seguintes. Com este caso clínico pretendemos demostrar alguns procedimentos perioperatórios adjuvantes à queratoplastia penetrante que foram eficazes para aumentar a sobrevida do enxerto corneano, num centro terciário sem capacidade para fazer cultura e transplantação de células estaminais límbicas.
Palavras-chave: Células-Tronco; Doenças da Córnea/cirurgia; Epitélio Corneano; Implantação de Prótese; Limbus Corneae; Queimaduras Oculares/complicações

INTRODUCTION

Limbal stem cells (LSC) are adult stem cells residing in the corneal limbus.[1] They play a role in corneal epithelium renewal and serve as an obstacle to the advancement of conjunctival cells onto the cornea, thus maintaining its transparency.[1] Limbal stem cell deficiency (LSCD) is a congenital or acquired corneal disease that can lead to severe visual impairment. Due to a lack of normal epithelium healing, patients with LSCD experience recurrent corneal erosions, chronic surface inflammation and conjunctivalization of the cornea, and often complain of pain, photophobia, and severely decreased vision.[2] When the condition is bilateral, there are few management options to restore vision but the results are still modest even with LSC transplantation.[2-4] We report the results of a surgical technique in a case of a patient with bilateral LSCD treated at a tertiary center with no resources to perform LSC therapy.

CASE REPORT

We report a case of a man who at 43 years old suffered a bilateral chemical burn with lime, which resulted in adhesions of the bulbar and palpebral conjunctiva (symblepharon) and a vascularized corneal scar (leucoma) in the right eye (OD), as well as vascularization and corneal opacification in the other eye (LSCD Stage III) (Figs. 1 and 2).[1] Visual acuity (VA) was light perception with good projection in the OD and counting fingers (CF) at 2 m in the left eye (OS). The patient underwent multiple treatments and surgical procedures over the years, starting with symblepharon surgery of the OD, which consisted of transplantation of autologous oral mucosa. Cataract phacoemulsification and corneal transplant (penetrating keratoplasty) (PK) were undertaken in the OD at 63 years of age, but this was later rejected and failed. Three years later, the implantation of a Boston Keratoprosthesis type 1 (Boston K-Pro) was attempted in the OD, with VA improving to 20/63 (Fig. 3). Unfortunately, two years later, corneal melting ensued, causing extrusion of the Keratoprosthesis, which had to be replaced with a new PK. A corneal abscess developed once again, causing corneal melting, and vision decreased to hand motion. The patient was forced to undergo a third PK, but VA did not

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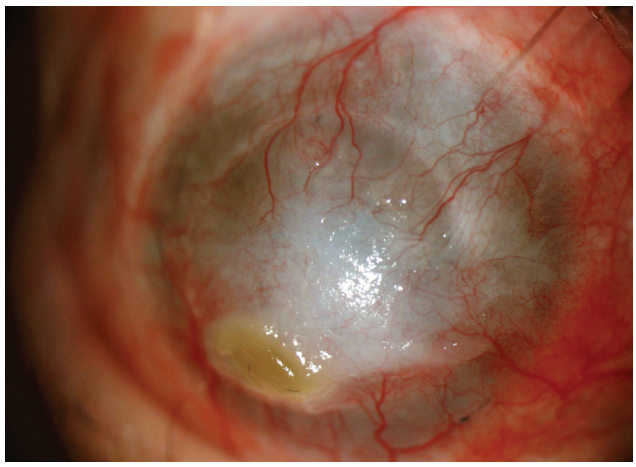

Figure 1 – Biomicroscopic photograph of the right eye, 23 years after the chemical injury and two years after the first penetrating keratoplasty. Conjunctivalization of the cornea, neovessels and inferior melting can be seen in the graft.

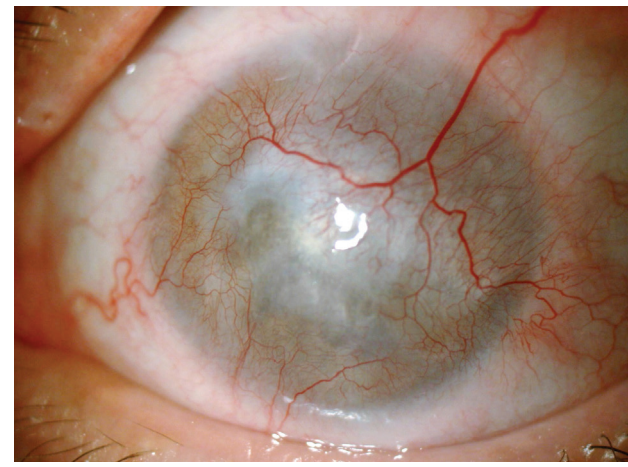

Figure 2 – Preoperative biomicroscopic photograph of the left eye. Conjunctivalization of the cornea with severe superficial and deep neovascularization is visible.

improve beyond CF.

At 73 years of age, immunosuppression treatment was initiated with oral cyclosporine (2 mg/kg daily) and tacrolimus ointment (0.2 mg/g) three times daily (tid) and autologous serum drops in the OS. Three months later, surgery was attempted in the OS (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18960/15054). Firstly, diathermy of neovessels and complete removal of the vascular pannus were performed, followed by a 360° conjunctival peritomy (an incision made at the limbus to reflect the conjunctiva and expose the Tenon's capsule) and partial excision of Tenon's capsule. Then, PK was performed and intrastromal injection of an anti-vascular endothelial growth factor (anti-VEGF) treatment (0.1 mL of ranibizumab, 10 mg/mL) was given in the periphery of the recipient's cornea. Finally, the transplant was fully covered with one layer of amniotic membrane, theepithelium was placed side up and the stromal side in contact with the ocular surface. The patient was kept under medical treatment with tacrolimus ointment tid, dexamethasone (1 mg/mL) tid, autologous serum drops and oral cyclosporine. Vision in the OS improved from CF at two meters to 20/50, and the graft was clear with no signs of vascularization (Fig. 4). Vision remained stable for two years, during which the patient was very satisfied with his quality of life. Two years after the procedure, intrastromal injection of ranibizumab, a new PK and cataract phacoemulsification were performed in the OS due to transplant rejection.

The patient is currently on fluorometholone 1 mg/mL tid, autologous serum drops and tacrolimus ointment. Visual acuity of the OS is 20/100 and the graft remains transparent with no epithelial defects or neovascularization.

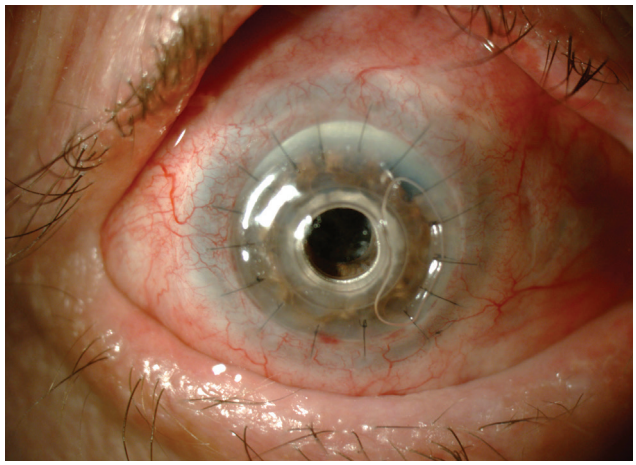

Figure 3 – Biomicroscopic photograph of the right eye after Boston type 1 keratoprosthesis implantation

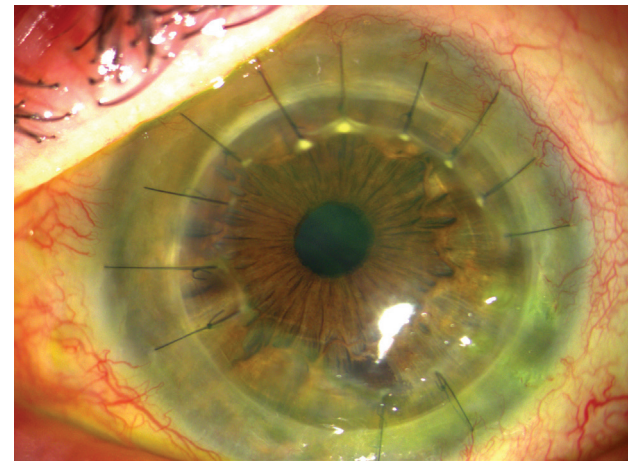

Figure 4 – Biomicroscopic photograph of the left eye, nine months after surgery. The cornea has a regular epithelium and there are no neovessels.

DISCUSSION

We presented a case of bilateral chemical burn that resulted in LSCD in both eyes. Allogenic limbal grafts are the mainstay for the treatment of bilateral total LSCD, such as kerato-limbal allograft (cadaveric donor) and living related conjunctival limbal allograft (with some risk of causing LSCD in the donor's eye).[5,6] Like ours, most ophthalmology centers do not have the technology to perform LSC culture and transplantation, which would have been a good option for our patient.[7] Nevertheless, there are limitations of LSC transplantation, particularly in bilateral LSCD cases, as both techniques require immunosuppression, and success rates vary between 33% to 77%.[5,8] Holoclar®, a stem-cell treatment, requires healthy cells from the patient's limbus.[6] Other non-limbal autologous sources of grafts include cultivated oral mucosal epithelial transplantation and autologous conjunctival epithelial transplantation, but both have been associated with corneal neovascularization. More studies are necessary to ascertain the safety and efficacy of mesenchymal stem cells as an LSC niche.[5,6] Finally, keratoprostheses do not require immunosuppression and lead to a fast visual recovery, although more than half of patients suffer from complications, such as glaucoma.[6,9] In this clinical case, attempts to restore vision in the OD with PK and Boston-KPro were unsuccessful and of limited value.

Regarding treatment of the OS, we managed to control inflammation and hence reduce the chances of graft rejection by improving the stability of the ocular surface, with autologous serum drops and systemic and topical immunosuppressants (tacrolimus and cyclosporine), effective perioperative treatments in LCSD.[2,3] During OS surgery, we performed partial removal of Tenon's capsule. Subconjunctival fibrosis and scar formation are mediated by human Tenon's fibroblasts, which modulate the deposition of collagen and accumulation of extracellular matrix[10]; also, they exhibit VEGF production upon IL-1β stimulation and further contribute to neovascularization and fibrosis.[11,12] Therefore, the partial removal of Tenon's capsule might have contributed to the transparency of the graft.

Chronic ocular inflammation plays a key role in the pathophysiology of corneal neovascularization.[1,5] In an attempt to halt neovessel growth in the graft, vessel diathermy and intrastromal injection of anti-VEGF treatment were performed, similarly to other LSCD cases.[13,14] Amniotic membrane release anti-angiogenic and anti-inflammatory factors and have shown good results in promoting epithelization of the corneal surface, while also reducing inflammation and neovascularization in partial LSCD.[15] Furthermore, there is a decline in immune function in elderly individuals and the patient's age and immunologic state should also be taken into consideration.

This report demonstrated the difficulties of treatment of bilateral LSCD in a center that does not have the resources to perform LSC therapy. Preoperative treatment with systemic immunosuppression, optimization of the ocular surface, and prevention of inflammation and neovascularization with tenectomy, intrastromal anti-VEGF and vessel diathermy before PK, might have been crucial to delay failure and rejection. In summary, a few surgical adjunctive techniques to PK provided satisfactory results for two years, a relatively short period of time, but which led to a significant change in the patient's quality of life.

AUTHOR CONTRIBUTIONS

RP: Data acquisition and analysis, draft of the paper, critical review.

JQG: Patient care, critical review and approval of the final version.

MJQ: Conception and design of the work, patient care, critical review and approval of the final version.

JM: Critical review and approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Tuberculose Ocular em Pediatria: Relato de Caso

Ocular Tuberculosis in Pediatrics: A Case Report

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RESUMO

Adolescente, 17 anos, sexo masculino, foi levado ao serviço de urgência por hipovisão esquerda e 'moscas volantes' de aparecimento nesse dia. Referiu contacto com tuberculose pulmonar quinze anos antes (mãe como caso índex); realizou profilaxia com isoniazida durante quatro meses. O exame oftalmológico apresentava uveíte posterior e intermédia à esquerda. O estudo analítico não apresentava alterações. A IgG para herpes *simplex* 1 veio positiva e as restantes serologias incluindo vírus varicela-zoster vieram negativas. A radiografia tórax não apresentava alterações. Após duas semanas, foi observada uma membrana epirretiniana com risco de descolamento tracional da retina. A prova de Mantoux apresentava endruração de 15 mm e o teste IGRA veio positivo. Foram colhidas secreções respiratórias e humor vítreo para cultura. Foi iniciada terapêutica quádrupla e prednisolona. Dez dias depois verificou-se um descolamento hialóide posterior com hematoma vítreo subjacente. Foi então submetido a vitrectomia posterior e endolaser periférico sem intercorrências. Um mês depois foram conhecidos os resultados dos exames culturais com crescimento de *Mycobacterium tuberculosis*. Iniciou desmame progressivo da corticoterapia. Realizou terapêutica antibacilar durante seis meses. Verificou-se resolução completa com normalização da acuidade visual.

Palavras-chave: Adolescente; Tuberculose Ocular/diagnóstico; Uveíte/diagnóstico

ABSTRACT

A 17-year-old male was taken to the emergency department for decreased left visual acuity and floaters beginning that same day. There was a history of exposure to pulmonary tuberculosis five years before (mother as index case) followed by a four-month period of isoniazid prophylaxis. The ophthalmic examination showed posterior and intermediate uveitis in the left eye. Laboratory tests were normal; IgG for herpes simplex 1 was positive and both the varicella-zoster virus and remaining serologic tests were negative. Chest radiography was normal. Two weeks later, an epiretinal membrane with risk of tractional retinal detachment was observed. The Mantoux tuberculin skin test showed an induration of 15 mm and the IGRA test was positive. Sputum and vitreous humor samples were collected. Quadruple therapy and prednisolone were started. Ten days later, a posterior vitreous detachment with underlying vitreous hematoma was observed. Posterior vitrectomy and peripheral endolaser were performed without complications. One month later, the microbiological results became available, with the identification of *Mycobacterium tuberculosis*. Corticosteroids were weaned progressively. Antituberculous drugs were maintained for six months. The patient made a full recovery.

Keywords: Adolescent; Tuberculosis, Ocular/diagnosis; Uveitis/diagnosis

INTRODUÇÃO

A tuberculose permanece uma das principais causas de morbimortalidade a nível mundial.[1] Esta doença pode envolver qualquer órgão, incluindo o olho.[2] A tuberculose ocular apresenta-se frequentemente sob a forma de uveíte, devendo ser considerada como diagnóstico diferencial perante qualquer inflamação intraocular.[2–5] Tendo em conta o amplo espetro de formas de apresentação da doença, é necessário um elevado grau de suspeição para que seja feito este diagnóstico.[6] A maioria dos doentes com tuberculose ocular não tem outras manifestações sistémicas da doença (como febre ou perda ponderal) o que também pode resultar em atrasos no diagnóstico. A confirmação microbiológica do diagnóstico é muitas vezes difícil de obter, sendo a maioria dos diagnósticos presuntivos.[3,4,6] O atraso no diagnóstico, e consequente atraso no início do tratamento, pode resultar em complicações oftálmicas e morbilidade visual significativa.[3,7,8]

CASO CLÍNICO

Adolescente, 17 anos, sexo masculino, foi levado ao serviço de urgência por queixas de hipovisão à esquerda e miodesópsias ('moscas volantes') com início no próprio dia. Negava dor ocular, olho vermelho ou fotofobia. Não referia sintomas constitucionais, queixas respiratórias ou musculosqueléticas. Apresentava história pessoal de aftas ocasionais. Referiu contacto com tuberculose pulmonar quinze anos antes (mãe como caso índex), tendo feito profilaxia com isoniazida durante quatro meses. Não apresentava história de viagens recentes ou contacto com animais. Ao exame objetivo apresentava bom aspeto geral, sem lesões cutâneas e sem dificuldade respiratória; auscultação cardiopulmonar sem alterações. O exame musculoesquelético revelava apenas ressalto da articulação temporomandibular à direita. O exame oftalmológico apresentava nódulos esbranquiçados redondos dispersos na retina periférica (*snowbanking*), vitrite com *snowballs*, edema retiniano e hemorragia retiniana nasal à papila no olho esquerdo. Foi

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Tabela 1 – Resultados analíticos no Serviço de Urgência e na Consulta Externa

		Serviço de Urgência	1.ª consulta
Hb (g/dL)		16,0	16,2
Leucócitos (/µL)		7750	7880
Neutrófilos (/µL)		5540	4700
Linfócitos (/µL)		1720	2400
Plaquetas (/µL)		249 000	296 000
Velocidade sedimentação 1ªh (mm)		---	4
Ureia (mg/dL)		47	28
Creatinina (mg/dL)		0,62	0,66
Proteína C reativa (mg/L)		1,1	0,77
Ácido úrico (mg/dL)		---	4,1
TGO/TGP (U/L)		---	17/14
ECA (U/L)		51	44
Urina II		---	pH 6,5 Densidade 1041 Sem proteinúria ou leucocitúria
Serologia	**Herpes *simplex* 1**	IgM negativo IgG positivo	---
	Herpes *simplex* 2	IgM negativo IgG negativo	---
	VVZ	IgM negativo IgG negativo	---
	Toxoplasmose	IgM negativo IgG negativo	---
	VIH	Negativo	---
Teste treponémico (TPPA/TP)		Negativo	---
Anticorpos antinucleares		Negativo	---

diagnosticada uveíte posterior e intermédia à esquerda. O estudo analítico inicial (Tabela 1) revelou IgG positiva para herpes *simplex* 1 e vírus varicela zoster e serologias negativas para toxoplasmose, vírus da imunodeficiência humana, herpes *simplex* 2 e *Treponema pallidum*. A radiografia de tórax não apresentava alterações (Fig. 1).

Foi observado em consulta de oftalmologia duas semanas depois, mantendo papilite acentuada com neovascularização, múltiplas hemorragias superficiais retinianas e pré-retinianas com múltiplas *snowballs* e vasculite retiniana. Observou-se membrana epirretiniana em formação com risco de descolamento tracional da retina. Foi então realizado novo estudo analítico sérico e urinário (Tabela 1) com hemograma, velocidade de sedimentação, proteína C reativa e enzima conversora da angiotensina normais. A prova de Mantoux (indução 15 mm) e *interferon gamma release assay* (IGRA) obtiveram resultados positivos. Foram colhidas secreções respiratórias para pesquisa de *Mycobacterium tuberculosis* após nebulização com soro hipertónico. Foi realizada cultura de humor vítreo e iniciada terapêutica quádrupla (isoniazida, pirazinamida, rifampicina e

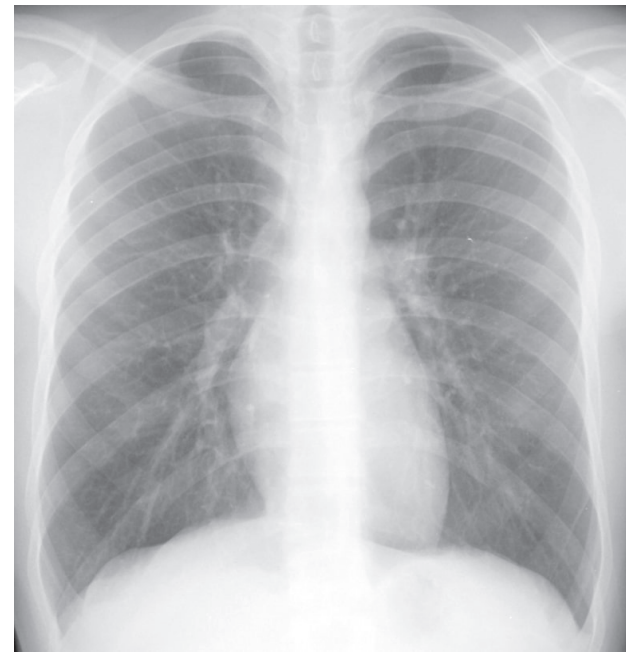

Figura 1 – Radiografia de tórax

etambutol) em associação a prednisolona oral.

Dez dias após o início de terapêutica referiu agravamento da acuidade visual à esquerda, em relação com descolamento hialóide posterior a 360º com hematoma vítreo subjacente. Foi então submetido a vitrectomia posterior e endolaser periférico que decorreram sem intercorrências. Verificou-se melhoria progressiva dos sinais inflamatórios do segmento posterior.

Aproximadamente um mês após o início dos medicamentos antituberculosos foi conhecido o resultado dos exames culturais, tendo-se verificado crescimento de *Mycobacterium tuberculosis* tanto na colheita de secreções respiratórias como de humor vítreo. Os resultados microbiológicos encontram-se explicitados na Tabela 2. Iniciou desmame progressivo da corticoterapia. O doente foi encaminhado para o centro de diagnóstico pneumológico onde foi realizada a identificação e verificado o rastreio dos contactos. Realizou terapêutica antibacilar durante seis meses (dois meses de terapêutica quádrupla e quatro de terapêutica dupla), sem efeitos adversos. Verificou-se resolução completa dos sinais inflamatórios oculares com normalização da acuidade visual.

DISCUSSÃO

A uveíte define-se como uma inflamação da úvea, a porção média do olho que inclui a íris, corpo ciliar e coroide.[9] A uveíte pode ser causada por patologias sem envolvimento extraocular sendo, contudo, mais frequente ocorrer no contexto de uma doença sistémica cujo diagnóstico etiológico inclui patologias infeciosas ou doenças inflamatórias sistémicas.[1,3,9] As causas infeciosas incluem múltiplos agentes como herpes vírus, citomegalovírus, toxoplasmose, tuberculose ou sífilis.[9] A tuberculose ocular pode afetar qualquer tecido ocular, sendo a manifestação mais frequente a uveíte (habitualmente posterior) na ausência de sintomas sistémicos.[3,5,6] Quando se apresenta sob a forma de uveíte anterior esta é geralmente granulomatosa.[5] A inflamação intraocular existente pode resultar em fenómenos de vasculite retiniana, potencialmente culminando, quando não adequadamente tratados, no descolamento tracional da retina e fenómenos de neovascularização.[10]

A colheita de material para estudo micobacteriológico deve ser realizada sempre que possível, uma vez que o diagnóstico definitivo depende do isolamento do *Mycobacterium tuberculosis*.[1,3] Contudo, as amostras necessárias para este isolamento (humor vítreo, humor aquoso ou retina) são de difícil colheita, implicando procedimentos invasivos não completamente inócuos para o doente, para além de evidenciarem baixa sensibilidade.[1,3] Neste contexto, a prova de Mantoux e o IGRA devem ser realizados em caso de suspeita.[1,3,11] A radiografia de tórax e o exame micobacteriológico de secreções respiratórias devem também ser realizados, uma vez que podem contribuir para o diagnóstico de tuberculose ocular, mesmo na ausência de sintomas respiratórios, como aconteceu neste caso.[1,3]

Perante um quadro clínico sugestivo e IGRA positivo, o tratamento deve ser iniciado.[3] O uso dos antibacilares parece ser eficaz no tratamento da tuberculose ocular, sendo o esquema terapêutico recomendado o mesmo que na tuberculose pulmonar.[5,12] O papel da corticoterapia não está totalmente estabelecido, devendo ser equacionado, uma vez que parece ser eficaz no controlo da inflamação intraocular.[5] A sua utilização deve ser feita em conjunto com a terapêutica antibacilar, podendo ser iniciada concomitantemente ou logo após o seu início.[5,12] Outros agentes imunossupressores poderão ser usados em casos de recorrência, após desmame da corticoterapia ou perante inflamação severa à apresentação.[13]

No nosso doente, a presença de uveíte posterior, a ausência de sintomas sistémicos e a história prévia de contacto com tuberculose conduziram à suspeita deste diagnóstico. A prova de Mantoux positiva e o resultado do IGRA reforçaram esta hipótese, suportando o início da terapêutica antibacilar enquanto os resultados culturais definitivos não se encontravam disponíveis. Neste caso foi possível o isolamento do *Mycobacterium tuberculosis* nas amostras de humor vítreo. O diagnóstico e o tratamento precoces tiveram provavelmente impacto na evolução favorável do doente.

No caso descrito, foi possível a identificação de *Mycobacterium tuberculosis* em amostras respiratórias apesar da ausência de sintomas. Uma vez que, de acordo com o consenso português publicado em 2017, o diagnóstico de tuberculose ocular provável pode ser feito através da identificação deste agente em amostras respiratórias ou extraoculares na ausência do isolamento em tecido ocular, é importante que, perante forte suspeita diagnóstica, seja feita a pesquisa do agente em todas as localizações possíveis.[3] A colheita de amostras respiratórias permite também a adequada identificação e o rastreio dos contactos,

Tabela 2 – Resultados microbiológicos

	Biologia molecular	Microscopia direta	Exame cultural	Antibiograma
Secreções respiratórias	Negativa	Negativa	Positivo	Sensibilidade rifampicina, pirazinamida, isoniazida, etambutol e estreptomicina
Humor vítreo	Negativa	Negativa	Positivo	Sensibilidade rifampicina, pirazinamida, isoniazida, etambutol e estreptomicina

limitando o contágio na comunidade.

O facto de este ser frequentemente um diagnóstico difícil implica que os clínicos o devam pesquisar ativamente. Os autores querem assim reforçar a importância de considerar a tuberculose ocular no diagnóstico diferencial da uveíte, nomeadamente quando a sua etiologia é desconhecida.

CONTRIBUTO DOS AUTORES

PMV: Redação do primeiro rascunho do artigo; revisão e aprovação da versão final.

CZ, VM: Avaliação clínica do doente (diagnóstico e tratamento); revisão e aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Unusual Presentation of Secondary Syphilis in the Oral Cavity

Apresentação Incomum de Sífilis Secundária na Cavidade Oral

Liliana CARVALHO✉[1], Berta HESPANHA[2], Joaquim TINOCO[3]
Acta Med Port 2023 Oct;36(10):687-688 ▪ https://doi.org/10.20344/amp.19043

Keywords: Mouth Diseases/diagnosis; Syphilis/diagnosis
Palavras-chave: Doenças da Boca/diagnóstico; Sífilis/diagnóstico

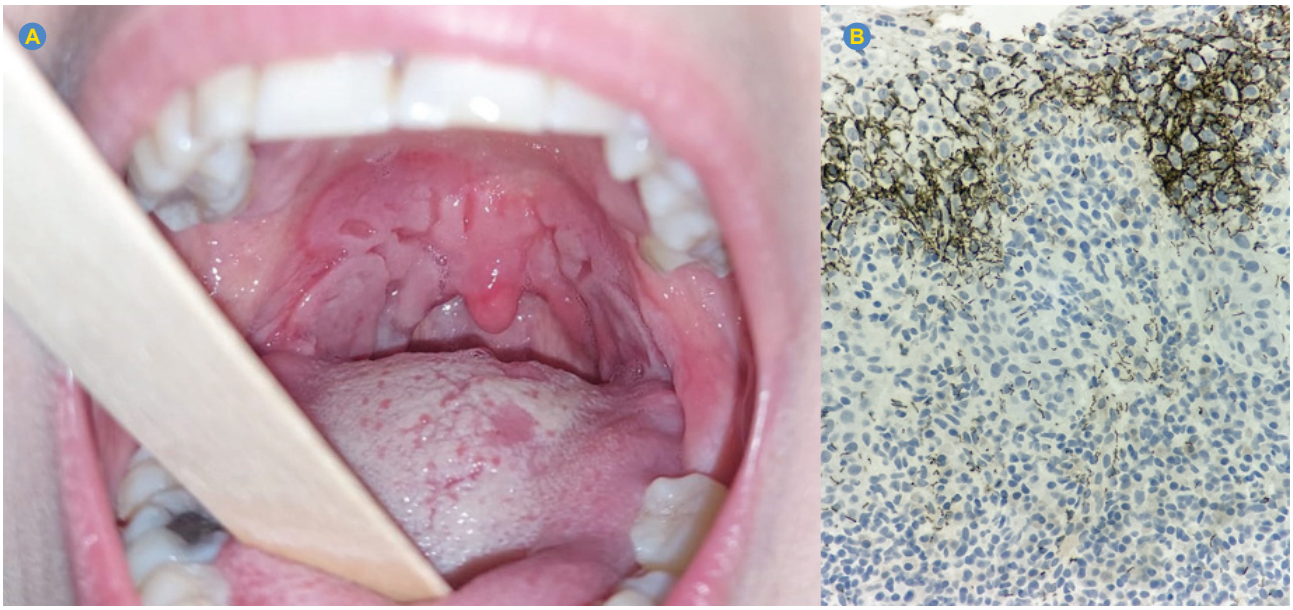

Figure 1 – (A) Slightly elevated and serpiginous lesion of the soft palate involving the palatoglossal arches bilaterally, surrounded by an irregular erythematous border; (B) Anti–*Treponema pallidum* antibody in immunohistochemistry showing multiple spirochetes in the lower part of the epithelium and in the vascular wall of the subepithelial connective tissue.

A 40-year-old woman was referred to the Otolaryngology department due to odynophagia and a soft palate lesion she had noticed two months ago. She denied other symptoms and had been receiving treatment with oral antibiotics, corticosteroids, and topical antifungals without any improvement.

She had no relevant prior medical history and did not disclose any risk factor for sexually transmitted diseases.

Apart from an elevated serpiginous soft palate lesion (Fig. 1A), the physical examination was unremarkable. An incisional biopsy revealed the presence of *Treponema pallidum* (Fig. 1B). Both TPHA testing and the VDRL test were positive. A diagnosis of secondary syphilis was established.[1]

The patient received treatment with intramuscular penicillin 2.4 million I.U[1] with complete remission.

Known as 'the great imitator',[2] syphilis can present as a myriad of signs and symptoms. Recognition of unusual oral presentations[3] like the presented case is key for a prompt diagnosis, especially in cases without any reported high-risk sexual behaviors.

AUTHOR CONTRIBUTIONS

LC, BH: Clinical and scientific description.
JMT: Iconography and histopathological caption.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

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PATIENT CONSENT

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COMPETING INTERESTS

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Are we PREPAREd? Concerning the "PREemptive Pharmacogenomics Testing for Preventing Adverse Drug Reactions (PREPARE) Study"

Estamos PREPARados? A Propósito do Estudo "Concerning the "PREemptive Pharmacogenomics Testing for Preventing Adverse Drug Reactions (PREPARE)"

Keywords: Drug-Related Side Effects and Adverse Reactions; Pharmacogenomic Testing; Genomic Medicine
Palavras-chave: Eficácia Medicamentosa; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Medicina Genômica; Testes Farmacogenómicos

Dear Editor,

As a multidisciplinary research team in Personalized Medicine, we read the paper recently published in Lancet by Swen JJ *et al*[1] with special interest.

Pharmacogenomics (PGx) significantly contributes to optimizing drug prescribing, improving patients' clinical outcomes, and mitigating adverse drug reactions (ADR).[1,2] Moreover, the efficacy rates of different drugs can vary widely, ranging from 25% to 80%.[2] ADRs account for about 6% of adult hospital admissions, and are one of the top ten leading causes of death and illness in developed countries, with a 10% increase in healthcare expenditures.[3,4] Currently, approximately 50% of commonly prescribed drugs already have an identified PGx profile, which is valuable for preemptive genotyping and brings clinical benefit to patients.[3]

The aforementioned article describes an open-label, multicenter, controlled, cluster-randomized, crossover implementation study of a 12-gene pharmacogenetic panel, considering 39 drugs. The study was conducted in 18 hospitals**,** nine community health centers, and 28 community pharmacies in seven European countries. It outlines the advantages of a PGx panel strategy combined with the guidelines developed by the Dutch Pharmacogenetics Working Group. Participants (6944) were randomly assigned either to genotype-guided doses [3342 (51.9%)] or standard care [3602 (48.1%)]. The authors reported a 30% reduction in clinically relevant ADR incidence, using a preemptive PGx panel.[1] This study provides further evidence to support a personalized medicine approach, with the added value of testing a panel of preemptive PGx in a multitude of healthcare institutions. It unveils certain limitations like potential bias in ADR reporting from an awareness effect and enhanced treatment monitoring. Furthermore, in real-life scenarios, polymedicated patients with comorbidities exhibit increased variability in drug response.

The European 1+Million Genomes Initiative and the Portuguese Strategy for Genomic Medicine (PT_MedGen) reflect the global interest in the implementation of genomic medicine in healthcare systems, promoting personalized approaches in rare diseases, oncology, and PGx. The United Kingdom, the Netherlands, and other countries are increasingly integrating PGx into their healthcare systems, allowing patients to receive personalized prescriptions. This new reality can improve treatment efficacy and patient safety, empower healthcare professionals in personalized care, and reduce costs for healthcare systems. The wider implementation is also crucial for real-world studies that consider the unique national frameworks and healthcare systems, by providing support with evidence-effective implementation plans. In Portugal, PGx is maturing and gaining momentum with the launch of the PT_MedGen strategy for genomic medicine.[5] Therefore, now is the time to prepare our clinical practice for PGx integration.

AUTHOR CONTRIBUTIONS

ACC: Conceptualization, literature review, and manuscript redaction.

MLC: Literature review and manuscript revision.

AV: Manuscript revision.

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COMPETING INTERESTS

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Hyperventilation Syndrome Following an Asymptomatic COVID-19 Infection

Síndrome de Hiperventilação Após uma Infeção COVID-19 Assintomática

Keywords: COVID-19; Hyperventilation
Palavras-chave: COVID-19; Hiperventilação

Hyperventilation syndrome (HVS) is characterized by a variety of symptoms induced by inappropriate breathing patterns, namely excessive ventilation.[1,2]

A 33-year-old woman with no comorbidities, occasional smoker, was evaluated at our clinic due to a six-month history of dyspnea (mMRC 3), chest tightness, and severe fatigue that started after the self-isolation period following an asymptomatic coronavirus disease 2019 (COVID-19) infection in January 2021. She also described episodes of anxiety, palpitations, lower limb paresthesia and blurred vision. On physical examination, the patient was tachypneic at rest (RR 32 - 36 bpm). She scored 35/64 in the Nijmegen questionnaire (a score above 23/64 is suggestive of hyperventilation syndrome).

The arterial blood gas analysis at rest revealed respiratory alkalosis (pH 7.506, pCO_2 23.6 mmHg; normal pH: 7.35 - 7.45, pCO_2: 35 - 45 mmHg). On the six-minute walk test (6MWT), she experienced severe dyspnea [end BORG dyspnea level (0 - 10): 10], chest tightness and lower limb paresthesias; the test was ceased at 3 minutes 27 seconds, after 168 meters, with no significant oxygen desaturation and normal cardiac response. Complete blood work – including autoimmunity testing, thyroid and kidney function, serum electrolytes, cardiac biomarkers, and HCG test – was normal. Pulmonary function tests and a chest radiograph revealed no significant changes. A thoracic computed tomography (CT) scan angiography excluded the presence of a pulmonary thromboembolism, and a ventilation/perfusion scan showed no significant mismatch. The patient performed an electrocardiogram which was unremarkable. A transthoracic echocardiogram was considered normal (LVEF 71%; PSAP 27 mmHg), as well as the myocardial perfusion scintigraphy and the cardiac magnetic resonance imaging (MRI). The patient also performed a cardiopulmonary exercise test, which revealed an exercise limitation (maximum VO2 7.1 mL/kg/min, 31% predicted), with an adequate gas exchange and cardiovascular response.

A diagnosis of post-COVID-19 HVS was suspected. The patient entered a pulmonary rehabilitation program, with aerobic exercises, respiratory muscle training, and psychological reconditioning. She experienced an improvement in her quality of life [initial EuroQoL (EQ)-5D 11/15; final EQ-5D: 7/15] and a satisfactory response on the last 6MWT performed – 462 m of distance walked (77% predicted). A re-evaluation arterial blood gas analysis performed at rest revealed a mild hypocapnia (pCO_2 33.2 mmHg; normal pCO_2: 35 - 45 mmHg). Due to the favorable response to the rehabilitation program, a referral to psychiatry assessment was not considered.

The combination of the Nijmegen score and Cardiopulmonary exercise is used to establish a diagnosis of HVS.[1] Following a COVID-19 infection, ruling out thrombotic lung disease and myocarditis is important.[3] Regarding pathophysiology, hypocapnia and anxiety seem to play an important role in the development of symptoms.[4] In patients with post-COVID-19 HVS, it has been suggested that inflammatory and/or microangiopathic changes in the pre-Bötzinger complex, a part of the ventral respiratory group of interneurons responsible for the control of breathing and the response to hypoxia, may lead to the dysregulation of the ventilatory drive. Respiratory rehabilitation is usually recommended for symptom management.

This is, to the best of our knowledge, the first report of a case of post-COVID-19 HVS in Portugal. As this is a rare disorder, clinical awareness is required to identify this often-missed manifestation of post-COVID-19.

AUTHOR CONTRIBUTIONS

IC: Writing of the manuscript.
AC, CR: Critical review of the manuscript.
FC: Conception and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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'Déjà Vu', a Mind Trick or a Warning Sign? A Case Report

'Déjà Vu', um 'Truque Mental' ou um Sinal de Alarme? Um Caso Clínico

Keywords: Adolescent; Déjà vu; Ganglioglioma/diagnosis
Palavras-chave: Adolescente; Déjà vu; Ganglioglioma/diagnóstico
Microbiana

Dear Editor,

The *déjà vu* (DV) phenomenon is a dissociative experience defined as the feeling of having already witnessed or experienced a current situation.[1] It is an established symptom in temporal lobe seizures and is also associated with disruptions in the prefrontal cortex or hippocampus, although its etiology is still unclear.[1]

We present the case of a 16-year-old male admitted to the emergency department due to an abnormal breathing pattern observed during sleep, followed by a lack of response upon stimulation. This only lasted a few seconds, and the patient developed lethargy, headache, and vomiting afterwards.

The patient mentioned having frequent episodes of DV, two to three times a day, that started two years before.

Since the clinical examination, computed tomography scan, and blood tests were normal, the patient was discharged to the outpatient pediatrics clinic, where he was observed one month later. There, he reported persistence of the DV episodes, but now with multiple episodes per day (about five to six), lasting for a few minutes and accompanied by headaches. There were no episodes of loss of consciousness or seizures. The patient denied dissociative symptoms – disruptions in the sense of self-identity, consciousness, memory, or perception of reality.

After the previous normal electroencephalogram (EEG), a brain magnetic resonance imaging (MRI) was performed, which found an expansive cortico-justacortical lesion on the median temporal right region, suggesting a diagnosis of ganglioglioma (Fig. 1).

The patient was referred to both Oncology and Neurosurgery clinics in our tertiary referral hospital, where biopsy and genetic testing were performed for tumor characterization.

The histopathological examination confirmed a glioneuronal tumor – WHO grade 1: low-grade ganglioglioma (GG).

The patient underwent tumor resection surgery, with successful removal of the tumor. He is now well and does not have any sequelae, as demonstrated by magnetic resonance imaging (MRI), electroencephalography (EEG), and an adequate performance in neuropsychological tests.

Ganglioglioma is a rare mixed neuronal-glial neoplasm, accounting for 0.5% - 5.0% of all pediatric central nervous system tumors. These are most common in the first two decades of life, affecting predominantly male patients with a median age of 12 years.[2]

Gangliogliomas are composed of neoplastic mature ganglion cells in combination with glial cells,[3] can be located anywhere on the neuraxis, but are usually located on the

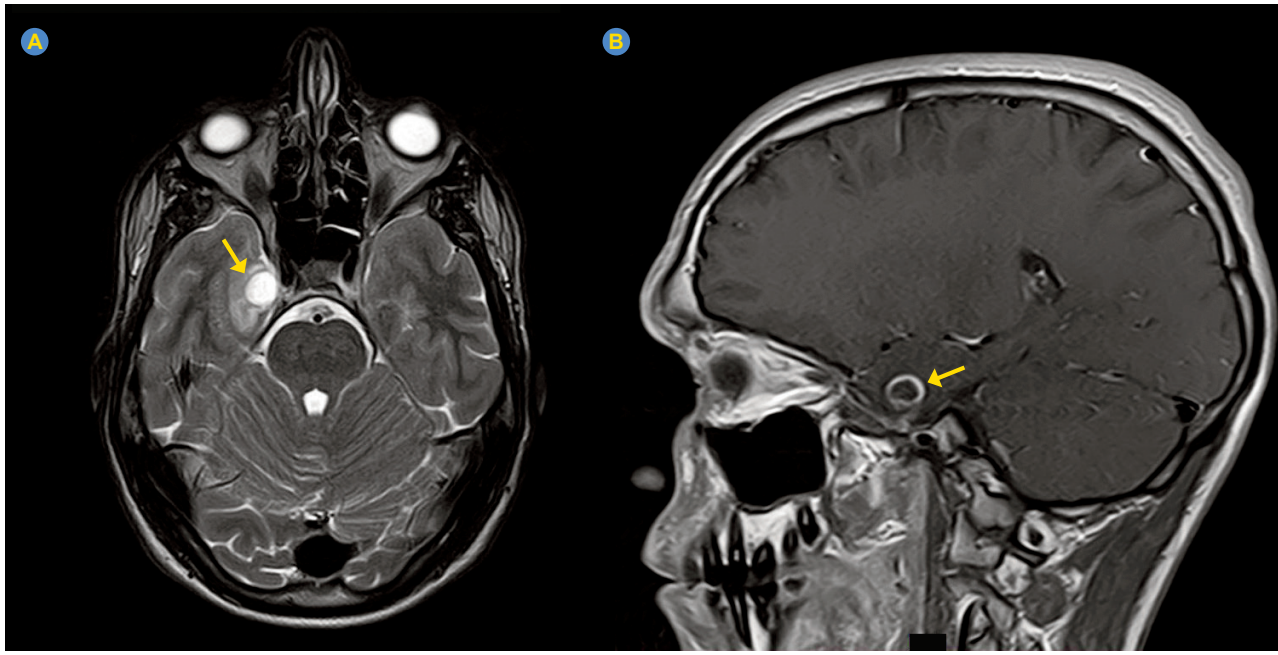

Figure 1 – MRI image: axial (A) and sagittal (B) views showing the tumor on the right temporal lobe (arrows)

temporal and frontal lobes and are therefore commonly associated with refractory seizures.[3] Long-standing epilepsy is frequent.[4]

Genetic mutations lead to MAPK pathway activation and increase cell proliferation. The most common mutation is *V600E* on the *BRAF* gene,[5] which is associated with a higher risk of recurrence after standard therapy in pediatric low-grade gliomas.[2]

Other mutations are *H3F3A* (Histone mutation), *IDH1* and *IDH2* (isocitrate dehydrogenase mutations). In this patient, no genetic mutation was identified.

The curative treatment for low-grade GGs is complete resection. With partial resection, adjuvant or salvage radiation treatment can also be considered.[3]

This case is relevant because it shows how a rather common psychological symptom can conceal an organic disease. In this case, it was the frequency, intensity, and duration of the episodes of DV, associated with other neurological symptoms (i.e., headache and seizure episode), that flagged the need to carry out further investigation and reach the final diagnosis.

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PREVIOUS AWARDS AND PRESENTATIONS

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AUTHOR CONTRIBUTIONS

CMF, RSO: Patient follow-up, data acquisition, writing of the manuscript.

JFR, AMR: Writing of the manuscript.

PC: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Resposta à Carta ao Editor "Anemia da Doença Renal Crónica: Que Terapêuticas Estão Disponíveis?" Relativa ao Artigo "Anemia da Doença Renal Crónica: O Estado da Arte"

Reply to the Letter to the Editor "Anemia of Chronic Kidney Disease: Which Therapeutics Are Available?" Regarding the Article "Anemia in Chronic Kidney Disease: The State of the Art"

Palavras-chave: Anemia/tratamento farmacológico; Doença Renal Crónica/complicações; Inibidores de Prolil-Hidrolase/uso terapêutico
Keywords: Anemia/drug therapy; Prolyl-Hydroxylase Inhibitors/therapeutic use; Renal Insufficiency, Chronic/complications

Na edição de abril de 2023 da Acta Médica Portuguesa, foi publicada uma Carta ao Editor intitulada "Anemia da Doença Renal Crónica: Que Terapêuticas Estão Disponíveis?"[1] na qual é referido que "o roxadustate está disponível em farmácias comunitárias para prescrição por qualquer médico". Esta situação não corresponde de todo à verdade. O roxadustate foi aprovado pela Agência Europeia do Medicamento e pelo Infarmed, está disponível para utilização em Portugal, mas com as seguintes condicionantes:

- Não está ainda definida a sua integração nos medicamentos a ceder aos doentes renais, de acordo com o estabelecido pela Portaria n.º 255/2018 publicada no Diário da República, 1.ª série, n.º 173, de 7 de setembro de 2018 (legislação em vigor) o que implica a sua não disponibilidade aos doentes renais crónicos (DRC) em geral, mas apenas para aquisição a título nominal, com custo suportado totalmente pelo doente ou por seguro/subsistema de saúde[2];
- O fármaco é de dispensa hospitalar exclusiva (hospitais públicos ou privados), não podendo ser adquirido por farmácias comunitárias;
- O fármaco está licenciado para o controlo da anemia na DRC e não está definido quem são os médicos que o podem ou não prescrever. Contudo, sendo a indicação em tudo semelhante à dos estimuladores da eritropoiese (eritropoietina recombinante), cuja legislação portuguesa regulamenta que apenas podem ser dispensados por nefrologistas, de acordo com o Despacho n.º 6370/2002, de 7 de março (Diário da República, 2.ª série, n.º 69, de 22 de Março de 2002), deduz-se que não possam ser prescritos por qualquer médico como afirmado.[3]

A necessidade de escrever um artigo em português[4] vocacionado para outras especialidades que não a nefrologia acerca da abordagem da anemia da doença renal crónica teve precisamente a ver, por um lado, com a importância de rever o tema para que não se façam usos abusivos de fármacos com riscos comprovados, como é o caso dos estimuladores da eritropoiese. Por outro lado, contribuiu também para alertar para o uso de fármacos inovadores, mas em que existe falta de dados de vida real dado o seu tempo limitado de utilização no mundo real. Neste cenário, não parece ser prudente sugerir sequer que poderá ser usado por qualquer médico, quando a própria *Food and Drug Administration* põe em causa a sua segurança.[5]

CONFLITOS DE INTERESSE

A autora declara não ter conflitos de interesse relacionados com o presente trabalho.

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