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

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

Andreia M. OLIVEIRA✉[1], Catarina FERREIRA COELHO[1], Filipa LOURENÇO[1], Inês CAMPOS PINTO[1], Joana ATABÃO[1], Raquel CABRITA[1], Rita PARAÍSO[1], Edgar MESQUITA[2], Dyna TORRADO[1], Pilar MARQUEZ[1], Vanessa Z. GUERREIRO[1]
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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

1. Unidade de Saúde Familiar Ria Formosa. Agrupamento de Centro de Saúde Central. Administração Regional de Saúde do Algarve. Faro. Portugal.
2. Laboratory for Integrative and Translational Research in Population Health (ITR). EPIUnit. Instituto de Saúde Pública. Universidade do Porto. Porto. Portugal.

✉ **Autor correspondente:** Andreia M. Oliveira. amarreiros@arsalgarve.min-saude.pt

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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

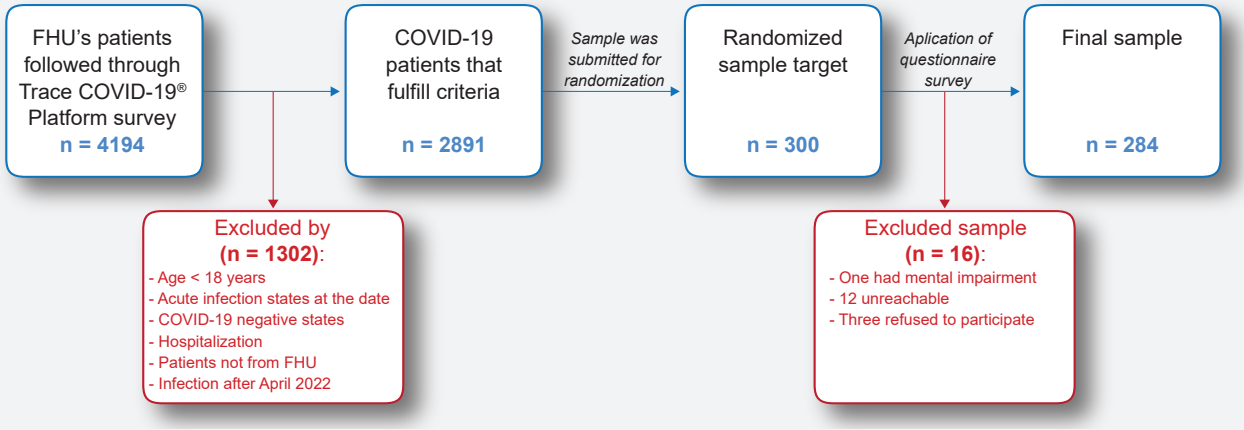

Figure 1 – Study flowchart
FHU: family health unit

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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