

**FEDERAL UNIVERSITY OF PARAIBA
CENTER OF EXACT AND NATURAL SCIENCES
POST-GRADUATE PROGRAM IN DECISION MODELS AND HEALTH**

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**CHARACTERISTICS OF LONG COVID: A SURVEY-BASED STUDY IN BRAZILIAN
PRIMARY HEALTH CARE.**

JOÃO PESSOA

2026

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PRIMARY HEALTH CARE.**

Thesis submitted for the degree of PhD to
the Postgraduate Program in Decision
Models and Health, Center of Exact Sciences
and Nature, Federal University of Paraíba.

Concentration field: Models in Health

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JOÃO PESSOA

2026

Catálogo na publicação
Seção de Catalogação e Classificação

F383c Ferreira, Assel Muratovna Shigayeva.
Characteristics of Long COVID: a survey-based study
in Brazilian primary health care / Assel Muratovna
Shigayeva Ferreira. - João Pessoa, 2026.
131 f. : il.

Orientação: Leandro de Araújo Pernambuco, João
Agnaldo do Nascimento.
Tese (Doutorado) - UFPB/CCEN.

1. COVID-19. 2. COVID Longa. 3. Atenção primária à
saúde. I. Pernambuco, Leandro de Araújo. II.
Nascimento, João Agnaldo do. III. Título.

UFPB/BC

CDU 578.834:614(043)

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João Pessoa, March 6, 2026

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I dedicate this thesis to my mother, sister, and Frederico, my best friends, whose unconditional love and enormous support have helped me achieve my dreams.

ACKNOWLEDGEMENTS

I would like to express deep appreciation to my supervisor, Dr. Leandro de Araújo Pernambuco, for exceptional guidance, priceless insights, and encouragement throughout my doctoral journey.

I also highly appreciate the support from co-supervisor, Dr. João Agnaldo do Nascimento, for excellent mentorship and constructive feedbacks, which have helped improve my research.

This thesis would not have been possible without the support from the Postgraduate Program in Decision Models and Health. I would like to thank all professors at the Program for sharing their expertise.

I would like to recognize the invaluable support of my colleagues from Long COVID research group, especially Dr. Flávia Emília Leite de Lima Ferreira, Dr. André Luís Bonifácio de Carvalho and Caio César Ferreira Alverga, whose help was greatly appreciated.

I would also like to express my gratitude to the healthcare providers from USFs and patients who took time to contribute to this PhD.

Special thanks to staff and fellow graduate students for providing support and advices during the PhD course.

I also thank all my friends and former colleagues in Brazil and Kazakhstan. Thank you for cheering me on.

Financial support: My deep gratitude to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES and Fundação de Apoio à Pesquisa do Estado da Paraíba - FAPESQ for the academic opportunities and funding.

ABSTRACT

In Brazil, the knowledge regarding Long COVID prevalence, its specific clinical outcomes and overall impact on population health is severely limited. To address these existing gaps, the PhD study **aimed** to describe the prevalence, risk factors and clinical outcomes of Long COVID, and its impact on health-related quality of life among adults diagnosed with mild to moderate during the 2021 COVID-19 pandemic in Brazilian primary care. A retrospective cross-sectional survey was conducted in six Family Health Care Units in João Pessoa, Paraíba, from May 2023 to July 2024, using two instruments: 1) a standardized questionnaire containing 18 validated clinical outcomes, and 2) a generic EQ-5D-5L instrument for measuring health-related quality of life (HRQOL). To define Long COVID, the study adopted the definition outlined by the WHO (2021).

Descriptive statistical analyses were used to describe the sociodemographic characteristics of the study population, COVID-19 vaccination status, symptoms, and the presence of comorbidities. The overall prevalence of Long COVID along with symptom-specific prevalence adjusted for sex and age, was estimated and compared between adults with and without Long COVID. EQ-5D-5L health index values and visual analogue scale (VAS) scores were analyzed to compare health-related quality of life between the two groups. Binary logistic regression models were used to examine the associations between Long COVID and clinical outcomes, risk factors, and health states.

Of 226 respondents, 69.0% met the definition of Long COVID and had at least one persistent symptom following SARS-CoV-2 infection. A total of 16 clinical outcomes were significantly associated with Long COVID. The largest adjusted odds ratios (aORs) were observed for short-term memory loss, anxiety, and impaired attention. The risk factors for Long COVID included five or more symptoms, female sex, age 40–49 years, and age 70 years or older. Individuals with Long COVID continued to experience significantly poorer health-related quality of life two years or more after mild-to-moderate infection compared with those without persistent illness, regardless of sex, age, ethnicity, educational level, or comorbidities. Adults with this condition are at higher risk of experiencing health issues related to anxiety or depression, pain or discomfort, and deterioration in usual activities.

This thesis highlights the need to target multidisciplinary services in primary care for COVID-19 survivors experiencing long-term health issues after infection. Furthermore, understanding the long-lasting health effects of SARS-CoV-2 infection and identifying adults at higher risk for enduring health issues can help health professionals, caregivers, and policymakers better address aspects of patients' lives that lack quality and develop a multidisciplinary approach in primary care for managing this condition.

Keywords: COVID-19, Long COVID, Primary Health Care

RESUMO

No Brasil, as evidências empíricas sobre a prevalência da COVID Longa, seus desfechos clínicos específicos e seu impacto geral na saúde da população são escassas. Para abordar essas lacunas científicas, a presente tese teve como **objetivo** descrever a prevalência, os fatores de risco e os desfechos clínicos da COVID Longa, bem como seu impacto na qualidade de vida relacionada à saúde de adultos diagnosticados com COVID-19 leve a moderada durante a pandemia de 2021, no âmbito da atenção primária à saúde brasileira. Trata-se de um estudo transversal retrospectivo, conduzido em seis Unidades de Saúde da Família (USF) no município de João Pessoa, Paraíba, no período de maio de 2023 a julho de 2024, utilizando dois instrumentos: (1) um questionário padronizado contendo 18 desfechos clínicos validados; e (2) o instrumento genérico EQ-5D-5L, destinado à mensuração da qualidade de vida relacionada à saúde. Para a definição de COVID Longa, o estudo adotou o conceito proposto pela Organização Mundial da Saúde (2021).

Análises estatísticas descritivas foram utilizadas para caracterizar as variáveis sociodemográficas, o estado vacinal contra a COVID-19, os sintomas e a presença de comorbidades. A prevalência geral de COVID Longa na população do estudo, bem como a prevalência de sintomas específicos ajustada por sexo e idade, foi estimada e comparada entre dois grupos: adultos com COVID Longa e adultos sem COVID Longa. Os valores do índice de saúde EQ-5D-5L e os escores da escala visual analógica (VAS) foram analisados com o objetivo de comparar a qualidade de vida relacionada à saúde entre os dois grupos. Modelos de regressão logística binária foram utilizados para examinar as associações entre COVID Longa e desfechos clínicos, fatores de risco e estados de saúde.

Entre os 226 participantes, 69,0% atenderam aos critérios para COVID Longa e apresentaram pelo menos um sintoma persistente após a infecção por SARS-CoV-2. Um conjunto de 16 desfechos clínicos apresentou associação estatisticamente significativa com a COVID Longa. As maiores razões de chances ajustadas (*aORs*) foram observadas para perda de memória de curto prazo, ansiedade e comprometimento da atenção. Os fatores de risco para COVID Longa incluíram a presença de cinco ou mais sintomas, o sexo feminino, a idade entre 40 e 49 anos e a idade igual ou superior a 70 anos. Indivíduos com COVID Longa continuaram a apresentar uma qualidade de vida relacionada à saúde significativamente pior dois anos ou mais após infecção leve a moderada, em comparação com adultos sem sintomas persistentes, independentemente do sexo, da idade, da etnia, do nível educacional ou da presença de comorbidades. Adultos com essa condição apresentaram maior risco de desenvolver problemas de saúde relacionados à ansiedade ou depressão, dor ou desconforto e comprometimento das atividades habituais.

A presente tese destaca a necessidade de direcionar serviços multidisciplinares na atenção primária a sobreviventes da COVID-19 que apresentam problemas de saúde de longo prazo após a infecção. Além disso, a compreensão dos efeitos prolongados da infecção por SARS-CoV-2 e a identificação de adultos com maior risco de desenvolver problemas de saúde persistentes podem auxiliar profissionais de saúde, cuidadores e formuladores de políticas públicas a abordar de forma

mais eficaz os aspectos da vida dos pacientes que apresentam comprometimento da qualidade de vida, bem como a desenvolver uma abordagem multidisciplinar na atenção primária para o manejo dessa condição.

Palavras-chave: Atenção primária à saúde, COVID-19, COVID Longa,

LIST OF TABLES

Table 1 - COVID-19 disease severity classification for adults, WHO, 2023.	27
Table 2 - Working definitions for SARS-CoV-2 variants.....	31
Table 3 – Clinical case definitions of Long COVID among adults.....	35
Table 4 - Clinical case definition of post COVID-19 condition in children and adolescents, WHO, 2023.	36
Table 5 - Selected international studies on the prevalence of Long COVID in adults.....	37
Table 6 - Selected Brazilian studies on the prevalence of Long COVID in adults	39
Table 7 - Selective studies on risk factors for Long COVID.....	41
Table 8 - The core outcome set (COS) and the core outcome measurement set (COMS) for adults with Long COVID	45
Table 9 - The core outcome set (COS) and the core outcome measurement set (COMS) for children and young people with Long COVID	46
Table 10 - Selective studies on health-related quality of life of adults with Long COVID	48
Table 11 - The list of USFs enrolled in the study, Joao Pessoa, state of Paraiba, 2025	51
Table 12 - Inclusion and exclusion criteria	52
Table 13 - Clinical case definition of Long COVID (WHO, 2021).....	55
Table 14 - Standardized Long COVID questionnaire panel	56
Table 15 - EQ-5D-5L descriptive system.	57
Table 16- Independent variables of a regression model.....	63
Table 17 - Variance inflation factor (VIF) of predictors	63
Table 18 - Goodness-of-fit (GOF) parameters of a multivariate logistic regression model.....	64
Table 19 - Classification table of a multivariate logistic regression model.....	64
Table 20 - The performance of India and US value sets after ROC analysis application.....	67
Table 21 - Descriptive statistics for the index value variable.....	69
Table 22 - Descriptive statistics for the visual analogue scale (VAS) variable	71
Table 23 - Variance inflation factor (VIF) of predictors	73
Table 24 - Goodness-of-fit (GOF) parameters of a multivariate logistic regression model.....	74
Table 25 - Classification table of a multivariate logistic regression model.....	74

Table 26 - Sociodemographic characteristics of the study population	76
Table 27 - Clinical characteristics of the study population	77
Table 28 - Presence of comorbidities, and the number of symptoms stratified by age.	78
Table 28 - Sex, presence of comorbidities, and the number of symptoms stratified by age (continuing).	79
Table 29 - Frequency of symptoms in adults with Long COVID vs. without Long COVID.....	81
Table 30 - Frequency of symptoms stratified by age.....	82
Table 31 - Unadjusted odds ratios (OR) for validated symptoms	84
Table 32 - Unadjusted odds ratios (OR) for self-reported symptoms.....	85
Table 33 - Risk factors associated with Long COVID	87
Table 34 - Proportions (%) of respondents to EQ-5D-5L descriptive system.....	88
Table 35 - Frequency of the 13 most reported health states and the frequency of the worst health state observed in a study population.....	90
Table 36 - EQ-5D-5L median index values comparing adults with versus without Long COVID	92
Table 37 - Unadjusted odds ratios for EQ-5D-5L dimensions with a predicted probability as of Long COVID membership “yes”.	94

LIST OF FIGURES

Figure 1 - Report on Virus Classification and Taxon Nomenclature, the <i>Orthocoronaviridae</i> subfamily, 2022.	22
Figure 2 - Recommendations to Healthcare Providers on Interpreting Antigen Test Results for Diagnostic Purposes.	32
Figure 3 - Participants selection flowchart.....	53
Figure 4 - ROC curves of US and Indian value sets of five EQ-5D-5L dimensions	68
Figure 5 - Histogram of the index value variable.....	70
Figure 6 - Histogram of the VAS variable.....	72
Figure 7 - Boxplots of the VAS and index values responses	72
Figure 9 - Adjusted odds ratios (aOR) for validated symptoms.....	83
Figure 10 - Adjusted odds ratios (aOR) for self-reported symptoms	85
Figure 11 - Proportions (%) of respondents reporting any health issues, plotted separately for individuals with Long COVID versus without Long COVID.....	89
Figure 12 - VAS median scores comparing adults with versus without Long COVID	93
Figure 13 - Adjusted odds ratios for EQ-5D-5L dimensions with a predicted probability for having Long COVID	95

LIST OF ACRONYMS

ACS	Agentes comunitários de saúde (Community health agents)
Ag-RDT	Antigen-rapid diagnostic test
ARI	Acute Respiratory Infection
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COMS	Core Outcome Measurement Set
COS	Core Outcome Set
COVID-19	Coronavirus Disease 2019
EDA	Exploratory Data Analysis
IBGE	Instituto Brasileiro de Geografia e Estatística (Brazilian Institute of Geography and Statistics)
ICTV	International Committee on Taxonomy of Viruses
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
LCQ	Long COVID Questionnaire
MCA	Multiple Correspondence Analysis
MERS	Respiratory Syndrome of Middle East
NAAT	Nucleic acid amplification test
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
OR	Odds Ratio
PHC	Primary Health Care
RNA	Ribonucleic acid
RSDQ	Routine Standardized Diagnostic Questionnaire
RT-PCR	Real time reverse-transcription polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SUS	Sistema Único de Saúde (the Unified Health System)
USF	Unidade de Saúde da Família (the Family Health Care Units)
VAS	Visual Analogue Scale
VBM	Variant being monitored
VOC	Variant of concern
VOHC	Variant of high consequence
VOI	Variant of interest
VUM	Variants under monitoring
WHO	World Health Organization

SUMMARY

1 INTRODUCTION	16
1.1 Justification	18
1.2 Research questions	19
1.3 Objectives	20
2 LITERATURE REVIEW	21
2.1 Coronavirus disease 2019 (COVID-19)	21
2.1.1 Taxonomy profile, origin, and historic perspective	21
2.1.2 COVID-19 outbreak: epidemiology, clinical characteristics, and risk factors.	26
2.1.3 SARS-CoV-2 variants and diagnostic testing	29
2.2 Long-COVID	34
2.2.1 Terminology and clinical definitions	34
2.2.2 Global and Brazilian estimates for the prevalence of Long COVID	37
2.2.3 Risk factors for Long COVID	40
2.2.4 Long COVID clinical outcomes	43
2.2.5 Quality of life of adults with Long COVID	47
3 METHODS	50
3.1 Study Design and Settings	50
3.1.1 Study Design	50
3.1.2 Settings	50
3.2. Study Population and Recruitment	52
3.2.1 Study Population	52
3.2.2. Recruitment	53
3.2.3 Ethical Considerations.	54
3.3 Data Collection and Data Management	54
3.4 Long COVID Definition	55
3.5 Standardized Long COVID Questionnaire	55
3.6 EQ-5D-5L instrument	57
3.7 Statistical Analyses	58

3.7.1 Descriptive Analysis of the Study Population Characteristics-----	58
3.7.2 Analysis of the Prevalence of Long COVID Outcomes -----	59
3.7.3 Logistic Regression Analyses -----	60
3.7.4 Unadjusted and Adjusted Odds Ratios for Long COVID Outcomes -----	61
3.7.5 Analysis of Risk Factors for Long COVID-----	62
3.7.6 Analysis of Health-Related Quality of Life (HRQOL) -----	65
3.7.6.1. Exploratory Analysis of EQ-5D-5L Profiles -----	65
3.7.6.2 EQ-5D-5L Value Set Analysis -----	66
3.7.6.3 Receiver Operating Characteristic (ROC) Curve. -----	67
3.7.6.4 EQ-5D-5L Index Values and VAS Scores Analyses-----	69
3.7.6.5. Analysis of the Association between Long COVID and HRQOL Outcomes -----	73
4 RESULTS -----	75
4.1 Sociodemographic and Clinical Characteristics of the Study Population -----	75
4.2. Prevalence of Long COVID Outcomes-----	80
4.3 Risk Factors associated with Long COVID -----	86
4.4 HRQOL among Adults with Long COVID-----	86
4.4.1 Results of a Descriptive Analysis of EQ-5D-5L Responses -----	86
4.4.2 Comparison of EQ-5D-5L Index Values -----	90
4.4.3 Comparison of VAS Scores -----	93
4.4.4 Association between Long COVID and HRQOL Outcomes -----	94
5 DISCUSSIONS-----	96
6 FINAL CONSIDERATIONS -----	106
REFERENCES-----	108
APPENDIX -----	126

1 INTRODUCTION

In the mid-December 2019, China's health authorities detected few cases of an atypical pneumonia that eventually was discovered to be caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). Since then, a new disease named coronavirus disease 2019 (COVID-19) has become a great challenge for global society and health systems. As of January 2026, over 779 million confirmed cases of disease and over 7.1 million deaths have been reported to the World Health Organization (WHO) (2), although the real toll is much greater (3).

Reports related to the presence of persistent symptoms following acute SARS-CoV-2 infection referred as of Long COVID emerged since the early stages of COVID-19 pandemic (4). Currently, Long COVID is internationally recognized as a growing global health challenge. Studies show that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as Long COVID, yet its prevalence varies (5). This condition represents many potentially overlapping entities, likely with different biological causes, possible risk factors and clinical features (6-11). It can impact the health of anyone exposed to SARS-CoV-2, regardless of age or severity of original symptoms (5, 7). The long-term health consequences of COVID-19 were observed among adults (6, 9) as well as in children (12, 13). Further, this condition can fluctuate and change over time, affecting nearly any system in the human body (8).

The term “Long COVID” is generally referred to the wide range of physical and mental health consequences experienced by some patients weeks or months after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection (5,8). Various terminologies of the condition were proposed including long haul COVID, post-acute sequelae of SARS-CoV-2 infection, chronic COVID syndrome or post-COVID-19 condition (Long COVID), the term officially used by the WHO (5). It is important to note that there is currently no internationally accepted agreement on a clinical definition of Long COVID (14).

In April 2021, WHO published the working Long COVID clinical case definition, which was developed through a Delphi consensus (5). Long COVID was defined as a condition occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from onset, with symptoms lasting for at least 2 months that cannot be explained by an alternative

diagnosis (5). Although it is recognized that the clinical case definition is likely to change as new evidence emerges (5). Additionally, the duration of Long COVID symptoms remains unclear. While some studies reported short and mid-term persistent symptoms after acute COVID-19 (9,15-17), other studies have shown continuous health problems more than one and two years (18-20) after acute infection in individuals than those of general population. Further, it is unknown whether prolonged symptoms and associated abnormalities would fully resolve or remain as life-long dysfunction (21).

Timely diagnosis of prolonged health problems following acute SARS-CoV-2 infection is key for preventing chronic or life-debilitating conditions. However, there is a debate about whether the list of possible symptoms reported in people who experienced Long COVID is too long to implement an effective diagnosis (4,21). Over 200 different symptoms have been identified as related to this illness, with some symptoms (e.g., fatigue, cognitive and mental dysfunction symptoms) being more frequent than others (6). Patients with Long COVID report a wide range of ongoing health problems: from mild/moderate symptoms to severe adverse effects on physical, cognitive, and psychosocial health (1,4). Thus, there is an urgent need for consensus on critically important outcomes to ensure that Long COVID is measured in a consistent manner both in research and clinical practice (21-23).

Differences in methods, population, and classification of cases (settings, severity, duration, number, and sets of symptoms) make it difficult to summarize the findings across studies (10, 11). While the highest burden of Long COVID is among those patients with a history of mild to moderate COVID-19 illness, the vast majority of studies were focused on severe COVID-19 and in high income countries (4, 7, 10). As a result, there is a paucity of evidence on Long COVID among nonhospitalized patients from low- and middle-income countries and from primary care (4, 10, 11).

With millions of people affected by COVID-19, the proportion of those who may develop Long COVID condition is of concern. Many people are in of need long-term follow-up, management and rehabilitation after acute phase of infection. In most health systems, these tasks are to be implemented by primary care providers. Since our understanding of the prevalence, risk factors and consequences of Long COVID and associated conditions are still evolving, more national studies are urgently needed.

1.1 Justification

Brazil, the largest and most populous country in Latin America, experienced one of the most devastating COVID-19 pandemic scenarios in terms of cases and death counts since its first recorded case in February 2020 [24]. During 2020-2021 pandemic, Brazil was among the most affected countries in the worldwide ranking and the disease' epicenter in Latin America (2). As of January 2026, over 39.3 million cases and 717 thousand of deaths were reported by the Brazilian Ministry of Health (25).

Several factors contributed to the devastating COVID-19 outbreak in the country. Political changes in Brazil during the past years accompanied by economic instability, demographic changes, persistent inequality, and social problems became some of predictors for catastrophic consequences due the COVID-19 pandemic (26, 27). Historically, uneven regional allocation of resources, chronic inequalities in health-care access and health outcomes have influenced morbidity and mortality scenario in Brazil with poorer areas experience a double burden of diseases (28).

Although SARS-CoV-2 has a high transmission potential and reaches all communities, some areas were more affected than others, as many regions did not have adequate health resources and infrastructure to face the pandemic effectively. For instance, during the 2020 pandemic, the North and Northeast regions of Brazil experienced the highest increase in the number of cumulative COVID-19 cases among all regions (27,29). This was particularly alarming since these regions present the lowest human development indices, and the highest proportion of poverty and low education rates in the country. Furthermore, the initial spread of COVID-19 infection and deaths in Brazil were mostly affected by patterns of socioeconomic vulnerability rather than population age structure and prevalence of existing chronic disease morbidity (27).

In Brazil, the Unified Health System (Sistema Único de Saúde -SUS) is a primary health care system, which since its establishment in 1988, has provided universal health coverage, helping to reduce inequalities in health-care access and the achievement of better health outcomes (30-32). The SUS is responsible for promoting health, conducting health surveillance, controlling disease vectors, providing health education, and ensuring continuity of care across primary, specialized

outpatient, and hospital levels. The Primary Health Care (PHC) concept plays a key role in the implementation of national policies for improving population health and promotion of health equity (30-32). It is one of the largest and most complex public health systems in the world (31). Approximately 80% of the Brazilian population depends exclusively on SUS for any issues related to health, especially vulnerable population (31, 32).

Brazil is known for its public health initiatives in addressing vaccine-preventable diseases over time (33). As many primary care providers in the world, SUS has faced a severe collapse during the COVID-19 pandemic, especially at its beginning. As the disease propagated, the national health care system was overburdened, resulting in a loss of control over the epidemic (26-29).

In the post pandemic period, COVID-19 remains an important public health problem in Brazil. Furthermore, as new evidence about Long COVID has emerged, the Brazilian health care system faces additional challenges. There is a need for the development of comprehensive national guidelines on management of Long COVID particularly at the primary care level. However, there is a scarcity of research evidence related to the burden of Long COVID, including its impact on health-related quality of life, prevalence of clinical outcomes and their duration, risk factors, regional differences, and other characteristics (35).

1.2 Research questions

To address research gaps outlined in the previous section, this thesis is set to describe Long COVID in adults diagnosed with mild to moderate COVID-19 illness in Brazilian primary care during the 2021 pandemic. The thesis aims to address the following research questions:

1. What is the overall prevalence of Long COVID in adults after symptomatic mild to moderate COVID-19?
2. What is the occurrence of specific clinical outcomes in adults after symptomatic mild to moderate COVID-19?

3. What is differentiation of the occurrence of Long COVID regarding individual's sociodemographic characteristics?
4. Is there any difference in occurrence of clinical outcomes between adults with Long COVID compared to those without Long COVID?
5. What are risk factors for developing Long COVID?
6. How Long COVID impacts a health-related quality of life of adults with Long COVID?

1.3 Objectives

Main objective: to evaluate the prevalence, risk factors and clinical outcomes of Long COVID, and its impact on health-related quality of life of adults diagnosed with mild to moderate COVID-19 illness in Brazilian primary care during the 2021 pandemic.

Specific objectives:

1. To assess the prevalence of Long COVID in adults after symptomatic mild to moderate COVID-19.
 - 1.1 To investigate the differentiation of the prevalence of Long COVID regarding individual's sociodemographic characteristics.
 - 1.2 To compare the occurrence of clinical outcomes of adults with Long COVID versus adults without Long COVID.
2. To evaluate risk factors associated with Long COVID.
3. To describe the impact of Long COVID on health-related quality of life of adults with Long COVID compared with those without Long COVID.
4. To assess the association of Long COVID with health-related quality of life issues.

2 LITERATURE REVIEW

This chapter provides the background for research questions posed in a thesis. The structured literature review was conducted to describe the existing evidence known about Long COVID, globally and in Brazil. As for a new disease, the origin of the Coronavirus Diseases 2019 (COVID-19), its clinical, and public health aspects were additionally described.

The chapter discusses the information on Long COVID aiming to highlight the existing data and research gaps. The eligible articles related to definition, clinical core outcome sets, and procedures for the accurate and timely measure of Long COVID, international and in Brazil, were principal subjects of the search. References of relevant articles from PUBMED, MEDLINE, Web of Science and Scielo databases published worldwide from January 2020 to September 2025 were included.

2.1 Coronavirus disease 2019 (COVID-19)

2.1.1 Taxonomy profile, origin, and historic perspective

In the mid-December 2019, China health authorities detected few cases of an atypical pneumonia that eventually was discovered to be caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Subsequent investigations discovered that the probable origin of a novel virus is related to the same family of Coronavirus that caused the severe acute respiratory syndrome (SARS) and to the Respiratory Syndrome of Middle East (MERS) outbreaks during 2003 and 2012 (36). Started from Wuhan city in China, a new disease called coronavirus disease 2019 (COVID-19) was rapidly disseminated across the world. As of March 2020, the WHO declared the disease outbreak as a pandemic of international concern (1). It was the sixth public health emergency of international concern declared in a century, following H1N1 influenza (2009),

Polio (2014), Ebola in West Africa (2014) Zika (2016) and Ebola in the Democratic Republic of Congo (2019) (37).

Taxonomy profile

Like other Coronaviruses, SARS-CoV-2 is a positive-sense single-stranded RNA virus with a crown-like spikes on the surface as seen under an electron microscope (36). SARS-CoV-2 is a member of the *Orthocoronavirinae* subfamily from the *Coronaviridae* family, in the order of *Nidovirales* (38). Classification of viruses is based on the collection and comparison of various characters that describe the virus and can then be used to distinguish one virus from another. The current taxonomy of Coronaviruses from the *Coronavirinae* subfamily are classified into 4 major genera based on genomic structure: Alpha-coronavirus (alphaCoV), Beta-coronavirus (betaCoV), Gamma-coronavirus (gammaCoV), and Delta-coronavirus (deltaCoV), where SARS-CoV-2 belongs to Beta-coronavirus genera (Figure 1) (39).

Figure 1 - Report on Virus Classification and Taxon Nomenclature, the *Orthocoronaviridae* subfamily, 2022.

Subfamily	Genus	Subgenus	Species
<i>Orthocoronavirinae</i>	BetaCoV	AlphaCoV	
		Embecovirus	Betacoronavirus 1 China Rattus coronavirus HKU24 Human coronavirus HKU1 Murine coronavirus Myodes coronavirus 2JL14
		Hibecovirus	Bat Hp-betacoronavirus
		Merbecovirus	Hedgehog coronavirus 1 Middle East respiratory syndrome related coronavirus Pipistrellus bat coronavirus HKU5 Tylonycteris bat coronavirus HKU4
		Nobecovirus	Eidolon bat coronavirus C704 Rousettus bat coronavirus GCCDC1 Rousettus bat coronavirus HKU9
		Sarbecovirus	Severe acute respiratory syndrome-related coronavirus- SARSr-CoV
		DeltaCoV GammaCoV	

Source: The Coronaviridae Study Group of the International Committee on Taxonomy of Viruses [39].
Abbreviations: CoV- coronavirus; SARSr-CoV- severe acute respiratory syndrome-related coronavirus.

The Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (ICTV), which is responsible for developing the classification of viruses and taxon nomenclature of the family Coronaviridae, assigned SARS-CoV-2 to the existing species severe acute respiratory syndrome-related coronaviruses (SARSr-CoV). Although phylogenetically related, SARS-CoV-2 is distinct from other zoonotic coronaviruses introduced to humans (38).

Origin of SARS-CoV-2

Currently, the knowledge about the origin of SARS-CoV-2 remains incomplete. Furthermore, the main host reservoir of the virus, the possible intermediate host candidates, and exact mechanisms for virus spillover into humans have not been clearly identified (40-41). Although the origin of SARS-CoV-2 is currently unknown, it is widely postulated to have a zoonotic transmission (42).

Among all possible animal hosts, it is confirmed that bats may represent the putative original virus reservoir since the closest sequences to SARS-CoV-2 found in the wild were obtained from bats (41). Over 200 novel coronaviruses have been identified in bats and approximately 35% of the bat virome sequenced to date is composed of coronaviruses (43). For instance, during an ecological surveillance of bats in the Guangdong province of China, a SARS-like CoV that closely matched the human SARS-CoV was isolated from the Chinese horseshoe bat (44). The search for the wild ancestors besides bats (e.g. pangolin, civets, mink) or for intermediate host among domestic animals (camels, dogs, cats) did not result in a direct linkage with SARS-CoV-2. No intermediate or reservoir species have ever been found, despite numerous investigations and to date there is no experimental data to support a direct spillover of SARS-CoV-2 from any animal species (43, 45).

Historic perspective

Human coronaviruses were described back in the 1960s and were officially accepted as a new genus of viruses (46). In the past two decades, the interest to this group of viruses have been substantially grown since the world experienced serious outbreaks of human coronavirus infection in 2002–2003 by SARS-CoV (47), in 2011 by MERS-CoV (48), and the latest pandemic of 2019 caused by SARS-CoV-2 (1).

Severe Acute Respiratory Syndrome (SARS).

Severe acute respiratory syndrome, called SARS, emerged in November 2002 from Fushan, Guangdong Province, southern region of China (49). By February 2003, a new virus spread across mainland China with more than 300 confirmed cases, around one third of which were health care workers (47). In March 2003, the WHO instituted a global effort to prevent the transmission and established a network of laboratories to determine a causative agent of SARS (47).

During the 2002–2003 outbreak, SARS infection was reported in 29 countries in South-East Asia, North America, and Europe. As of August 2003, 8422 infected individuals were identified, with 916 SARS-related fatalities (47, 50). A range of animal species were suspected as the prime disease reservoirs (palm civet, the Chinese ferret badger, racoon dog, ferrets, domestic cats), however, whether all they are the natural reservoir of SARS-like coronaviruses remains unproven (47). Due to the global public health effort towards infection control, after the last cases reported in January 2004, no human SARS cases have been detected since, and the SARS pandemic was declared to be over (51).

Throughout the outbreak of SARS in 2003, two main criteria were developed and used to define disease cases (51). The first criteria included a person presenting after 1 November 2002 with a history of high fever (greater than 38 °C) and cough or breathing difficulty, and one or more exposures during the 10 days prior to onset of symptoms. A probable case was defined by the WHO to have three criteria as follows: 1) a suspect case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest Xray; 2) a suspect case of SARS that is positive for SARSCoV by one or more assays; and 3) a suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause.

The incubation period of SARS is on average 2-7 days (52, 53). Common symptoms are fever, chills, coughing, malaise, myalgia, headache, and less common symptoms include diarrhea, vomiting, abdominal pain and others. The duration of stay in hospital for those who recovered was typically long, with a mean in excess of 25 days. Longer durations of stay were associated with older patient age and the presence of co-morbidities (53, 54). The mean time from admission to death was estimated as 36 days with a high variance, with an average case fatality rate around 10%. About 20-30% of patients admitted in hospitals with SARS required intensive care and subsequent mechanical ventilation (52-54).

Middle East respiratory syndrome (MERS).

In June 2012, 10 years after the first emergence of SARS-CoV, a novel coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), was discovered in Saudi Arabia from the biological material of a man died of acute pneumonia (55). Overall, 27 countries from the Middle East, North Africa, Europe, the United States of America, and Asia have reported cases of MERS-CoV infection with the largest number reported by the Kingdom of Saudi Arabia (84%, 2193/2600). 935 MERS deaths have been reported to WHO with crude case fatality rate 36% (56).

In terms of a natural reservoir, a serological survey showed a high prevalence of MERS-CoV-neutralizing antibodies in dromedary camels from Saudi Arabia, Qatar, Oman and the Canary Islands (51, 57). Most human-to-human transmission has occurred in health care facilities, and this remains a prominent feature of the epidemiology of MERS-CoV (56).

The revised case definition of MERS includes a person with laboratory confirmation of MERS-CoV infection, irrespective of clinical signs and symptoms (57). The clinical spectrum of MERS-CoV infection ranges from asymptomatic to acute respiratory illness presenting acute respiratory distress syndrome (ARDS) and other life-threatening complications such as septic shock and multi-organ failure. Approximately 36% of laboratory confirmed cases have had a fatal outcome (58). Common symptoms include fever, headache, non-productive cough, dyspnea, and myalgia. Other symptoms can include sore throat, coryza, nausea and vomiting, dizziness, sputum production, diarrhea, and abdominal pain. The median incubation period for MERS-CoV is approximately 5 days (range 2-14 days). In MERS-CoV patients, the median time from illness onset to hospitalization is approximately 4 days. In critically ill patients, the median time from onset to intensive care unit admission is approximately 5 days, and median time from onset to death is approximately 12 days (59). The risk of death among secondary cases was found to range from 20 to 35% (59).

2.1.2 COVID-19 outbreak: epidemiology, clinical characteristics, and risk factors.

After the outbreak of SARS-CoV and MERS-CoV, COVID-19 is the third major coronavirus outbreak, which proved to be the deadliest among all the previous outbreaks (60). The disease was declared a public health emergency with an international level of concern by the end of January 2020 and to characterize the outbreak as a pandemic on 11 March 2020 (61). As of March 2024, 229 countries and territories reported more than 774 million confirmed cases and more than 7 million deaths (2).

Brazil, the largest and most populous country in Latin America, presented one of the most devastating pandemic scenarios among affected countries in terms of death counts since its first recorded death in March 2020 (24, 25). By Mid-March 2024, Brazil took the 2nd place with registered 702 000 deaths and 6th place with 37.5 million confirmed cases in world cumulative cases ranking (2, 25). Although SARS-CoV-2 has a high potential for contamination and reaches all communities, the pandemic scenario in the country was marked by uneven mortality pattern based on regional socio-economic and demographic differences (26).

The human-to-human transmission of SARS-CoV-2 occurs through direct, indirect, or close contact with infected people (61). Viral particles were found in saliva, respiratory and ocular secretion, blood, urine, and stool, but it is primarily spread through direct person-to-person respiratory droplets. Importantly, the transmission can occur at asymptomatic or presymptomatic stages and peaks with symptoms onset (61). The incubation period of infection varies from 3-7 days on average, for up to 14 days, although it may differ by SARS-CoV-2 variant.

The clinical presentation of COVID-19 varies from asymptomatic to critical illness (2,62). According to WHO guideline (62), the clinical manifestation of symptomatic patients with SARS-CoV-2 infection can be grouped into 4 main categories: a) mild disease; b) moderate disease; c) severe disease; d) critical disease (Table 1).

Approximately 80% of people with COVID-19 have a mild to moderate respiratory illness (2, 63, 64). The diagnosis of disease in these cases is complicated by the diversity of symptoms. Moreover, COVID-19 symptoms are mostly unspecific and hardly distinct from other viral respiratory illnesses such as influenza and respiratory syncytial virus.

Table 1 - COVID-19 disease severity classification for adults, WHO, 2023.

Severity	Clinical outcome	Description
Mild disease	-	Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	Pneumonia	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including $\text{SpO}_2 \geq 90\%$ * on room air.
Severe disease	Severe Pneumonia	Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea) plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or $\text{SpO}_2 < 90\%$ on room air.
Critical disease	Acute respiratory distress syndrome (ARDS)	<i>Onset:</i> within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. <i>Chest imaging:</i> radiograph, CT scan or lung ultrasound: bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. <i>Origin of pulmonary infiltrates:</i> respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factors present.
	Sepsis	Acute life-threatening organ dysfunction caused by a dysregulated host response to suspect or proven infection.
	Septic shock	Persistent hypotension despite volume resuscitation, requiring vasopressor to maintain $\text{MAP} \geq 65$ mmHg and serum lactate level > 2 mmol/L.
	Acute thrombosis	Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute stroke.

Source: WHO. Clinical Management of COVID-19. Living Guideline (62).

*Caution: The oxygen saturation threshold of 90% to define severe COVID-19 is arbitrary and should be interpreted cautiously.

Among various signs and symptoms, patients can commonly experience fever or chills, cough, sore throat, fatigue, shortness of breath, new loss of taste or smell, myalgia, headache, nausea or vomiting, diarrhea (64). Although, the prevalence and predictive value of those symptoms vary by population and the type of studies applied (65). For example, the different prevalence of fever among patients with COVID-19 found in a large meta-analysis encompassing

1092 studies with 3 342 969 patients can be attributed to the different thresholds used in the studies (66). Different resources, new variants of virus, vaccine administration and other factors might be the reasons that patients in different outbreak stages had different manifestations (63, 65, 66).

Critical disease occurred in 5%, with complications such as respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, multi-organ failure and exacerbation of underlying comorbidities (67). The risk of progressing to severe disease increases with age and the number of underlying conditions. Patients aged ≥ 65 years, and patients who are unvaccinated or/and have certain underlying conditions are at a higher risk of progressing to severe or critical COVID-19 (67, 68).

The risk factors responsible for severe COVID-19 are cardiovascular diseases, cancer, chronic lung diseases, diabetes, chronic kidney diseases, chronic liver diseases, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking, and being a recipient of immunosuppressive therapy or a transplant. The risk appears to be higher in patients with multiple chronic conditions (66, 68). Besides advanced age, other demographic characteristics, such as male sex and non-white ethnic groups, have emerged as being associated with a higher risk of severe outcomes and death from COVID-19 (27,68). Black/African American people, Hispanic people, and American Indian/Alaska Native people experience rates of hospitalization that are more than 2 times higher and rates of COVID-19–related death that are approximately 2 times higher than those experienced by White people (67).

There has been a change in the presentation of COVID-19 symptoms among confirmed cases due to the administration of vaccines in the latter half of the pandemic and emerge of new SARS-CoV-2 variants (69). The evidence shows significant reduction in certain clinical symptoms as well as in the severity of disease (68, 69). For example, the results of a cohort study conducted in a 2021 (68) found that despite a substantial number of diagnosed infections per day during the Omicron period, persons with SARS-CoV-2 infection during this period were significantly and substantially less likely to progress to severe clinical outcomes, including hospitalization and death.

Many studies have shown that of people infected with SARS-CoV-2, a certain proportion never developed symptoms or developed symptoms later (70]. Meta-analysis of 94 studies in 2022 suggested that asymptomatic infection in SARS-CoV-2 Omicron variant-positive individuals represents 32% (95% CI 25.3–39.5%) of all SARS-CoV-2 infection, with 20% (17–25%) of people

remaining asymptomatic throughout the course of infection (70). Yet, it is still unclear what percentage of people who initially appear asymptomatic progress to clinical disease and what proportion of patients who remain truly asymptomatic throughout the course of infection (71).

Patients with COVID-19 may experience complications associated with coinfections (72). The National Institutes of Health (NIH) suggests grouping these complications into four main categories: a) coinfections at presentation; b) reactivation of latent infections; c) nosocomial infections; and d) opportunistic fungal infection (73). The first category represents patients with SARS-CoV-2 who are also diagnosed with other concomitant viral or bacterial infections. In the case of reactivation of latent infection, there are reports which have shown reactivation of certain chronic infectious diseases, such as, for example, virus hepatitis B, aspergillosis, mucormycosis, and tuberculosis (73-77).

The reinfection after recovery from prior COVID-19 was reported by many countries during disease outbreak (77). However, the data regarding its prevalence, risk factors, severity and timing are evolving. The possible reasons for reinfection that were mentioned are insufficient immune response after the first infection and the emergence of new variants of virus. SARS-CoV-2 infections among persons who are fully vaccinated, known as a vaccine breakthrough infection, also have been reported (78).

2.1.3 SARS-CoV-2 variants and diagnostic testing

Like other viruses, SARS-CoV-2 is constantly evolving through genetic mutations or viral recombination (79). These mutations over the course of pandemic, resulting in variants that are different from the original SARS-CoV-2 virus. It is widely recognized that the viral evolution may affect some virus's properties, such as disease severity, response to vaccines and the performance of diagnostic tests (79). Further, the data on emergence, clinical outcomes and transmission of new variants are rapidly growing, particularly for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics (73).

Throughout the COVID-19 pandemic, many variants of SARS-CoV-2 have been found globally. In May 2021, WHO released labels (Greek letters) for emerging variants to assist with public discussion and scientific communication (79). In the beginning of 2023, WHO announced that, going forward, the Greek letters will only be assigned to variants of concern (VOCs), while variants of interest (VOIs) will be referred to using established scientific nomenclature systems such as Pango or Nextstrain (80, 81). These nomenclature systems are being used by researchers and public health agencies worldwide to track the transmission of SARS-CoV-2.

Considering existing challenges regarding SARS-CoV-2 nomenclature systems, the WHO established Virus Evolution Working Group which is closely monitoring SARS-CoV-2 variants, their phenotypes and their impact on countermeasures (82). In October 2023, the group updated their recommendations on working definitions and primary actions for virus's variants [79]. Labels for SARS-CoV-2 variants, their links to existing phylogenetics-based classification and nomenclature systems, and their key scientific and clinical features have been published and updated continuously by the WHO at <https://www.who.int/activities/tracking-SARS-CoV-2-variants> (83).

Currently, WHO uses 3 types of classification:

- Variant under monitoring (VUM),
- Variant of Interest (VOI),
- Variant of Concern (VOC).

The U.S. Department of Health and Human Services (HHS) SARS-CoV-2 Interagency Group (SIG), which also monitoring emerging variants, uses 4 types of classification: Variant of high consequence (VOHC), Variant of concern (VOC), Variant of interest (VOI) and Variants being monitored (VBM) (84). Table 2 summarizes information regarding currently available definition of SARS-CoV-2 variants.

The Omicron variant was labeled as a variant of concern (VOC) in November 2021 and represents the most divergent VOC seen to date (84). Since its emergence, the Omicron variant rapidly became the dominant variant across the globe. Its subvariants BA.1, BA.1.1, and BA.2 emerged in early to mid-2022, followed by the subvariants BA.4, BA.5, BQ.1, BQ.1.1, XBB, EG.5, HV.1, and FL.1.5.1. Generally, the Omicron subvariants are more transmissible than previous

SARS-CoV-2 variants and are not susceptible to any of the anti-SARS-CoV-2 monoclonal antibodies that were previously authorized for the treatment and prevention of COVID-19 (85).

Table 2 - Working definitions for SARS-CoV-2 variants.

Classification	Definition
Variant Under Monitoring (VUM) ¹	A SARS-CoV-2 variant with genetic changes that are suspected to affect virus characteristics and early signals of growth advantage relative to other circulating variants, but for which evidence of phenotypic or epidemiological impact remains unclear, requiring enhanced monitoring and reassessment pending new evidence.
Variant of Interest (VOI) ¹	A SARS-CoV-2 variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, virulence, antibody evasion, susceptibility to therapeutics and detectability; AND identified to have a growth advantage over other circulating variants in more than one WHO region with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.
Variant of Concern (VOC) ¹	A SARS-CoV-2 variant that meets the definition of a VOI and, through a risk assessment meets at least one of the following criteria when compared with other variants: • Detrimental change in clinical disease severity; OR • Change in COVID-19 epidemiology causing substantial impact on the ability of health systems to provide care to patients with COVID-19 or other illnesses and therefore requiring major public health interventions; OR • Significant decrease in the effectiveness of available vaccines in protecting against severe disease.
Variant of High Consequence (VOHC) ²	In addition to the possible attributes of a variant of concern (VOC), variants designated as VOHC include impact on medical countermeasures such as: • demonstrated failure of diagnostic test targets. • evidence to suggest a significant reduction in vaccine effectiveness, a disproportionately high number of infections in vaccinated persons, or very low vaccine-induced protection against severe disease. • significantly reduced susceptibility to multiple EUA or approved therapeutics. • more severe clinical disease and increased hospitalizations.

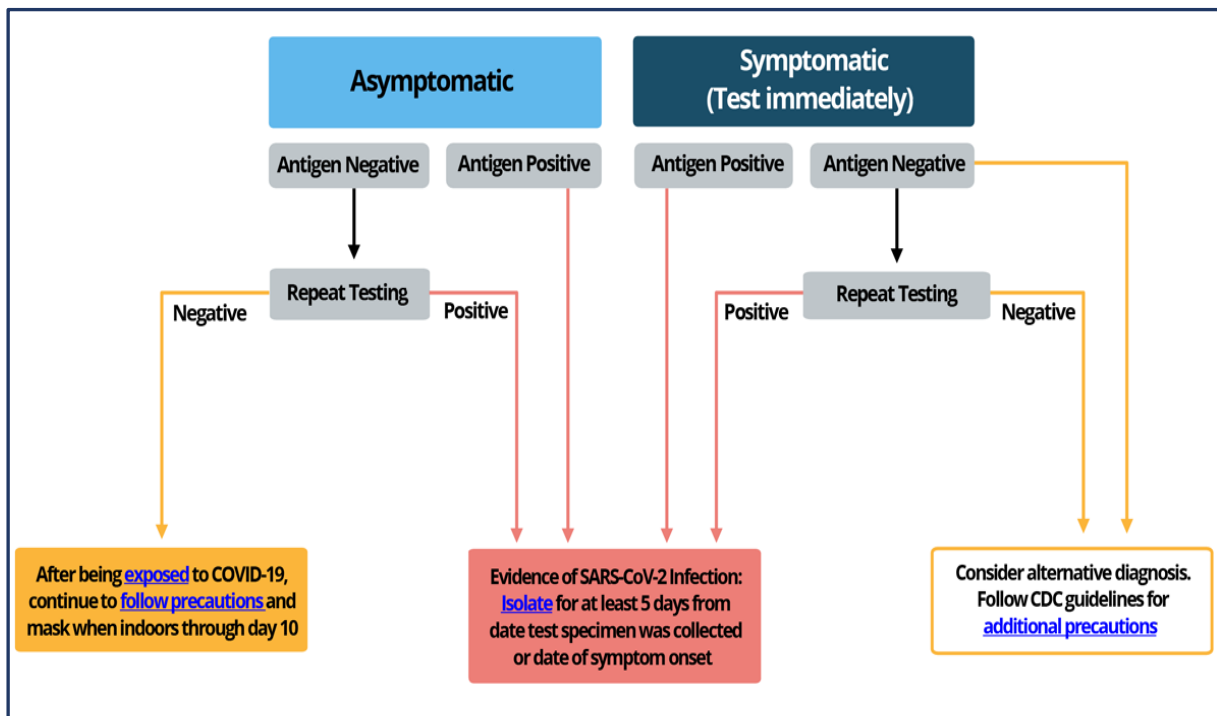
Source: author

¹- WHO working definitions, 4 October 2023 (79); ²- Centers for Disease Control and Prevention (CDC) working definitions, 1 March 2024 (84).

The timely and accurate diagnosis of SARS-CoV-2 infection is essential to the overall prevention and outbreak control (86). All suspected COVID-19 cases should be tested for SARS-CoV-2 independently of vaccination status or previous diseases history (87). The testing strategy should be considered according to different epidemiological situations and some specific factors such as limited resources, remote areas, vulnerable populations or populations with increased risk of severe disease (Figure 2) (88).

Currently, the following testing techniques for COVID-19 are available: a) Detection of viral RNA, through manual or automated nucleic acid amplification tests (NAAT), such as real time reverse-transcription polymerase chain reaction (rRT-PCR); b) Detection of viral antigens through immunodiagnostic techniques, such as lateral flow assays (LFAs), commonly called rapid diagnostic tests or Ag-RDTs; c) Detection of host antibodies through serological techniques, such as LFAs, enzyme linked immunosorbent assays (ELISAs), or chemiluminescent immunoassays (CLIAs) (86, 87).

Figure 2 - Recommendations to Healthcare Providers on Interpreting Antigen Test Results for Diagnostic Purposes.



Source: Centers for Disease Control and Prevention (88).

Among all available tests, NAATs are the most sensitive tests and considered as a "gold standard" for detecting SARS-CoV-2 infection (86). Antigen tests or Ag-RDTs are generally less sensitive than NAATs and recommended to use as a complementary testing strategy: when NAATs are not available or in situations where results could be delayed. Negative antigen test result does not rule out an infection and should be interpreted as preliminary, also the performance of NAAT test will be required. In situations where test sensitivity is of paramount importance, NAAT testing should take place as soon as possible, and no longer than 48 hours after the initial antigen testing. If the results are discordant, the NAAT result should be interpreted as definitive (87).

Testing of asymptomatic individuals with NAAT or Ag-RDTs is currently recommended only for specific groups including contacts of confirmed or probable COVID-19 cases and frequently exposed groups such as health care workers and long-term care facility workers (86). According to WHO recommendations, self-testing, using SARS-CoV-2 Ag-RDTs, should be offered in addition to professionally administered testing, although the accuracy of self-testing needs to be continually assessed (62).

Antibody tests can detect recent or prior SARS-CoV-2 infection or vaccination, although it is not recommended for diagnosis of COVID-19 (87). Virus-specific antibodies can be detected in the blood of patients who have recovered from COVID-19 or people who have been vaccinated against COVID-19 (87). Most people who had been infected develop neutralizing antibodies within 2-4 weeks after infection as a part of natural immune response (89, 90).

Individuals with mild or asymptomatic infection tend to have lower antibody levels than those with severe disease, and some studies have suggested that in some individuals waning of antibody levels occurs within several months after infection (87, 91). However, up to date, it remains unclear how long SARS-CoV-2 antibodies persist following infection or vaccination and how much cellular versus humoral immunity contributes to protection after natural infection. Antibody tests results should be interpreted cautiously considering potential false positive or false negative results, waning of antibodies with time after infection or vaccination and possible failure to develop detectable antibodies.

Overall, diagnostic testing for SARS-CoV-2 is an essential tool in preventing and controlling the spread of disease and must be implemented strategically, addressing the use of available resources to maintain the highest level of public health impact (87). The national testing

strategy should focus on strengthening the country's capacity for detection of epidemic prone diseases, including SARS-CoV-2, appropriately prioritizing testing capacity and developing the cost-effective implementation of clearly defined public health countermeasures.

2.2 Long-COVID

2.2.1 Terminology and clinical definitions

Many people who had COVID-19 return to their baseline of health. However, some people may experience heterogeneous symptoms or sequels weeks or months after initial SARS-CoV-2 infection (4). This phenomenon, now known as a Long COVID or Post-COVID condition, have been the subject of global public health awareness since the initial stages of COVID-19 pandemic when reports began to emerge regarding its serious impact on individuals' health. Mechanism by which Long COVID develops, and its heterogeneous nature have not yet fully understood, although some of their impact on individual's health is recognized (2).

A variety of terminology for Long COVID are used in literature, such as Long COVID, post-COVID syndrome, post-COVID conditions, long-haul COVID, post-acute COVID-19, long-term effects of COVID, and chronic COVID. The term post-acute sequelae of SARS CoV-2 infection is also used to refer to a subset of Long COVID. Further, several definitions of new conditions have been proposed since its recognition (Table 3).

In September 2020, following the request of member states to be able to document conditions that occur in the context of COVID-19, the WHO released specific International Classification of Diseases 10 (ICD-10) and ICD-11 codes for Long COVID (92).

After completion of two-round Delphi exercise, followed by a mixed consensus process, in October 2021, WHO published a clinical case definition of post-COVID condition (Long COVID) (5).

Table 3 – Clinical case definitions of Long COVID among adults

Source	Description
NICE	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.
CDC	Long COVID: The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing–remitting pattern and progression or worsen over time, with the possibility of severe and life-threatening events even months or years after infection. Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes.
Scientific American	Individuals whose symptoms persist or develop outside the initial viral infection, but the duration and pathogenesis are unknown.
Royal Society	The onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more.
Haute Autorité de Santé (HAS)	Three criteria: Having presented with a symptomatic form of Covid-19; presenting with one or more initial symptoms 4 weeks after the start of the disease; and none of these symptoms can be explained by another diagnosis.

Source: WHO, 2022 (5).

Abbreviations: NICE- National Institute for Health and Care Excellence; CDC- Centers for Disease Control and Prevention; Haute Autorité de Santé (HAS)- French National Authority for Health.

According to this document, Long-COVID is formulated as following: “post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction, but also others and generally have an impact on everyday functioning. Symptoms may also fluctuate or relapse over time.” (5). As was mentioned by authors, as new evidence will continue to emerge and knowledge about disease will increase, the current definition is likely to change .

In addition to clinical definition of Long COVID for adults, in February 2023, WHO released a clinical case definition of post COVID-19 condition (Long COVID) in children and adolescents by expert consensus (Table 4) (93).

Table 4 - Clinical case definition of post COVID-19 condition in children and adolescents, WHO, 2023.

Post COVID-19 condition in children and adolescents occurs in individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19.

Current evidence suggests that symptoms more frequently reported in children and adolescents with post-COVID-19 condition compared with controls are fatigue, altered smell/anosmia and anxiety. Other symptoms have also been reported.

Symptoms generally have an impact on everyday functioning such as changes in eating habits, physical activity, behavior, academic performance, social functions (interactions with friends, peers, family) and developmental milestones.

Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. They may also fluctuate or relapse over time. Workup may reveal additional diagnoses, but this does not exclude the diagnosis of post COVID-19 condition.

This can be applied to children of all ages, with age-specific symptoms and impact on everyday function taken into consideration.

Source: WHO, 2023 (93).

This clinical case definition was developed considering the need for separate definition for children and adolescents and with the intention to better understand the characteristics, risk factors, frequency that led to Long COVID in these groups of population. Pre-defined domains from the adult case definition by Delphi consensus together with commissioned systematic review and meta-analysis was used as a base for development of this clinical case definition (93).

Both clinical case definitions-for adults and for children/adolescents- have common strengths and limitations. These are the first Long COVID clinical definitions built on robust protocol-based Delphi methodology which included participation of a multi-disciplinary groups of experts representing all WHO regions (5, 93). However, the relatively small samples and short periods of follow-up in early studies of Long COVID, are subject of possible bias. Moreover, the heterogeneity of pathophysiological mechanisms and symptoms/syndromes, high variety of scenarios for recovery after COVID-19, different group of populations, and other characteristics, make it "overtly ambitious to produce a single, universal definition that might work well for clinical, research, policy and advocacy purposes, and for all care levels and severities" (5). Although these clinical definitions of Long COVID are likely temporary, as our knowledge about condition is rapidly changing and new data is continuing to emerge, this framework provides a strong foundation for ongoing and future research and clinical management (5, 93).

2.2.2 Global and Brazilian estimates for the prevalence of Long COVID

According to WHO, approximately 10-20% of people with COVID-19 may develop prolonged ongoing or new symptoms after infection (94, 95). Table 5 demonstrates selective estimates of Long COVID prevalence based on different studies and countries (14-18, 96-107).

Table 5 - Selected international studies on the prevalence of Long COVID in adults

Country	Authors	Population	Prevalence
United Kingdom	Sudre et al. (2020)	4182 Self-reported	13% (28 days after symptom's onset)
	Sigfrid et al. (2021)	327 Post-hospital follow-up	93.3% (3 months after discharge)
	Whitaker et al. (2022)	76,155 Community-based survey	37.7% (3 months after infection)
	ONS ^a (2022)	8193 Population representative	70% (beyond 3 months after infection)
	Subramanian et al. (2022)	384,137 Nonhospitalized	5.4% (3 months after infection)
China	Huang et al. (2021)	1733 Post-hospital follow-up	76% (6 months after discharge)
	Zhang et al. (2024)	1359 Post-hospital follow-up	54% (3 years after infection)
	Hu et al. (2025)	65,880 Meta-analysis	50% (overall)
			47% (7-12 months) 54% (>24 months)
Russia	Munblit et al. (2021)	2649 Post-hospital follow-up	10.8% (3 to 6 months after discharge)
India	Naik et al. (2021)	1234 Post-hospital follow-up	40.1% (91 days after discharge)
USA	Donnelly et al. (2020)	2179 Post-hospital follow-up	19.9% (readmitted at 60 days)
	Taquet et al. (2021)	273, 618 (electronic health records)	57% (at least one symptom)
South Africa	Jassat et al. (2023)	2626 Post-hospital follow-up	53.5% (3 months after discharge)
		1074 Nonhospitalized	31.6% (3 months after infection)
Netherlands & Belgium	Goërtz et al. (2020)	2113 Self-reported	99% (3 months after infection)
France	Carvalho-Schneider et al. (2020)	150 Post-hospital follow-up and outpatient evaluation	66% (60 days after symptom's onset)
Italy	Lombardo et al. (2021)	303 Post-hospital follow-up	81% (1 year after infection)

Source: Author

Abbreviation: ONS- Office of National Statistics

Available data suggests that among 3.92 billion infected individuals with SARS-CoV-2 in 2020 and 2021, 144.7 million (3,7%) cases globally suffered from common Long COVID clusters (95). There is large variation in estimates of population-based prevalence and incidence of Long COVID. The lack of unified terminology and definition across studies, high heterogeneity of reported symptoms and their sets, differences in methods based on different populations, settings and periods of follow-up are some of the reasons for difficulties summarizing data on the prevalence of this condition (4, 14).

The prevalence of Long COVID varies significantly across the studies, with far more available data that followed hospitalized patients with severe COVID-19 (4, 7, 108). Further, several meta-analyses and systematic reviews described a high heterogeneity in the estimated prevalence of Long COVID or specific persistent symptoms across the studies (7, 10, 11, 108). A meta-analysis on the global prevalence of Long COVID among a total of 1.68 million COVID-positive patients reported a higher pooled prevalence in hospitalized cohorts than in nonhospitalized cohorts (0.54 vs. 0.34, respectively) [10]. In contrast, in another meta-analysis of a total of 735,006 adults, about 45% of COVID-19 survivors experienced at least one long-haul symptom, regardless of hospitalization status (11). Both meta-analyses described the geographical asymmetry of available studies with majority of data from Europe, and a small number of the studies from the continents of South America, Africa, and Oceania (10, 11).

In a meta-analysis based on 211 international studies with a total population of 13.4 million individuals, the pooled estimated prevalence of persistent symptoms was significantly higher in COVID-19 patients as compared with controls (108). In terms of the duration of prolonged symptoms, in a systematic review of 57 studies comprising more than 250 000 survivors of COVID-19, the median proportions of those who experienced at least one persistent symptom at 1 month and 6 or more months after acute infection were found to be equally high (55% vs. 54%, respectively) (109). Additionally, there are studies that observed persistent symptoms one and two years after acute COVID-19 suggesting that Long COVID is a chronic potentially life-long illness (18, 20).

In nonhospitalized patients the occurrence of persistent symptoms after the initial infection varies significantly: for instance, 2% and 10% of prolonged symptoms within three months was reported from the United Kingdom (17, 97), while a study from Netherlands and Belgium reported

over 99% patients who did not fully recover within three months (16). An analysis of the data from 273,618 electronic health records demonstrated that 57% of COVID-19 survivors had at least one feature of Long COVID recorded between 3 and 6 months after a diagnosis, which was significantly higher when compared with individuals with influenza (15).

Relatively few studies from Brazil explored persistent symptoms among COVID-19 survivors. Table 6 shows selective estimates on the prevalence of Long COVID in Brazil (110-121).

Table 6 - Selected Brazilian studies on the prevalence of Long COVID in adults

Region	Authors	Population	Prevalence
Southeast	Battistella et al. (2022)	801 Post-hospital follow-up	70.8% (3 to 11 months after discharge)
	Miranda et al. (2022)	646 Post-hospital follow-up	50.2% (14 months after discharge)
	de Oliveira et al. (2022)	439 Post-hospital follow-up	84% (median 138 days after discharge)
	Nakayama et al. (2022)	565 Post-hospital follow-up	62.6% (beyond 3 months after discharge)
	Bonifacio et al. (2022)	175 Mixed	80% (beyond 4 months after infection)
	Azambuja et al. (2024)	710 Community (99.8% hospitalized)	22% (median 160 days)
	Prata et al. (2024)	189 Hospitalized	43% (12 months persistent dyspnea)
Midwest	Lapa et al. (2023)	400 Post-hospital follow-up	81% (3 months after discharge)
	Titze-de-Almeida et al. (2022)	236 Nonhospitalized	41.5% (5-8 months since diagnosis)
	Braga et al. (2022)	614 Mixed	100% (8 months after infection)
South	Laskovski et al. (2023)	140 Nonhospitalized (on-line survey)	44.3% (1 year after infection)
	D'Ávila et al. (2023)	289 Health-care workers	36.2% (6 months after infection)

Source: Author

Similar to other countries, most studies on Long COVID in Brazil are among hospitalized COVID19 patients. The estimated prevalence of Long COVID depends on the severity of initial acute infection, settings, duration of symptoms, and methodology of assessment.

The studies based on previously hospitalized (110, 112, 113, 115) or mixed cases (114, 117, 118) reported long-lasting symptoms in 41.5%-100% of patients. One Brazilian study based on on-line survey of 140 non-hospitalized adults reported Long COVID in 44.3% of adults one year after acute infection (27). Importantly, the vast majority of available data on Long COVID are from Southeast region, followed by Mideast and South regions of Brazil (Table 6). There is scarce of evidence on Long COVID prevalence from Northeast region.

2.2.3 Risk factors for Long COVID

Anyone who has been infected with the virus can experience Long COVID (4). However, there are people or groups of people who may be more susceptible to developing this condition (4, 7, 17, 108). Although the exact underlying mechanisms behind Long COVID manifestations are not entirely clear, some mechanisms may be explained by direct and indirect factors. Direct factors are results of the viral infection itself driven by virus persisting and /or mutations along with human specific biological factors responding to viral infection (9). Indirect effects are those that shape where people work or live including their social, economic, and behavioral conditions.

Females, people who had severe COVID-19, and those who have underlying health conditions are examples of groups that are more likely affected by Long COVID (4). Table 7 provides selected studies on risk factors for Long COVID (7, 10, 15, 17, 104, 106, 107, 110, 112, 113, 115, 116, 122-127).

A meta-analysis of 97 studies, with a total population of 993, 336 that explored risk factors for Long COVID, identified several common risk factors, such as female sex, older age, disease severity, multiple comorbidities and longer hospital stay (108). The majority of included studies in this meta-analysis were based on previously hospitalized or mixed COVID-19 cohorts (160 studies of hospitalized or mixed cohorts vs. 86 studies of nonhospitalized cohorts) (108). Another meta-

analysis of 50 included Long COVID studies describes female sex and pre-existing asthma as common risk factors (10).

Table 7 - Selective studies on risk factors for Long COVID

Country	Authors	Population/design	Risk factors
International	Luo et al. (2024)	993,336 Meta-analysis	Female sex; advanced age; severe COVID-19; multiple comorbidities; long hospital stay; high body mass.
	Chen et al. (2022)	1.68 million Meta-analysis	Female sex; pre-existing asthma.
	Michelen et al. (2021)	10, 951 Systematic review	Female sex, increasing age; multiple comorbidities.
United Kingdom	Sudre et al. (2021)	4182 On-line survey	Female sex; age >50 years; more than five symptoms.
	Whitaker et al. (2022)	76,155 Community-based survey	Female sex; increasing age; hospitalization with COVID-19; obesity; smoking; deprivation; low household income
	Subramanian et al. (2022)	384,137 Electronic health records (primary care)	Female sex; age 18-30 years; ethnic minority groups; multiple comorbidities; smoking; high body mass.
Norway	Bloomberg et al. (2021)	312 Cohort follow-up	Age 16-30 years; number of symptoms (home isolated adults with mild COVID-19).
USA	Hill et al. (2023)	8325 Case-control study	Female sex; age 40-69 years; severe COVID-19; multiple comorbidities; obesity.
	Taquet et al. (2021)	273, 618 Electronic health records	Female sex, age >65 years, hospitalization with COVID-19
Africa	Dryden et al. (2022)	1873 Hospitalized adults cohort	Female sex; severe COVID-19 (admission to intensive care).
India	Naik et al. (2021)	1234 Hospitalized adults cohort	Hypothyroidism; severe COVID-19
Korea	Kim et al. (2021)	900 Online survey	Female sex; age ≥50 years; moderate to severe COVID-19
China	Hu et al. (2025)	65880 Meta-analysis	Female sex; age ≥60 years; severe COVID-19; multiple comorbidities
Zambia	Zulu et al. (2022)	327 Nonhospitalized adults cohort	Five or more symptoms.
Brazil	Reis et al. (2022)	305 Online cross-sectional survey	Older age associated with olfactory disorder
	Battistella et al. (2022)	801 Hospitalized adults cohort	Female sex; older adults; multiple comorbidities
	Lapa et al. (2023)	400 Hospitalized adults cohort	Female sex; obesity; hypercholesterolemia
	de Oliveira et al. (2022)	439 Hospitalized adults cohort	Adults with a median age 57 years; longer hospital stays; ICU stay
	Nakayama et al. (2022)	565 Hospitalized adults cohort	Female sex; mechanical ventilation; length of hospital stays.
	Laskovski et al. (2023)	140 Nonhospitalized adults cohort	Female sex, anxiety/depression are predictors of functional limitation 1 year after infection.

Source: Author

Other risk factors that were identified by this study (10) but weren't meta-analyzed are severe COVID-19, older age, number of symptoms, obesity and pre-existing chronic conditions. Both meta-analyses (108, 10) noted common limitations of included studies such as a high heterogeneity (periods of follow up, demographic characteristics, Long COVID classification, instruments for symptoms' measurement etc.), self-reported tools used by majority of studies, and disproportionally higher number of studies from Europe compared to other continents. Additionally, those adults with Long COVID without access to testing, patients without strong health-seeking behavior, and asymptomatic individuals might have been misrepresented in the studies, especially those that were conducted in the early stages of the pandemic (10).

Female sex and multiple symptoms were consistently reported by many studies as a common risk factor for Long COVID, regardless of hospitalization (7, 10, 17, 107, 108, 125, 126). Old age is a universally accepted risk factor of poor outcomes in COVID-19 hospitalization. However, there are conflicting findings on the association between Long COVID and older age. Studies have identified different age groups as those that are potentially at risk for developing post-COVID conditions, possibly due to differences in observed populations, age stratification and severity of infection. Some studies reported increased risk with older age (7, 105, 108), while other studies reported increased risk among young and middle-aged adults (9, 98, 101, 106). Estimated risk factors for Long COVID by age more likely dependent on initial severity of infection (129).

The presence of multiple comorbidities (7, 108) and some chronic conditions, such as obesity (105, 106, 108), arterial hypertension, diabetes (129), asthma (10) hypothyroidism (104) were indicated as some of predictors of Long COVID in adults.

Health inequities may put some people from racial or ethnic minority groups and some people with disabilities at greater risk for developing Long COVID (106, 130). A recent data based on retrospective analysis of 62339 electronic health records positively tested for COVID-19 individuals, suggests that racial/ethnic minority groups (Black and Hispanic) may experience a higher overall burden of potential Long COVID compared to white individuals (130). These population groups are more likely to experience severe acute COVID-19 and have poorer access to medical care, which may increase the risk for Long COVID (130).

There is new evidence emerging related to impact of environmental factors for Long COVID development (131). Air toxicants, particulate matter compositions, neighborhood

deprivation, and food access being associated with increased risk of post-acute sequelae of SARS-CoV-2 infection related to nervous, blood, circulatory, endocrine, and other organ systems.

To date, the studies that explored risk factors for Long COVID among Brazilian population are severely limited. Additionally, the population from Northeast and North region did not represented in available studies. Most studies from Brazil involving patients who were previously hospitalized and likely experienced severe SARS-CoV-2 infection (Table 7) (110, 112, 113, 115).

Of those studies that explored risk factors in hospitalized cohorts, female sex (110, 112, 115, 116), older age (110, 113, 127), critical COVID-19 (113, 115), multiple comorbidities (110, 116), and obesity (112) were identified as predictors for persistent COVID-19 outcomes. A study based on observation of 400 previously hospitalized adults, did not confirm the association of Long COVID with length of hospitalization and severity of infection (112). Two studies from Brazil explored risk factors among nonhospitalized adults (116, 127). A cross-sectional on-line survey of 305 health workers described older age as predictor of persistent olfactory dysfunction (127), although this study was mainly focused on prolonged olfactory and taste disorders. Another study that assessed the functional status of 140 nonhospitalized COVID-19 survivors, found female sex and anxiety with depression as predictors for limited functional status (116).

2.2.4 Long COVID clinical outcomes

Timely diagnosis of prolonged health problems following acute SARS-CoV-2 infection is a key to providing effective health management and informing public health policies. However, a rapid increase in the number of reported symptoms/syndromes and their substantial heterogeneity became a common problem which hampers the progress in definition of Long COVID, the ability to compare its outcomes across the studies and ultimately to apply the knowledge for clinical practice (21, 132).

People with Long COVID can experience a wide range of ongoing, relapsing, or new symptoms or combination of symptoms which can damage one organ or multiple organs, and can range from mild to severe forms, for some cases resulting in disabilities (4, 5). The direct and

indirect impacts of COVID-19 on general well-being, mental health, psychosocial, neurological, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and other sequelae have been reported in adults following COVID-19 (4, 94). Among wide range of appearing symptoms, the most frequently reported are general symptoms, respiratory and heart symptoms, neurological symptoms, digestive system symptoms, and others (4, 6, 7, 10, 11). There is a debate about whether the list of possible symptoms reported in people who experienced Long COVID is too long to implement an effective diagnosis (14). Over 200 different symptoms have been identified as related to this illness, with some symptoms (e.g., fatigue, cognitive and mental dysfunction symptoms) being more frequent than others (6).

To address the issue of complexity and heterogeneity of findings in Long COVID research and clinical practice, and to help ensure that reliable outcomes are assessed consistently, the core outcome set (COS) for post COVID-19 condition (PC-COS) in adults was developed in 2021 and published in 2022 (14, 133). The development of PC-COS was based on two-round online modified Delphi consensus process and was undertaken by the group of multidisciplinary, international experts and people who experienced Long COVID symptoms, in collaboration with the COMET (Core Outcomes Measures in Effectiveness Trials) initiative. Inclusion of people with lived experience and their opinion was crucial for the development process and, as previous practice shown, the patient perspective may differ from the opinion of experts (132, 133).

Initially, eleven outcomes reached consensus for the COS and to be measured and reported in adults with Long COVID in clinical research and practice: fatigue, pain, post-exertion symptoms, work or occupational and study changes, survival and functioning symptoms, and conditions for each of cardiovascular, respiratory, nervous system, cognitive, mental health, physical outcomes (133). The recovery was added as a 12th outcome for COVID-19 which has relevance to Long COVID.

After a PC-COS was defined, in 2023, the study group developed and released consensus agreement for the instruments (tools, procedures) that should be applied for the measurement of each outcome (132). The instruments for measure survival (time until death), recovery (the Recovery Scale for COVID-19), and respiratory outcomes (the Dyspnoea Scale) in adults were compromised for the final core outcome measurement set (COMS). Although no single measurement instrument reached consensus for nine of the 12 core outcomes. However, among

319 potential instruments, 19 instruments with high level of support but without consensus were considered for use with the nine remaining outcomes (Table 8).

Table 8 - The core outcome set (COS) and the core outcome measurement set (COMS) for adults with Long COVID

COS	COMS
Physiological or clinical outcomes	
1. Cardiovascular functioning, symptoms, and conditions	Symptom Burden Questionnaire for Long COVID–circulation subscale, New York Heart Association Functional Class scale
2. Fatigue or exhaustion	Fatigue Assessment Scale, Fatigue Severity Scale Functional Assessment of Chronic Illness Therapy–fatigue subscale
3. Pain	Brief Pain Inventory
4. Nervous system functioning, symptoms, and conditions	Central Sensitisation Inventory
5. Cognitive functioning, symptoms, and conditions	Cognitive Failures Questionnaire, Montreal Cognitive Assessment–Blind version
6. Mental functioning, symptoms, and conditions	GAD-7 questionnaire, PTSD Checklist for DSM-5
7. Respiratory functioning, symptoms, and conditions	Modified Medical Research Council Dyspnoea Scale
8. Post-exertion symptoms	DePaul Symptom Questionnaire
Life impact outcomes	
9. Physical functioning, symptoms, and conditions	Symptom Burden Questionnaire for Long COVID–impact on daily life subscale
10. Work or occupational and study changes	Work Ability Index, Work Productivity and Activity Impairment questionnaire, WHO post-COVID-19 Case Report Form occupational status item
Survival	
11. Survival	Time until death
Outcome from previous COS	
12. Recovery	Recovery Scale for COVID-19
Multidomain instruments	
EuroQol 5-Dimension 5-Level survey	
Short Form (36) Health Survey	
WHO Disability Assessment Schedule 2.0 12-item version	
Post-COVID-19 condition-specific instruments^b	
COVID-19 Yorkshire Rehabilitation Screening Scale	
Symptom Burden Questionnaire for Long COVID	

Source: Munblit et al., 2022 (133).

Abbreviations: COS- core outcome set; COMS- core outcome measurement set.

As a next step in a COS development process, the core outcome set, and the core outcome measurement set for research and clinical practice in post-COVID-19 condition (Long COVID) in children and young people was finalized and published in March 2024 (Table 9) (134).

Table 9 - The core outcome set (COS) and the core outcome measurement set (COMS) for children and young people with Long COVID

COS	COMS
1. Cardiovascular functioning, symptoms and conditions	-
2. Gastrointestinal functioning, symptoms and conditions	PedsQL Gastrointestinal Symptoms Scales
3. Fatigue or exhaustion	PedsQL Multidimensional Fatigue Scale
4. Post-exertion symptoms	-
5. Neurocognitive functioning, symptoms and conditions	PedsQL Cognitive Functioning Scale
6. Physical functioning, symptoms and conditions	EQ-5DY instrument
7. Work/occupational and study changes	-

Source: Sevlanova et al., 2023 (134).

Abbreviations: COS- core outcome set; COMS- core outcome measurement set.

Seven outcomes achieved the pre-defined consensus definition for inclusion in the COS: fatigue; post-exertion symptoms; work, occupational and study changes; as well as functional changes, symptoms and conditions relating to cardiovascular, neurocognitive, gastrointestinal and physical outcomes (134).

It is important to mention that the COS was defined as an agreed minimum set of outcomes that should be measured and reported in studies on Long COVID and does not prohibit researchers from including other outcomes (132, 133). Moreover, the list of symptoms associated with Long COVID is constantly growing with different patterns/clusters/phenotypes emerging, which demands a future structure and harmonization of the most relevant outcomes to be applied in scientific trials and for clinical practice.

Given the complex nature of the condition, with implications for many aspects of the lives of those affected, the National Institute for Health and Care Excellence (NICE) guidelines advise that assessment and management should be tailored to the individual's problems, after excluding any coexisting illness that may be giving rise to the symptoms reported (4,23). Moreover, further development, in association with patients and their experience, of contextually appropriate guidelines on diagnosis and management of Long COVID for health professionals, especially in

primary care, based on relevant and systematic studies, is a priority to planning a policy response to this emerging condition (4).

2.2.5 Quality of life of adults with Long COVID

Quality of life is defined by the World Health Organization (WHO) as “individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (135). It is a multidimensional concept incorporating in a complex way the person’s physical state and well-being, mental health, social relationships, level of independence, personal beliefs and their relationship to salient features of the society (135).

It is well-recognized that the COVID-19 pandemic had a negative impact on population wellbeing (4, 136). However, the long-term effects on health-related quality of life (HRQOL) of those who survived the acute infection have been less documented (19, 20, 137-142).

There is heterogeneity of HRQOL results across the studies with respect to the differing populations, instruments for HRQOL measuring, severity of infection, time of follow up and clinical outcomes (137, 139, 141). Similarly with estimates for the prevalence and risk factors for Long COVID, the majority of studies on HRQOL have followed previously hospitalized cases with patients who likely experienced severe infection (137, 141). Table 10 provides selective studies (meta-analyses and systematic/structured reviews) on health-related quality of life of COVID-19 survivors (19, 136, 137, 140, 141, 142).

In a meta-analysis of seven cohort studies that reported HRQOL out of twenty-four cohort studies with a follow-up beyond 6 months, more than half of observed population of adults with persistent symptoms had decreased HRQOL (Table 10) (137). Notably, while some studies included in this meta-analysis reported larger declines in HRQOL of those who experienced severe illness (143, 144), there is a study that showed substantially worse health outcomes among adults who experienced mild infection (145). This meta-analysis did not found statistically significant

correlation between HRQOL measures and severity of infection, thus both hospitalized and nonhospitalized adults had decreased quality of life beyond 6 months after acute infection (137).

Table 10 - Selective studies on health-related quality of life of adults with Long COVID

Authors	Study/Instrument	Population	HRQOL
Ma et al. (2022)	Meta-analysis 40 observational studies Follow-up >6 months EQ-5D-5L	10,945	6 to 12 months of follow-up: 33.3% (pain/discomfort) 33.5% (anxiety/depression) >12 months of follow up: 35.3% (pain/discomfort) 35.4% (anxiety/depression) Mean 4.5 months of follow-up: 52% (decreased HRQOL)
Sanches-Ramirez (2021)	Meta-analysis 24 studies Follow-up >6 months Nijmegen Clinical Screening Instrument (NCSI), EQ-5D-5L	5,323	No significant correlation between HRQoL and disease severity
Malik et al. (2022)	Meta-analysis 12 studies Follow-up 1-6 months EQ-5D-5L	4,828	1 to 6 months of follow-up: 59% (decreased HRQOL) 42% (pain/discomfort) 38% (anxiety/depression) 36% (mobility) 28% (usual activities)
Dorri et al. (2021)	Systematic review 21 studies SF-36, WHOHRQOL, EQ-5D-5L	49,650	All studies reported that a HRQoL was reduced in survivors at follow- up time compared to pre-COVID-19 time or controls.
de Oliveira et al. (2023)	Systematic review 1 to 6 months after infection 35 studies SF-36, PROMIS scale, EQ-5D-5L	10,54	1 to 6 months after infection 31%-67% (depending on instrument and severity of infection)
Poudel et al. (2021)	Structured review 12 studies (11-observational, 1-experimental) SF-36, EQ-5D-5L, pulmonary disease-specific HRQoL tools	5,816	The lowest HRQoL score was among the elderly adults; The lowest mean QOL value was from middle-income countries as compared with high-income countries.

Source: author

Abbreviation: HRQOL- health-related quality of life

Another meta-analysis of more than ten thousand adults with Long COVID notified the poor individuals' HRQOL one year after acute infection (19). Additionally, the pooled estimates from twenty-one cohort studies of 49,650 COVID-19 survivors showed a significant decrease of HRQOL compared to pre-COVID-19 times or controls (140). In a meta-analysis based on the

studies that applied the generic EQ-5D-5L instrument, estimated 59% of adults with long COVID had experienced some issues with HRQOL. Of those, more than third of observed population had issues with pain or discomfort (42%), anxiety or depression (38%), mobility (36%) and with usual daily activities (28%).

All reviews (19, 136, 137, 139-142) reported common limitations in the respect of a high heterogeneity of included studies, insufficient standardization, and lack of controls or comparators in most of the studies. Further, there were lack of studies covering non-hospitalized patients with COVID-19 and those patients under 18 years (136); a lack of subgroup data (male vs female), and use of self-rating scales to assess the prevalence of psychological problems (140); and no data available on outcomes studied before the patients contracted COVID-19 (137). Considering the global scale of COVID-19 illness, a comprehensive understanding of patient' long term health consequences beyond the acute phase, including the health-related quality of life, are necessary to help implement adequate healthcare and rehabilitation programs.

3 METHODS

3.1 Study Design and Settings

3.1.1 Study Design

This is an exploratory, empirical quantitative study with a cross-sectional design and primary data collection. A retrospective cross-sectional survey was conducted in Brazilian primary health care facilities in João Pessoa, Brazil, from May 2023 to July 2024. Two instruments were applied to investigate Long COVID in adults diagnosed with mild-to-moderate COVID-19 during the 2021 pandemic: 1) the standardized questionnaire with a set of validated clinical outcomes, and 2) a generic instrument for measuring the health-related quality of life (HRQOL).

The present thesis is a part of the scientific project “Estudo da magnitude das condições Pos-COVID e suas consequências na saúde da população no município de João Pessoa-PB” funded by Fundação de Apoio à Pesquisa do Estado da Paraíba -FAPESQ, where author of this thesis, Assel Muratovna Shigayeva Ferreira, was enrolled as an investigator.

3.1.2 Settings

The study was conducted in six Family Health Care Units (Unidade de Saúde da Família - USF), in João Pessoa city of Paraíba state, Brazil. Located in the Northeast region, Paraíba is one of 27 federative units (states) of Brazil and the third most densely populated state in its region. The capital city of Paraíba, João Pessoa, represents 21% of the state population and has the highest demographic density in the region (3.970.27 inhab./km²). According to the Brazilian Institute of Geography and Statistics (IBGE), estimated population of the city was 897,633 inhabitants in 2025 (146).

The Family Health Care Units (Unidade de Saúde da Família - USF) are ambulatory primary health care facilities, which located throughout all territory of Brazil. USF are operated under the guidance of the National Family Care Strategy (Estratégia Saúde da Família- ESF) and the National Primary Health Care Policy (Política Nacional de Atenção Básica) established by the Brazilian Ministry of Health (147). Each USF is composed of family health teams, made up of doctors, nurses, nursing assistants, and community health workers. Additional specialized services are provided by multidisciplinary teams, including nutritionists, psychologists, social workers, psychiatrists, pharmacists, speech and hearing therapists, gynecologist/obstetricians, pediatricians, geriatricians, and others according to local needs (148).

In João Pessoa city, the health services' network, in which USFs make a part, is organized in five sanitary districts that cover the entire territorial extension and population of the city. The health teams cover 2,000 to 4,000 individuals in households across a geographic area, localized as near to the users as possible. The USF provides continuous basic assistance organized for the enrolled population, with guaranteed access to diagnostic and laboratory support on ambulatory level (149). Territories covered by USFs enrolled in the study varied in terms of the populations served and their level of socio-environmental vulnerability (Table 11). Moreover, four out of the six USFs enrolled in the study served populations with high and very high levels of socio-environmental vulnerability, characterized by elevated social vulnerability and the presence of environmental risk and degradation (150, 151).

Table 11 - The list of USFs enrolled in the study, Joao Pessoa, state of Paraiba, 2025

The Family Health Care Units (USFs)	Sanitary district (territory)	Level of socio-environmental vulnerability ^a
USF 1 (USF Grotão)	Sanitary District II (Grotão)	Very high
USF 2 (USF Saúde para Todos)	Sanitary District I (Bairro dos Novais)	Very high
USF 3 (USF São Jose)	Sanitary District V (Manaira)	Very low
USF 4 (USF Nova União)	Sanitary District III (Mangabeira)	Average and high
USF 5 (USF Bancarios)	Sanitary District V (Bancarios)	Low
USF 6 (USF viver Bem)	Sanitary District IV (13 de Maio)	High

Source: Prefeitura Municipal de João Pessoa, 2025 (150).

^a- Topografia Social de João Pessoa, 2009 (151).

3.2. Study Population and Recruitment

3.2.1 Study Population

Table 12 summarizes inclusion criteria of the study. The population in this study was composed of adults who fulfilled the following eligibility criteria: age ≥ 18 years, adults with a history of mild-to moderate COVID-19 illness diagnosed in the period between 1 January and 31 December 2021, laboratory confirmed SARS-CoV-2 infection, and those who could be reached (patients with a valid address/contact information, and those who were permanently living in Joao Pessoa).

The mild-to moderate COVID-19 diagnosis was provided by professional doctors, who were affiliated at the USFs. The mild COVID-19 cases were considered symptomatic patients without evidence of viral pneumonia or hypoxia. The moderate COVID-19 included patients with clinical signs of non-severe pneumonia, who did not require hospitalization (152).

Table 12 - Inclusion and exclusion criteria.

Inclusion criteria:

- a) Symptomatic individuals with mild to moderate confirmed SARS-CoV-2 infection, who attended in USF (outpatient facilities) in the period between 1 January and 31 December 2021.
 - b) Age 18 years and older
 - c) Confirmed SARS-CoV-2 infection with positive test results by any authorized viral tests (i.e., nucleic acid amplification test or antigen test)
 - d) Individuals that could be reached
-

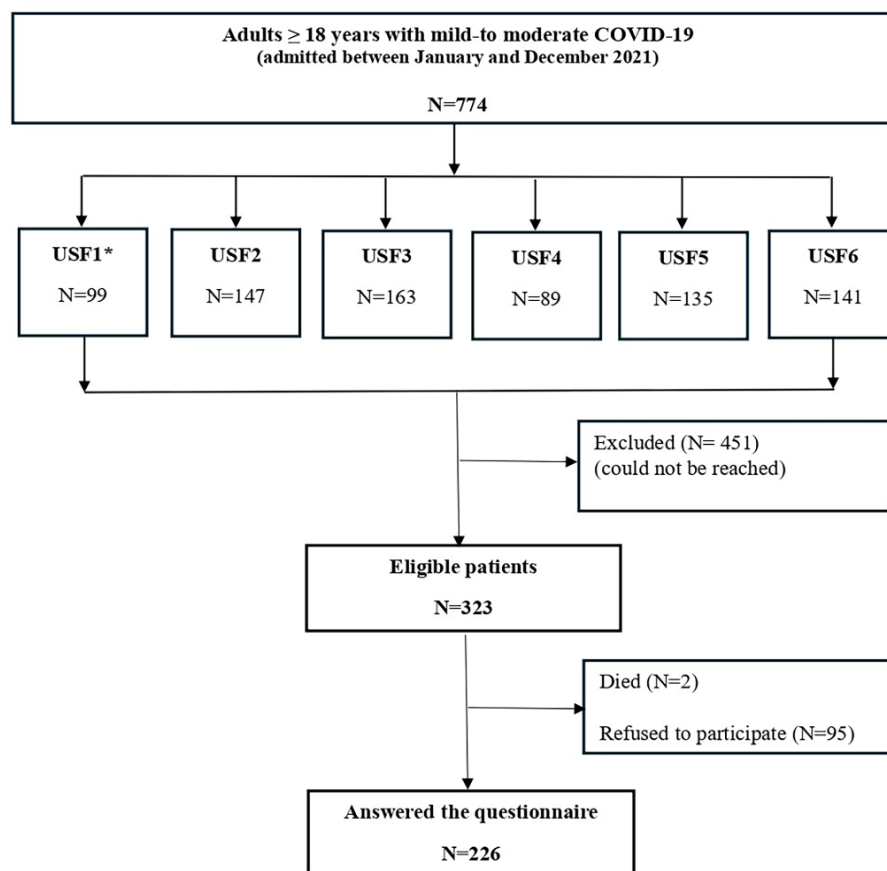
Source: Author; USF- Unidade de Saúde da Família

Sampling. Respondents were selected on the basis of their positive COVID-19 test results and their willingness to participate. The sample consisted of all adults who attended the referent USFs, had a positive SARS-CoV-2 test result, and agreed to be interviewed.

3.2.2. Recruitment

The list of potentially eligible individuals with their respective COVID-19 laboratory results and contact information were obtained from USF medical records and electronic archives. The recruitment areas varied in terms of the population to allow for ethnic and sociodemographic diversity among study participants. Recruitment into the study was performed by trained study's interviewers. Potentially eligible participants were contacted via home visits or phone calls. All individuals were asked about their willingness to participate in the study and provided paper-based informed consent. Figure 3 shows the selection procedure of study participants.

Figure 3 - Participants selection flowchart



*- the Family Health Care Units (Unidade de Saúde da Família-USF)

Source: author

3.2.3 Ethical Considerations.

The study was constructed using primary data and subject identification. Therefore, the project protocol was assessed by the Research Ethics Committee (Comitê de Ética em Pesquisa- CEP), as established in Resolution 510, April 7, 2016, of the Brazilian National Health Council (153). The study does not involve therapeutic interventions or any kinds of clinical or diagnostic interventions and presents minimal risk to participants. Informed consent was obtained from each participant before an interview.

The study was approved by Ethical review board of the Federal University of Paraiba (UFPB), as required for conducting research involving humans (nº5.376.051; CAAE: 55764722.4.0000.5188).

3.3 Data Collection and Data Management

A standardized Long COVID questionnaire and a generic EQ-5D-5L instrument were administered through “KoboTool”- a free electronic platform designed for secure data collection, management, and visualization (154). Both instruments were administered at the same appointment to interview study participants. The phone application version was installed by each team member who provided the interviews.

Each interviewer passed through the selection process and was trained and supervised by a senior investigator, who has expertise in conducting qualitative studies. Certain tactics were adopted to reduce potential interview bias : 1) the selection of the interviewers with the following training was conducted twice (at the beginning and at the midpoint of the survey); 2) all interviewers were trained to strictly follow the interview guide and avoid any influencing commentaries/actions during the interview.

All participants were interviewed in person, mostly via home visits or in USF, per their preference. The assistance was provided by the interviewers for those participants who could not administer responses (e.g. unable read/write). The average time to complete the survey was estimated as 30 minutes per interview. After each interview, the data were archived and transferred/converted to secure electronic database. Each participant was assigned unique identifier to ensure that personal data is secured.

3.4 Long COVID Definition

To define Long COVID symptoms, the study followed the Long COVID definition outlined by WHO (Table 13) (5). We asked patients if any of the listed symptoms occurred within a period of 3 months after SARS-CoV-2 infection and if they lasted at four time points: less than 1 month, 1 to 2 months, 2 to 3 months, and more than 3 months. The cases that meet the Long COVID definition were considered those that occurred within 3 months after SARS-CoV-2 infection onset, had a duration of at least 2 months and could not be explained by any alternative diagnosis. Table 13 shows clinical definition for Long COVID outlined by WHO.

Table 13 - Clinical case definition of Long COVID (WHO, 2021)

Long COVID (Post-COVID-19 condition) occurs in individuals with a history of **probable or confirmed SARS-CoV-2** infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time.

Notes

There is no minimum number of symptoms required for the diagnosis; symptoms involving different organs systems and clusters have been described.

Source: WHO, 2021 (5).

3.5 Standardized Long COVID Questionnaire

The development and validation of the standardized questionnaire is fully described in the dissertation authored by Alverga C.C.F. (155). This process comprised three stages: (i) concept matrix of a set of core symptoms by mapping Long COVID clinical outcomes from systematic reviews/meta-analyses and cohort studies (the prototypical stage); (ii) the content validation of the instrument by 9 health professionals (the empirical stage); and (iii) the test-retest reliability was assessed by interviewing 37 patients with Long COVID

(the reproducibility stage). The content validity index was calculated for each item of the instrument, and Cohen's Kappa coefficient was used to estimate the agreement between test and retest responses (155).

After completion of the validation process, 18 Long COVID clinical outcomes (also referred as validated symptoms in this thesis) were included and organized in a final questionnaire (Table 14). The final standardized questionnaire consisted of 47 questions and was originally written in Brazilian Portuguese (Appendix).

Table 14 - Standardized Long COVID questionnaire panel

General Information	Complete name, date of birth and contact information of the participant
Age	at the time of interview.
Sex	encoded as 4 sub-groups: female, male, other, prefer not to declare.
Race	encoded as 6 sub-groups: White, Black/African, Asian/Oriental, Indigenous, Mixed race, Unknown race.
Education	encoded as 10 sub-groups: complete elementary school, incomplete elementary school, complete high school, incomplete high school, complete technical/professional course, incomplete technical/professional course, complete higher education, incomplete higher education, complete post-graduation, incomplete post-graduation.
Preexisting chronic conditions	any self-declared chronic diseases
COVID-19 Vaccination	The participants were asked if they received COVID-19 vaccine(s), how many doses and what type of vaccine(s)
Validated Clinical Outcomes	
<i>Neurological symptoms</i>	
1.	fatigue
2.	post-exertional malaise
3.	muscle pain
4.	dizziness
5.	short-term memory loss
6.	mental confusion
7.	loss of attention
8.	difficulty thinking
9.	executive functioning difficulties
10.	difficulty in solving problems
<i>Other symptoms</i>	
11.	sore throat
12.	dyspnea
13.	chest pain
14.	joint pain
15.	dry cough
16.	difficulty breathing
17.	diarrhea
18.	anxiety
Self-reported symptoms	- additional symptoms
Duration of symptoms	- less than one month; 1 to 2 months; 2 to 3 months; more than 3 months

Source: author.

3.6 EQ-5D-5L instrument

The generic EuroQol 5-dimension 5-level (EQ-5D-5L) instrument was used to access the health-related quality of life (HRQOL) of the study population.

The EuroQOL-5 dimensions (EQ-5D) is a generic instrument which has many applications that aid decision making in health (156). The EQ-5D, a preference-based measure of health status, is widely used around the world in clinical trials, population studies and real-world clinical settings. In particular, it was designed to be a brief generic measure with the purpose of assigning a single summary value to each possible health profile (157). Moreover, this instrument is one of the recommended tools by an international Delphi consensus for the HRQOL measurement of Long COVID in adults (132).

Table 15 describes the principal components of the EQ-5D-5L instrument. This instrument comprises two measurement components - a short descriptive system and a visual analogue scale (EQ-VAS) (156).

Table 15 - EQ-5D-5L descriptive system.

Dimensions	Description
Mobility	Problems in walking
Self-care	Problem with washing or dressing
Usual activities	Usual (habitual) activities
Pain/Discomfort	Pain or discomfort
Anxiety/Depression	Anxious or depressed
Levels	
Level 1	No problems
Level 2	Slight problems
Level 3	Moderate problems
Level 4	Severe problems
Level 5	Extreme problems

Source: EuroQol Group, 2025 (156).

The descriptive system of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) is accompanied by five response levels (no problems, slight problems, moderate problems, severe problems, unable to/extreme problems).

The participants were asked to indicate their health state by checking the most appropriate response level for each dimension. Each response was coded with a 5-digit number, which represents different health states (e.g. 11111-no problem in any dimension, 55555- the extreme problems in all dimensions) (156).

The EQ-VAS measures the individuals overall current health on a visual analogue scale ranges from 0 to 100, where the endpoints are labelled “*The best health you can imagine*” and “*The worst health you can imagine*.” We asked participants to mark the number on the scale that reflects their current perception of own health. In a case when respondents sometimes found it difficult to draw a line from the box to the scale, we followed Euro-QoL recommendations and asked respondents to simply ‘mark an X on the scale to indicate how your health is ‘today’ and then to ‘write the number you marked on the scale in the box below’.

This study was officially registered on Euroqol (Registration ID: 73890) and qualified as a non-commercial study, hence no license was required for its administration. The self-administered EQ-5D-5L version in Brazilian Portuguese was obtained officially from Euroqol (version 1.2, 01.03.2023) (Appendix).

3.7 Statistical Analyses

This section describes the statistical procedures that were used to assess the prevalence, risk factors, and the health-related quality of life of adults with Long COVID. The group of adults with Long COVID was compared with a comparator (adults without Long COVID). The specific study outcomes, definitions, analysis strategy, and statistical analytical tests were outlined prior to performance of statistical analysis and followed the study objectives.

All statistics and data analyses were performed in IBM SPSS Statistics, Version 29.0.2.0 (20).

3.7.1 Descriptive Analysis of the Study Population Characteristics

Demographic characteristics of the study population, race/ethnic background, educational level, the COVID-19 vaccination history, COVID-19 related symptoms and the presence of comorbidities were drawn from a standardized questionnaire. Variables were expressed as the means and standard deviations (SD) for continuous variable (age) and as absolute values along with frequencies (%) for categorical variables. Responses that were “not declared” or “unknown” were coded as missing values.

Categorical variables: For analysis, participants' age grouped as either <60 and ≥60 years old or in six age bands: 18-29, 30-39, 40-49, 50-59, 60-69, and 70 years and older. The ethnic group was categorized as either (White, African, Asian, Mixed race, Indigenous) or two-categorical (white/nonwhite). Education level was categorized either as 10 categories of original grouping in the standardized questionnaire or as two-categorical (< 12 and ≥ 12 years of schooling) according to the number of years of schooling (Table 14). Comorbidities were categorized as either present/absent (yes/no) or by their quantity (none, one, two, or more than two preexisting chronic conditions). The participants were asked if they had been vaccinated before SARS-CoV-2 infection. COVID-19 vaccination status was categorized as not vaccinated or received ≥ 1 dose. COVID-19-related symptoms were categorized by their number as either dichotomous variables (<5 and ≥5 symptoms) or as five categories (none, 0–4, 5–9, 10–15, and more than 15 symptoms).

3.7.2 Analysis of the Prevalence of Long COVID Outcomes

This section outlines the statistical analyses referent to Objective 1 of the thesis to estimate the prevalence of Long COVID among the study population, and to compare sociodemographic characteristics and occurrence of clinical outcomes among adults with Long COVID and those without Long COVID.

The prevalence was expressed as percentage (%) by dividing the number of adults who reported at least one persistent symptom by the total number of study population.

The prevalence of Long COVID was estimated as follows:

$$\text{Prevalence} = \frac{N \text{ of adults who reported at least 1 persistent symptom}}{N \text{ of study population}} \times 100, \text{ where,}$$

- prevalence of Long COVID;
- the study population comprises adults with confirmed COVID-19 infection;
- persistent symptoms were considered those that occurred within 3 months after SARS-CoV-2 infection onset and had a duration of at least 2 months (Table 14).

Occurrence of each validated symptom was estimated by dividing the number of adults with a symptom by the total number of participants, with 95% confidence intervals (95% CI) were estimated for proportions via the Clopper–Pearson test. The Clopper–Pearson interval, also called the exact interval, is an alternative to

calculating binomial confidence intervals using normal approximation (158). The prevalence of comparative group of adults without Long COVID was also estimated.

Characteristics of participants and occurrence of COVID19 related symptoms were compared between adults with Long COVID and those without Long COVID. Differences between the age means of the two groups were assessed using a Student's t-test for independent variables. Between-categorical group comparisons were performed with the two-tailed chi-squared test or Fisher's exact test, as appropriate. The chi-squared test applies an approximation assuming the sample is large, while the Fisher's exact test runs an exact procedure especially for small-sized samples (159). The results were considered statistically significant with the p value less than the prespecified alpha of 0.05 ($p < 0.05$).

3.7.3 Logistic Regression Analyses

Binomial logistic regression was used in this thesis as a method of statistical analysis for the Objective 1.2 to compare occurrence of validated symptoms between those with and without Long COVID; Objective 2 to assess risk factors for Long COVID, and Objective 4 to assess the association of Long COVID with health-related quality of life. This statistical method was deemed appropriate because the outcome (dependent variable) is dichotomous, i.e., with or without Long COVID.

Binomial logistic regression is based on binomial probability theory (160), and used to estimate probability of a binary or dichotomous outcome (e.g., yes/no, present/absent, fail/success, 0/1). Logistic regression estimates the log odds of the outcome as a linear combination of the predictor variables (160):

$$\ln(P/(1 - P)) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \dots + b_k X_k, \text{ where}$$

P - probability of an outcome Y (yes/no)

$(P/1-P)$ - the odds of an outcome

$\ln(P/(1 - P))$ – log odds of an outcome

b_0 – the intercept

$b_1, b_2, \dots, b_k$ - coefficients for predictor variables $X_1, X_2, \dots, X_k$

Source: Harris JK, 2021 (160)

Logistic regression method relies on the assumptions that outcome is binary/dichotomous, observations are independent (e.g., do not come from repeated measures study design), absence of perfect collinearity among independent variables, and linear relations between a predictor and log-odds of the outcome (158). Logistic regression uses the maximum likelihood estimation for fitting coefficients, aiming to maximize the probability of classifying observations into one of two outcome categories (158 160). Several tests exist to assess model's goodness of fit, i.e., how close the values predicted by the model are close to the observed values (160).

In this thesis, the logistic regression analysis included univariate (with one predictor), and multivariate regression models. In the following relevant sections, I detail how logistic regression was applied for respective objectives and provided model's goodness-of-fit tests as relevant.

3.7.4 Unadjusted and Adjusted Odds Ratios for Long COVID Outcomes

To understand the relationship between Long COVID and observed symptoms, the unadjusted odds ratio (OR) and adjusted odds ratios (aOR) with respective 95% confidence intervals (95% CI) were estimated for 18 validated symptoms and for additional self-reported symptoms.

Reporting the unadjusted ORs for the main predictor or predictors of interest may contribute to understanding how covariates influence the relationship between the predictor and outcome (160). The series of univariate logistic regressions were performed with each predictor (symptom) to estimate the unadjusted odds ratios.

Dependent variable (Outcome): The dichotomized Long COVID variable, coded as “No” and “Yes,” was used as the dependent variable in the regression model.

Independent variables (Predictors): 18 validated symptoms (Table 14).

Then, adjusted odds ratios (aOR) with 95% CI for each outcome were estimated using multivariate logistic regression controlled by confounders. Confounders are factors that may influence both predictors and an outcome, thus adjusting for potential confounders is crucial for producing valuable evidence in outcome studies, since potential confounders can lead to misleading causal relationships, thereby obscuring the true

effects (161). The *stepwise* regression was used as a selection procedure for appropriate confounders. *Forward elimination* approach was applied as follows:

- stepwise regression started with an empty model with no confounder,
- then progressed by sequentially adding confounders, one at a time,
- the default entry criterion based on p-value ($p < 0.05$) in SPSS used to add confounders one by one,
- the stopping rule used when no remaining variable satisfies the entry criterion.

The variable “sex” ($p = 0.017$) was included as a confounder based on in a stepwise regression analysis. Additionally, two variables “comorbidities” and “age” were included as confounders, irrespective of the p-value associated with them in the bivariate analysis. The confounders entered in a multivariate regression model: variable “sex” (male -reference/female), variable “age” (age 18–29 years-reference, age 30–39, 40–49, 50–59, 60–69, and 70+ years), and variable “comorbidities” (none-reference/any). A 95% CI for an odds ratio were estimated to show the range of values where the true population value of the odds ratio likely lies (158).

3.7.5 Analysis of Risk Factors for Long COVID

This section provides description of the statistical analyses referent to Objective 2 of the thesis to identify risk factors associated with Long COVID.

To identify risk factors for Long COVID and to examine the relationship between Long COVID and the set of predictive independent variables, binary logistic regression was employed. The univariate logistic regressions used to estimate unadjusted OR with respective 95% confidence intervals. Multivariate logistic regression analysis was used to estimate adjusted OR with respective 95% confidence intervals for all predictors included into the model. The results were considered statistically significant with the P value less than the prespecified alpha of 0.05 ($p < 0.05$).

Dependent variable (Outcome): The dichotomized Long COVID variable, coded as “No” and “Yes,” was used as the dependent variable in the regression model.

Independent variables (Predictors): Table 16 shows the list of predictors included in a regression analysis.

Table 16- Independent variables of a regression model

Factor	Coding variable	Reference
Symptoms		
< 5	0	reference
≥ 5	1	
Sex		
Male	0	reference
Female	1	
Age		
18-29	0	reference
30-39	1	
40-49	2	
50-59	3	
60-69	4	
70+	5	
Ethnicity		
White	0	reference
Non-White	1	
Education		
< 12	0	reference
≥ 12	1	
Comorbidities		
none	0	reference
any	1	
specific comorbidity ^a		
no	0	reference
yes	1	

Source: author

^a - variables of arterial hypertension and diabetes

Multicollinearity represents a high degree of linear intercorrelation between explanatory variables in a multiple regression model and leads to incorrect results of regression analyses (160). The results of analysis of the variance inflation factor (VIF) for multicollinearity are presented in Table 17.

Table 17 - Variance inflation factor (VIF) of predictors

Predictors	Tolerance	VIF
Symptoms	0.950	1.052
Sex	0.956	1.046
Age	0.309	3.235
Ethnicity	0.965	1.036
Education	0.967	1.034
Comorbidities	0.355	2.820
Arterial hypertension	0.376	2.659
Diabetes	0.756	1.324

Source: author

Abbreviation: VIF- variance inflation factor

The analysis of VIF showed moderate collinearity of predictors ($1 < \text{VIF} < 5$), which was acceptable for including in a final regression model. The Hosmer-Lemeshow test, the Pearson chi-square, deviance, pseudo-R square values (Cox & Snell R square, Nagelkerke R square), and classification table in SPSS were examined to assess the model's goodness-of-fit (GOF). In general, GOF tests examine a null hypothesis that the structure of the fitted model is correct and how well the independent variables in the model predict the outcome (162, 163). Table 18 shows the GOF parameters of the logistic regression model.

Table 18 - Goodness-of-fit (GOF) parameters of a multivariate logistic regression model

Model Summary			Hosmer and Lemeshow test	
-2 Log Likelihood	Cox & Snell R square	Nagelkerke R square	Chi-square	Sig.
196.495	0.300	0.422	2.552	0.859

Source: author

The explained variation in the dependent variable in our model ranges from 30.0% to 42.2% (the Cox & Snell R-square and Nagelkerke R-square methods, respectively). The Hosmer and Lemeshow test showed that the model failed to reject the null hypothesis, meaning the observed and predicted values are not significantly different (p value=0.859), which indicates that the model fits the data well.

A classification table in SPSS is a table generated by logistic regression model that compares the actual, observed categories of a dependent variable with the predicted categories, showing how well the model predicts a binary dependent variable. Table 19 shows the classification table of a final logistic regression model.

Table 19 - Classification table of a multivariate logistic regression model

Observed	Predicted		% correct
	No	Yes	
No	45	24	65.2
Yes	18	136	88.3
Overall percentage			81.2

Source: author

The classification table provides the following information: (i) The percentage accuracy in classification (PAC); (ii) Sensitivity, which is the proportion of positive cases that were correctly classified by a model as "yes" (i.e., true positives); (iii) Specificity, which is the proportion of negative cases that were correctly classified by a model as "no" (i.e., true negatives); (iv) The positive predictive value; and (v) The

negative predictive value. The model correctly classified 81.2% of the data with 136 cases correctly predicted as “yes” (true positive) and 45 cases correctly predicted as “no” (true negative).

3.7.6 Analysis of Health-Related Quality of Life (HRQOL)

This section outlines the statistical methods for addressing Objective 3 and 4 of the theses to assess relations between Long COVID and health related quality of life. The application of statistical procedures for estimation of health-related quality-of-life (HRQOL) in this thesis followed the recommendations outlined by EuroQol (156, 157) for analysis of EQ-5D-5L. The appropriate statistical approaches were chosen and adopted for the population of this study.

3.7.6.1. Exploratory Analysis of EQ-5D-5L Profiles

According to the recommendation of Euroqol (160), exploratory analysis of health profiles within the EQ-5D-5L instrument provides important insights and should always be the starting point for HRQOL analysis of EQ-5D-5L outcomes.

The absolute numbers and proportions (%) of participants' responses were estimated for each level of problem (none, slight, moderate, severe and extreme) for each dimension (mobility, self-care, usual activities, anxiety/depression, pain/discomfort) of an EQ-5D-5L descriptive system, and for a visual analogue scale (VAS). Additionally, the absolute numbers and proportions (%) were also calculated separately for dichotomized variables of each dimension with two levels of responses (level 1 coded as-no problem, levels 2 to 5- any problems). The three missing values withing an education variable were treated as missing completely. Between-categorical group comparisons were performed with the chi-squared test or Fisher's exact test, as appropriate. The results were considered statistically significant with the p value less than the prespecified alpha 0.05.

Examining health profiles data by reporting the number and percentage of patients reporting each level of problem on each dimension of the EQ-5D-5L generates useful information about health within study population that helps in interpreting more complex statistical analysis (157). However, reporting data in this manner doesn't tell us how these problems combine in adults reporting them; thus, the cumulative frequency of health profiles was also calculated. In this manner, the extent to which the observations are distributed across 3,125 health profiles were summarized.

3.7.6.2 EQ-5D-5L Value Set Analysis

The values, presented in country-specific value sets, are a major feature of the EQ-5D instrument, permitting to describe population health as the EQ-5D-5L describes 3,125 possible unique health profiles (157). The participants' responses for each dimension were coded with a 5-digit number according to the level of severity (e.g. 11111-no problem in any dimension, 55555- the extreme problems in all dimensions) [156]. The 5-digit code then was transformed into the "index value" referent to individual's unique health state estimated with a use of a value set.

As of September 2025, EQ-5D-5L value sets that undertaken the standardized valuation EuroQol study protocol were available for 34 countries around the world (157). The Brazilian value set for EQ-5D-5L was not developed at the time of the data analysis for this thesis. In absence of value set for a country, EuroQol recommends considering using available published EQ-5D-5L value set of another country (164). However, there is no consensus in regards of recommendations of which country value set to choose and what are exact criteria to apply when choosing value set of another country (164).

Choosing the EQ-5D-5L value set for analysis. The use of available EQ-5D-5L value set from one of the Latin America countries was one of the solutions for this study. However, there are some limitations that prevent me from using a value set from Uruguay and Peru, two Latin America' countries with available estimates for EQ-5D-5L value sets. Among limitations: (i) in the study from Uruguay younger and higher educated respondents were over-represented (164, 165); (ii) Uruguayan study was conducted in the first wave of EQ-5D-5L valuation, where rigorous quality control process were not standardized (164); (iii) Peruvian study was conducted using a smaller sample compared to usual valuation protocols (166).

Two value sets were obtained to estimate health index values for this study: the United States (US) value set (167) and a value set from India (168). The decision to consider these two value sets was based on following observations: (i) Both countries, United States and India, have large multi-ethnic populations; (ii) the US data were collected using robust data quality control; (iii) the US value set is recommended by EuroQol for international studies (163); (iv) Indian valuation study is the largest valuation study worldwide with an use of ten composite time trade-off tasks along with a robust and transparent quality control (168); Both value sets were obtained from official EuroQol site (<https://euroqol.org/information-and-support/resources/value-sets/>). The syntax code for US (Pickard et al.) value set was obtained for further computation of index values.

3.7.6.3 Receiver Operating Characteristic (ROC) Curve.

The EuroQol recommends performing sensitivity analysis using other country(s) EQ-5D-5L value sets, to assess the impact of the choice on results and conclusions (164). The receiver operating characteristics curve (ROC) analysis is a useful tool for evaluating the accuracy of a binary classifier model (169).

For ROC analysis in SPSS, both the US and India value sets entered as “test variables”, while EQ-5D-5L dimensions entered as “state variables”. The comparative analysis of value sets was performed for each 5D health dimension separately (Table 20). Value of state variables was considered as having health problems with a smaller test result indicate positive actual state. Area under the curve (AUC) classifier with 95% confidence interval along with standard error under the nonparametric assumption were estimated.

Table 20 - The performance of India and US value sets after ROC analysis application

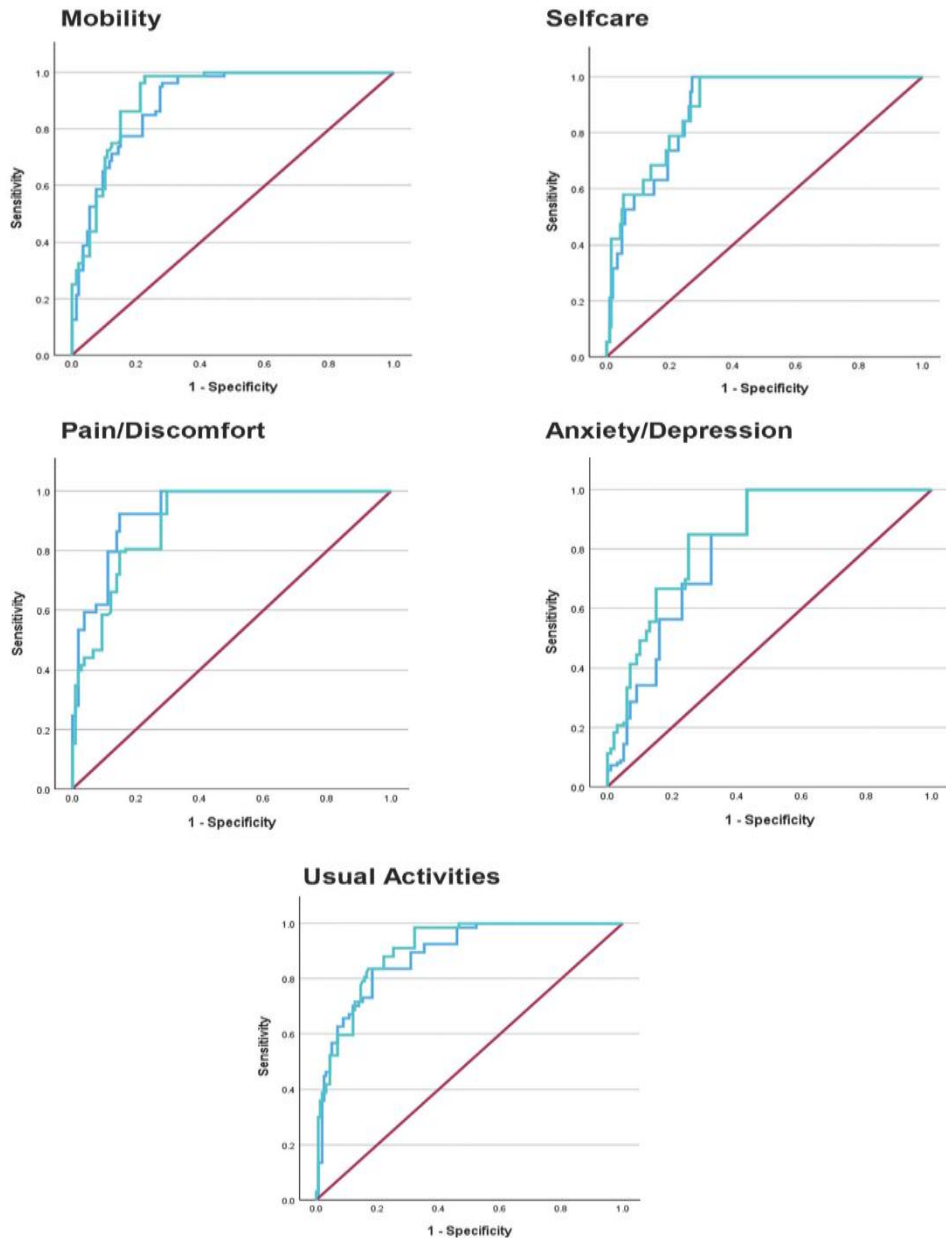
	Value set	AUC	SE	95%CI	p-value	GI	K-S metric
Mobility	US	0.915	0.018	0.880-0.950	<0.001	0.830	0.761
	India	0.898	0.020	0.860-0.937	<0.001	0.797	0.682
Self-care	US	0.896	0.028	0.841-0.950	<0.001	0.792	0.705
	India	0.887	0.028	0.833-0.943	<0.001	0.774	0.729
Usual activity	US	0.905	0.019	0.868-0.943	<0.001	0.811	0.666
	India	0.888	0.022	0.845-0.931	<0.001	0.776	0.653
Pain/discomfort	US	0.898	0.021	0.857-0.938	<0.001	0.795	0.704
	India	0.932	0.016	0.900-0.964	<0.001	0.863	0.776
Anxiety/ depression	US	0.843	0.027	0.790-0.895	<0.001	0.685	0.599
	India	0.802	0.031	0.741-0.863	<0.001	0.604	0.570

Source: author

Abbreviation: AUC -the area under the curve, SE-standart error, CI-confidence interval, GI- the Gini index, K-S metric- the maximum Kolmagorov-Smimov metric.

The following additional classifier evaluation metrics were considered while choosing better performed value set: the maximum Kolmogorov-Smirnov metric, and Gini index (Table 20). Overall performance of both value sets was considered “good/excellent” with AUC higher than 0.8 and 0.9, dependent of HRQOL dimensions (Table 2; Figure 4).

Figure 4 - ROC curves of US and Indian value sets of five EQ-5D-5L dimensions



Source: author

— Indian value set

— US value set

— Reference line

The statistical parameters for US value set demonstrated better AUC for all five EQ-5D-5L dimensions, except for pain/discomfort compared to India value set (0.898 vs. 0.932), those the US value set was applied in a final model to estimate the value indexes for the population in this study.

3.7.6.4 EQ-5D-5L Index Values and VAS Scores Analyses

EQ-5D-5L health states, coded as 5-digit number for respondents were transformed into index values using the US value set (167). A continuous health-index variable, indexed on a 0-to-1 cardinal scale, was then analyzed. For the measurement variables, statistics of central tendency and statistics of dispersion were applied (170). The following descriptive statistical measures were applied: minimum and maximum values; the mean with its standard deviation (SD); the 95% confidence interval for the mean; the median and interquartile range (IQR); variance; skewness; and kurtosis.

Normality was assessed using the Kolmogorov–Smirnov test, the Shapiro–Wilk test, and a histogram as a graphical visualization of the data distribution (Table 21).

Table 21 - Descriptive statistics for the index value variable

Parameters	Statistics	S.E.	Significance
Mean	0.805	0.013	
95%CI	0.779–0.831		
5% trimmed mean	0.823		
Median	0.874		
Variance	0.039		
Std. deviation	0.196		
Minimum	0.264		
Maximum	1.000		
IQR	0.736		
Skewness	-1.089	0.163	
Kurtosis	0.557	0.324	
K-S test	0.160		<0.001
S-W test	0.868		<0.001

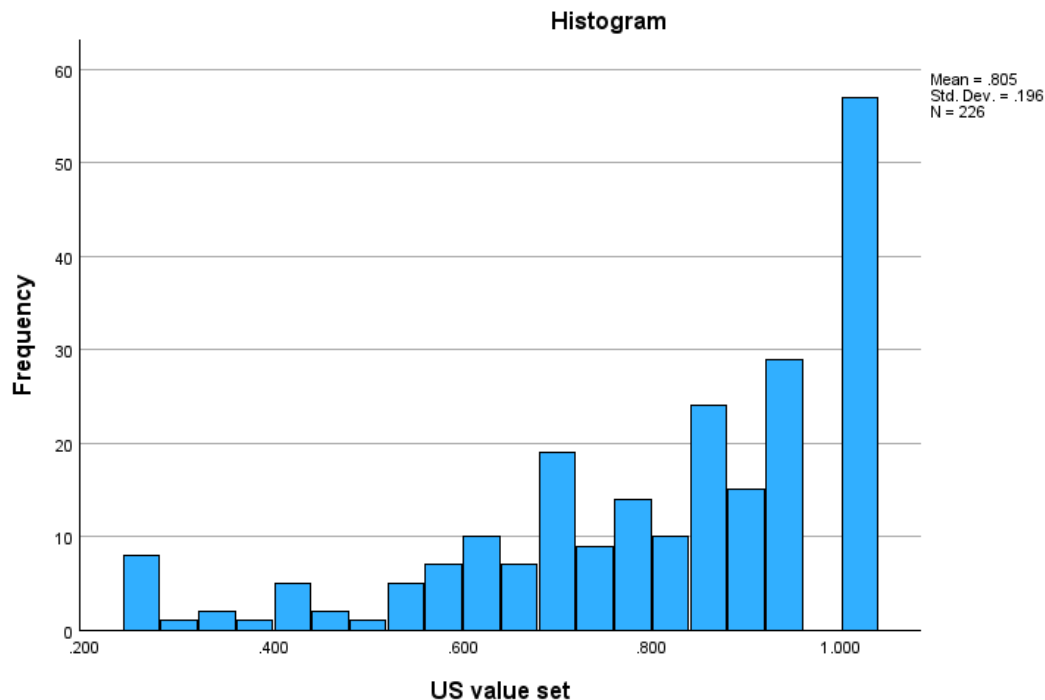
Source: author

Abbreviation: CI- confidence interval, SE- standard error, IQR- interquartile range, K-S test- Kolmogorov-Smirnov test; S-W test- Shapiro-Wilk test

The results of the distributional analysis showed that the index-value variable was non-normally distributed, exhibiting a left-skewed distribution (Figure 5). This was indicated by a mean lower than the

median, a skewness value less than -1.0 , and significant Kolmogorov–Smirnov and Shapiro–Wilk test results ($p < 0.05$), all of which suggest that the data differ from a normal distribution.

Figure 5 - Histogram of the index value variable



Source: author

The comparison of EQ-5D-5L index values between the two groups (with Long COVID and without Long COVID) and among the subgroups were conducted using nonparametric statistical tests appropriate for non-normally distributed variables. The following subgroups were included in the comparative analysis: Long COVID status, number of symptoms, sex, age, ethnicity, education, and comorbidities.

The Mann-Whitney U and the Kruskal-Wallis H non-parametric tests were applied to determine differences between two groups. Nonparametric tests do not assume underlying distribution and hence may be referred to as distribution-free tests. Nonparametric tests convert the raw values into ranks and then perform calculations on these ranks to obtain a test statistic (159). The Mann–Whitney U-test was applied to compare two independent variables: sex (male vs female), symptoms (none vs any), number of symptoms (<5 vs ≥ 5), age (<60 years vs ≥ 60 years), ethnicity (white vs nonwhite), education (<12 years vs ≥ 12 years of schooling), comorbidities (none vs any). The Kruskal-Wallis H test was applied to determine if there was any statistically significant differences between six age groups.

The Visual Analogue Scale (VAS), a continuous variable indexed on a 0-to-100 cardinal scale, was analyzed in the same manner as the health-index values (156). First, descriptive statistics—including measures of central tendency, measures of dispersion, and tests of normality—were applied (Table 22, Figure 6).

Table 22 - Descriptive statistics for the visual analogue scale (VAS) variable

Parameters	Statistics	S.E.	Significance
Mean	70.43	0.013	
95%CI	67.99–72.87		
5% trimmed mean	71.03		
Median	70.00		
Variance	346.59		
Std. deviation	18.617		
Minimum	30		
Maximum	100		
IQR	21		
Skewness	-0.432	0.162	
Kurtosis	-0.556	0.322	
K-S test	0.143		<0.001
S-W test	0.945		<0.001

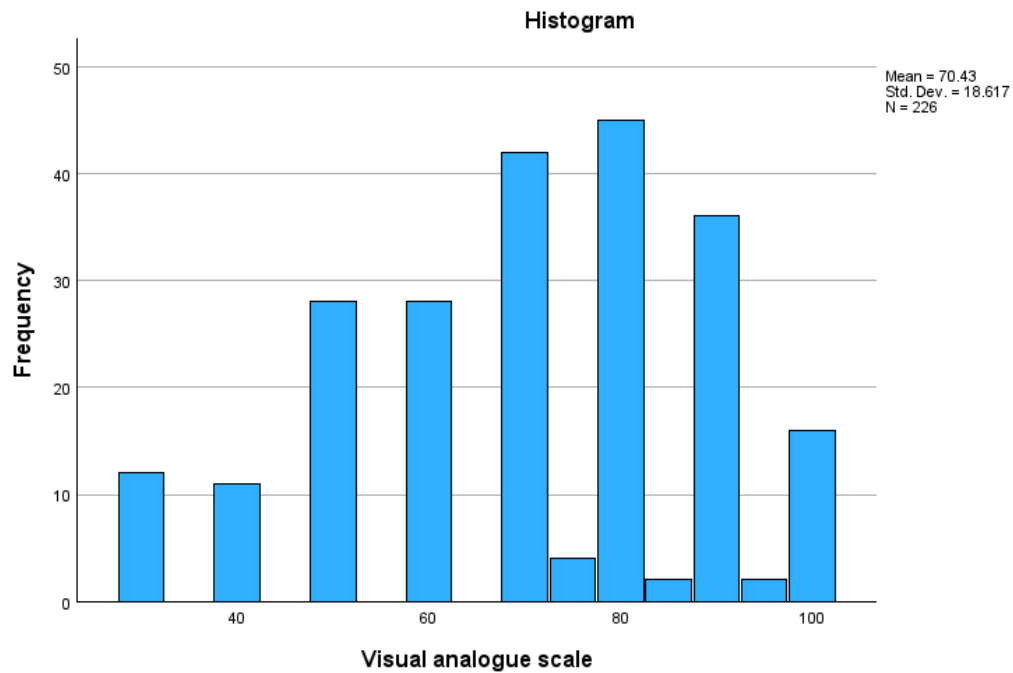
Source: author

Abbreviation: CI-confidence interval, SE- standard error, IQR- interquartile range, K-S test- Kolmogorov-Smirnov test; S-W test- Shapiro-Wilk test

The results of the descriptive analysis of the VAS variable showed that the values were more widely dispersed around the mean, as reflected by a higher variance, and that the data exhibited an asymmetrical left-skewed distribution (Table 22, Figure 6). This was indicated by a mean lower than the median and by significant Kolmogorov–Smirnov and Shapiro–Wilk test results ($p < 0.05$), all of which suggest that the data differ from a normal distribution.

Second, comparisons of VAS responses between the two groups (with Long COVID vs. without Long COVID) were conducted using nonparametric tests. The Mann–Whitney U test was applied to compare two-category independent variables (sex, ethnicity, education, presence of symptoms, number of symptoms, and comorbidities), and the Kruskal–Wallis H test was used to compare variables with three or more categories (age groups).

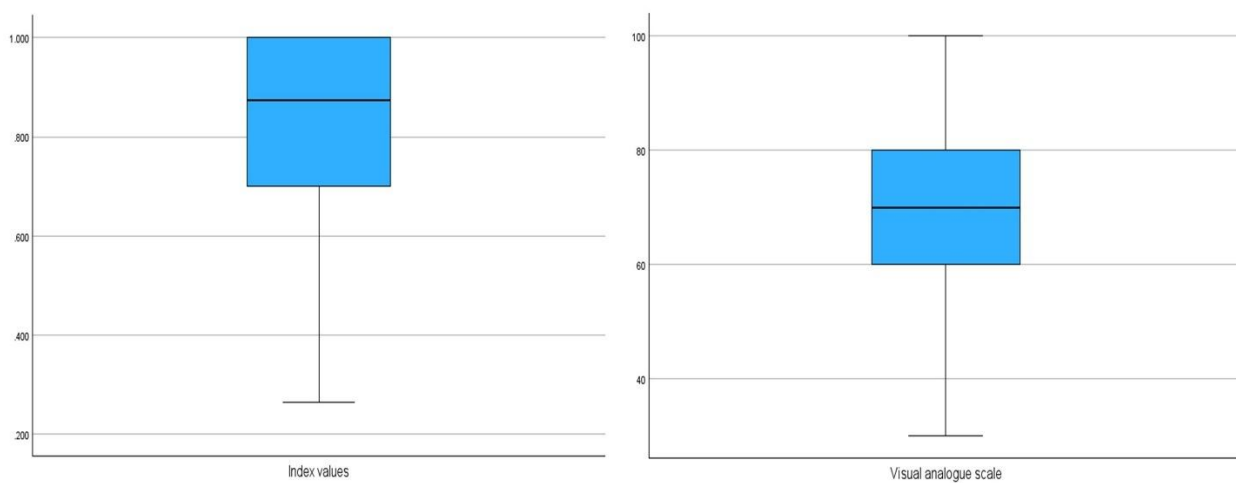
Figure 6 - Histogram of the VAS variable



Source: author

Both variables of VAS and index values were examined for outliers by application of z-score method (which measures how many standard deviations a data point is from the mean), and interquartile method (which calculating the range between the first (Q1) and third quartiles (Q3) of the data). Figure 7 shows the boxplots of the VAS and index values variables.

Figure 7 - Boxplots of the VAS and index values responses



Source: author

Two extreme values of VAS responses were handled using a Winsorizing approach. This approach involves modifying the weights of outliers or replacing the extreme values with expected values (171). This method also allows for weight modification without trimming the dataset. Two extreme VAS response values below the lower threshold of 5th percentile were replaced with the value of the lower threshold, and Figure 7 shows boxplots after replacing the extreme values.

3.7.6.5. Analysis of the Association between Long COVID and HRQOL Outcomes

The binary logistic model was applied to investigate the relationship between the EQ-5D-5L health dimensions and Long COVID.

Dependent variable (Outcome): The dichotomized Long COVID variable, coded as “No” and “Yes,” was used as the dependent variable in the regression model.

Independent variables (Predictors): The responses for EQ-5D-5L dimensions-mobility, self-care, usual activities, pain/discomfort, anxiety/depression- coded as no issues and any issues. Additional covariates included were sex (female-reference), age (6 categories of 10-year intervals, with age 18-29 years-reference), and comorbidities (none/any, no comorbidities-reference).

Univariate logistic regression models were used to estimate unadjusted OR for the association between each EQ-5D-5L dimension and Long COVID, with respective 95% confidence intervals. Multivariate logistic regression analysis was used to estimate adjusted OR with respective 95% confidence intervals controlling for selected covariates. Table 23 shows the results of a test for multicollinearity of independent variables. The analysis of VIF showed the moderate collinearity of predictors ($1 < \text{VIF} < 5$), which was acceptable for including in a final regression model.

Table 23 - Variance inflation factor (VIF) of predictors

Predictors	Tolerance	VIF
Mobility	0.617	1.619
Self-care	0.888	1.126
Usual activities	0.680	1.470
Pain/discomfort	0.742	1.348
Anxiety/depression	0.879	1.137

Source: author

Abbreviation: VIF- variance inflation factor

The univariate logistic regressions used to estimate unadjusted OR with respective 95% confidence intervals. Multivariate logistic regression analysis was used to estimate adjusted OR with respective 95% confidence intervals for all predictors. The results were considered statistically significant with the P value less than the prespecified alpha of 0.05 ($p < 0.05$).

The Hosmer-Lemeshow test, the Pearson chi-square, deviance, pseudo-R square values (Cox & Snell R square, Nagelkerke R square), and classification table in SPSS were examined to assess the model's goodness-of-fit (GOF). Table 24 shows the GOF parameters of a logistic regression model.

Table 24 - Goodness-of-fit (GOF) parameters of a multivariate logistic regression model

Model Summary			Hosmer and Lemeshow test	
-2 Log Likelihood	Cox & Snell R square	Nagelkerke R square	Chi-square	Sig.
193.187	0.318	0.448	9.939	0.269

Source: author

The explained variation in the dependent variable in this model ranges from 31.8% to 44.8%, based on the Cox and Snell R^2 and Nagelkerke R^2 statistics, respectively. The Hosmer-Lemeshow test failed to reject the null hypothesis, indicating that the observed and predicted values were not significantly different ($p = 0.269$; $p > 0.05$). This suggests that the model fits the data well. Table 25 shows the classification table of a final logistic regression model.

Table 25 - Classification table of a multivariate logistic regression model

Observed	Predicted		% correct
	No	Yes	
No	46	24	65.7
Yes	15	141	90.4
Overall percentage			82.7

Source: author

The model correctly classified 82.7% of the data, with 141 cases correctly predicted as 'yes' (true positives) and 46 cases correctly predicted as 'no' (true negatives).

4 RESULTS

This chapter provides the results of statistical analyses conducted to describe the prevalence of Long COVID clinical outcomes, associated risk factors, and the health-related quality of life of a study population comprising adults with Long COVID diagnosed with mild-to-moderate COVID-19 illness in Brazilian primary care. The results follow the objectives of the study outlined in Section 1.3 of this thesis.

4.1 Sociodemographic and Clinical Characteristics of the Study Population

Table 26 and Table 27 summarize the sociodemographic and clinical characteristics of the study population. In total, 226 adults with a history of mild-to-moderate SARS-CoV-2 infection responded to the questionnaire. The mean age of the study population was 49.5 years (SD=15.3), and 68.1% were female. Among participants, 73.0% were non-White with the highest proportion 52.7% of adults of mixed race. Of all participants, 71.7% had fewer than 12 years of schooling consisting of those who had not completed elementary school.

The proportion of adults with pre-existing chronic conditions was 36.7%. The most common comorbidities were arterial hypertension and diabetes (25.2% and 11.1%, respectively). The vast majority of the study population (98.7%) received at least one dose of the COVID-19 vaccine at primary care (Table 27).

Characteristics of adults with Long COVID.

Of all participants, 69.0% (156/226) met the definition of Long COVID and had at least one persistent symptom after COVID-19 illness (Table 26). Thirty-one percent (70/226) of the study population did not report persistent symptoms, and 7.1% were completely symptom-free 3 months after infection onset.

Of all adults with Long COVID, 73.1% were female, 68.6% were younger than 60 years, 73.1% were non-White, and 68.6% had fewer than 12 years of schooling (Table 26).

Table 26 - Sociodemographic characteristics of the study population

Variables	All		With		Without		p-value ^a
			Long COVID		Long COVID		
	N=226		N=156		N=70		
	n	%	n	%	n	%	
Total	226	100	156	69.0	70	31.0	-
Sex							
Male	72	31.9	42	26.9	30	42.9	0.017
Female	154	68.1	114	73.1	40	57.1	
Age (Years), Mean (SD)	49.5 (15.3)		51.0 (14.9)		46.0 (15.6)		0.021
< 60	159	70.4	107	68.6	52	74.3	0.386
≥ 60	67	29.6	49	31.4	18	25.7	
18-29	22	9.7	11	7.1	11	15.7	0.081
30-39	44	19.5	27	17.3	17	24.3	
40-49	50	22.1	40	25.6	10	14.3	
50-59	43	19.1	29	18.6	14	20.0	
60-69	40	17.7	27	17.3	13	18.6	
70+	27	11.9	22	14.1	5	7.1	
Race/Ethnicity							
White	61	27.0	42	26.9	19	27.1	0.973
Non- White	165	73.0	114	73.1	51	72.9	
African	44	19.5	31	19.9	13	18.6	0.803
Mixed race	119	52.7	81	51.9	38	54.3	
Indigenous	2	0.9	2	1.3	0	0	
Asian	0	0	0	0	0	0	
Education (years)							
< 12	162	71.7	107	68.6	55	78.6	0.113
≥ 12	61	27.0	47	30.1	14	20.0	
Missing value	3	1.3	2	1.3	1	1.4	
Education (categories)							
Elementary school							0.394
complete	15	6.6	9	5.8	6	8.6	
incomplete	46	20.4	33	21.2	13	18.6	
High school							0.827
complete	72	31.9	46	29.5	26	37.1	
incomplete	18	8.0	11	7.1	7	10.0	
Technical/professional							0.087
complete	10	4.4	0	0	2	2.9	
incomplete	1	0.4	8	5.1	1	1.4	
Higher education							0.606
complete	29	12.8	22	14.1	7	10.0	
incomplete	17	7.5	14	9.0	3	4.3	
Post-graduate course							0.423
complete	13	5.8	10	6.4	3	4.3	
incomplete	2	0.9	1	0.6	1	1.4	
Missing value	3	1.3	2	1.3	1	1.4	

Source: author

Abbreviations: Standard deviation (SD),

^a-statistical significance p<0.05

Compared with those without Long COVID, patients with Long COVID were older (mean age 51 vs. 46 years, $p=0.02$), were more likely to be female (73.1% vs. 57.1%, $p=0.017$), and did not differ significantly in other demographic characteristics (Table 26). The most frequent comorbidity in this group was arterial hypertension (27.6%), followed by diabetes mellitus (10.9%) and musculoskeletal disorders (5.8%) (Table 27).

Table 27 - Clinical characteristics of the study population

Variables	All		With Long COVID		Without Long COVID		p-value ^a
	N=226		N=156		N=70		
	n	%	n	%	n	%	
COVID-19 vaccination (doses)							
none	3	1.3	2	1.3	1	1.4	0.928
≥ 1	223	98.7	154	98.7	69	98.6	
Comorbidities							
none	143	63.3	94	60.3	49	70.0	0.483
any	83	36.7	62	39.7	21	30.0	
Arterial hypertension	57	25.2	43	27.6	14	20.0	0.226
Diabetes mellitus	25	11.1	17	10.9	8	11.4	0.906
Musculoskeletal diseases	11	4.9	9	5.8	2	2.9	0.347
Respiratory diseases	4	1.8	4	2.6	-	-	0.176
Cardiac diseases	3	1.3	1	0.6	2	2.9	0.177
Other ^b	18	8.0	16	10.3	2	2.9	0.026
Validated symptoms (N=18)							
none	16	7.1	0	0	16	22.9	<0.001
any	210	92.9	156	100	54	77.1	
<5	78	34.5	28	17.9	50	71.4	<0.001
≥5	148	65.5	128	82.1	20	28.6	
1 to 4	62	27.4	28	12.4	34	15.0	<0.001
5 to 9	69	30.5	57	25.2	12	5.3	
10 to 15	61	27.0	55	24.3	6	2.7	
>15	18	8.0	16	7.1	2	0.9	
<i>Neurological symptoms</i>							
none	28	12.4	2	1.3	26	37.1	<0.001
any	198	87.6	154	98.7	44	62.9	
<5	153	67.7	90	57.7	63	90.0	<0.001
≥5	73	32.3	66	42.3	7	10.0	
Self-reported symptoms (N=40)							
none	78	34.5	57	36.5	21	30.0	0.339
any	148	65.5	99	63.5	49	70.0	
<5	225	99.6	155	99.4	70	100	0.502
≥5	1	0.4	1	0.6	0	0	

Source: author

^a- statistical significance $p<0.05$,

^b - category ``Other Comorbidities`` includes anemia, asthma, allergy, chronic sinusitis, thyroid diseases, eye conditions.

Among adults with Long COVID, the proportion of those who reported five or more symptoms, was significantly greater compared to group of adults without Long COVID (82.1% vs. 28.6%, $p<0.001$). In this group, 24.3% had between 10 and 15 symptoms, and 7.1% (16/156) reported more than 15 symptoms (Table 27).

The analyses of the occurrence of neurological symptoms showed that 98.7% of adults with Long COVID had at least one neurological impairment (Table 27). This proportion was significantly greater than that observed in adults without persistent symptoms (98.7% vs. 62.9%, $p<0.001$). The comparison of the proportions of individuals who reported more than five neurological symptoms showed a significantly greater proportion among adults with Long COVID than among those without Long COVID (42.3% vs. 10.0%, $p<0.001$).

The participants were asked whether they had experienced any persistent symptoms after COVID-19 illness other than those included in a set of validated outcomes. Overall, forty self-reported symptoms were registered. There was no statistically significant difference in the proportion of self-reported symptoms between the two groups- individuals with Long COVID and those without Long COVID (Table 27).

Comorbidities and number of reported symptoms stratified by age

Table 28 summarizes the number and proportion of comorbidities and symptoms stratified by age. The proportions of comorbidities among adults with Long COVID increased gradually with age, with the highest proportion (68.2%) recorded in individuals aged 70 years and older. A comparison between the two groups—those with and without Long COVID—showed a higher proportion of adults reporting five or more symptoms in the Long COVID group, with statistically significant differences between the two groups in the 30–39, 40–49, 50–59, and 60–69-years.

Table 28 - Presence of comorbidities, and the number of symptoms stratified by age.

Variables	All N=226		With Long COVID N=156		Without Long COVID N=70		p-value ^a
	n	%	n	%	n	%	
18-29	22/226	9.7	11/22	50.0	11/22	50.0	
Comorbidities							
yes	2/22	9.1	1/11	9.1	1/11	9.1	1.0
no	20/22	90.9	10/11	90.9	10/11	90.9	
Symptoms^b							
<5	6/22	27.3	2/11	18.2	4/11	36.4	0.635
≥5	16/22	72.7	9/11	81.8	7/11	63.6	

Table 29 - Sex, presence of comorbidities, and the number of symptoms stratified by age (continuing).

Variables	All N=226		With Long COVID N=156		Without Long COVID N=70		p-value ^a
	n	%	n	%	n	%	
30-39	44/226	19.5	27/44	61.4	17/44	38.6	
Comorbidities							
yes	5/44	11.4	5/27	18.5	0/17	0.0	0.139
no	39/44	88.6	22/27	81.5	17/17	100.0	
Symptoms^b							
<5	22/44	50.0	7/27	25.9	15/17	88.2	<0.001
≥5	22/44	50.0	20/27	74.1	2/17	11.8	
40-49	50/226	22.1	40/50	80.0	10/50	20.0	
Comorbidities							
yes	18/50	36.0	14/40	35.0	4/10	40.0	1.0
no	32/50	64.0	26/40	65.0	6/10	60.0	
Symptoms^b							
<5	11/50	22.0	4/40	10.0	7/10	70.0	<0.001
≥5	39/50	78.0	36/40	90.0	3/10	30.0	
50-59	43/226	19.0	29/43	67.4	14/43	32.6	
Comorbidities							
yes	17/43	39.5	13/29	44.8	4/14	28.6	0.343
no	26/43	60.5	16/29	55.2	10/14	71.4	
Symptoms^b							
<5	17/43	39.5	5/29	17.2	12/14	85.7	<0.001
≥5	26/43	21.8	24/29	82.8	2/14	14.3	
60-69	40/226	17.7	27/40	67.5	13/40	32.5	
Comorbidities							
yes	21/40	52.5	14/27	51.9	7/13	53.8	1.0
no	19/40	47.5	13/27	48.1	6/13	46.2	
Symptoms^b							
<5	11/40	27.5	3/40	11.1	8/13	61.5	0.002
≥5	29/40	72.5	24/27	88.9	5/13	38.5	
70+	27/226	11.9	22/27	81.5	5/27	18.5	
Comorbidities							
yes	20/27	74.1	15/22	68.2	5/5	100.0	0.283
no	7/27	25.9	7/22	31.8	0/5	0.0	
Symptoms^b							
<5	11/27	40.7	7/22	31.8	4/5	80.0	0.125
≥5	16/27	59.3	15/22	68.2	1/5	20.0	

Source: author

Abbreviations: LC- Long COVID,

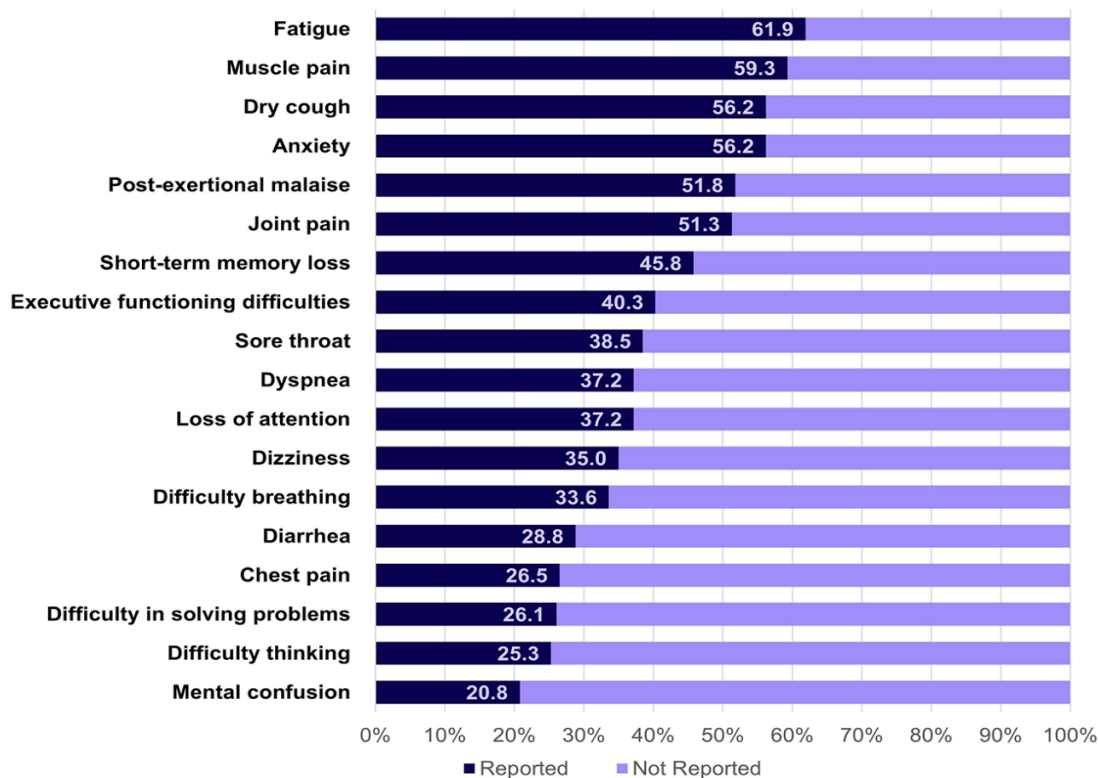
^a-two-tailed Fisher's exact test; statistical significance p<0.05, ^b- validated symptoms.

4.2. Prevalence of Long COVID Outcomes

Validated symptoms.

Figure 8 shows the occurrence of symptoms 3 months or more after COVID-19 illness reported by study participants. Of 18 validated symptoms, the most frequently reported by all respondents were fatigue (61.9%), muscle pain (59.3%), dry cough (56.2%), anxiety (56.2%), post-exertional malaise (51.8%), and joint pain (51.3%) (Figure 8). They were followed by short-term memory loss (45.8%), executive functioning difficulties (40.3%), sore throat (38.5%), dyspnea (37.2%), loss of attention (37.2%), dizziness (35.0%), difficulty breathing (33.6%), diarrhea (28.8%), chest pain (26.5%), difficulty thinking (25.3%), and mental confusion (20.8%).

Figure 8- The frequency of validated symptoms



Source: Author

Table 29 summarizes the frequency of symptoms reported by individuals with Long COVID versus those without prolonged condition. Sixteen symptoms out of all validated clinical

outcomes had significantly higher occurrence in adults with Long COVID than in those without Long COVID (Table 29). The greatest differences between these two groups were found for short-term memory loss (62.6% vs 8.6%, $p<0.0001$), loss of attention (50.0% vs. 8.6%, $p<0.0001$), anxiety (71.8% vs. 21.4%, $p<0.0001$), joint pain (65.4% vs. 20.0%, $p<0.0001$), difficulty thinking (33.5% vs. 7.1%, $p<0.0001$), dizziness (45.5% vs. 11.4%, $p<0.0001$), difficulty breathing (42.3% vs 14.3%, $p<0.0001$), and post-exertional malaise (62.8% vs. 27.1%, $p<0.0001$).

Table 30 - Frequency of symptoms in adults with Long COVID vs. without Long COVID

Symptoms ^b	With LC N=156			Without LC N=70			p-value
	n	%	95%CI	n	%	95%CI	
Fatigue	112	0.718	0.640–0.787	28	0.4	0.285–0.524	<0.0001
Anxiety	112	0.718	0.640–0.787	15	0.214	0.125–0.329	<0.0001
Muscle pain	105	0.673	0.593–0.746	29	0.414	0.298–0.538	0.00026
Joint pain	102	0.654	0.574–0.728	14	0.2	0.114–0.313	<0.0001
Dry cough	101	0.647	0.567–0.722	26	0.371	0.259–0.495	<0.0001
Post-exertional malaise	98	0.628	0.547–0.704	19	0.271	0.172–0.391	<0.0001
Short-term memory loss ^a	97	0.626	0.545–0.702	6	0.086	0.032–0.177	<0.0001
Loss of attention	78	0.5	0.419–0.581	6	0.086	0.032–0.177	<0.0001
Executive functioning difficulties	76	0.487	0.406–0.568	15	0.214	0.125–0.329	<0.0001
Dizziness	71	0.455	0.375–0.537	8	0.114	0.051–0.213	<0.0001
Dyspnea	70	0.449	0.369–0.530	14	0.2	0.114–0.313	0.00034
Difficulty breathing	66	0.423	0.344–0.505	10	0.143	0.071–0.247	<0.0001
Sore throat	65	0.417	0.338–0.498	22	0.314	0.209–0.436	0.144
Difficulty thinking ^a	52	0.335	0.262–0.416	5	0.071	0.024–0.159	<0.0001
Diarrhea	51	0.327	0.254–0.407	14	0.2	0.114–0.313	0.051
Difficulty in solving problems	50	0.321	0.248–0.400	9	0.129	0.061–0.230	<0.0001
Chest pain	49	0.314	0.242–0.393	11	0.157	0.081–0.264	0.014
Mental confusion	43	0.276	0.207–0.353	4	0.057	0.016–0.140	<0.0001

Source: author

Abbreviations: LC- Long COVID, Confidence interval (CI),

^a- one missing value,

^b- validated symptoms.

Table 30 shows the results of analysis of symptoms' frequency stratified by age. Fatigue was frequently reported by adults of all ages, with the highest proportion (60.0%) among those aged 40-49 years.

Table 31 - Frequency of symptoms stratified by age

Symptoms	18-29 (n=22)		30-39 (n=44)		40-49 (n=50)		50-59 (n=43)		60-69 (n=40)		70+ (n=27)	
	LC	No LC	LC	No LC	LC	No LC	LC	No LC	LC	No LC	LC	No LC
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
FA	9 (40.9)	6 (27.3)	19 (43.2)	6 (13.6)	30 (60.0)	3 (6.0)	22 (51.2)	4 (9.3)	18 (45.0)	8 (20.0)	14 (51.9)	1 (3.7)
PEM	6 (27.3)	5 (22.7)	11 (25.0)	3 (6.8)	30 (60.0)	2 (4.0)	21 (48.8)	2 (4.7)	15 (37.5)	5 (12.5)	15 (55.6)	2 (7.4)
ST	1 (4.5)	7 (31.8)	9 (20.5)	2 (4.5)	22 (44.0)	3 (6.0)	14 (32.6)	4 (9.3)	12 (30.0)	5 (12.5)	7 (25.9)	1 (3.7)
MP	7 (31.8)	7 (31.8)	13 (29.5)	7 (15.9)	29 (58.0)	3 (6.0)	22 (51.2)	5 (11.6)	21 (52.5)	6 (15.0)	13 (48.1)	1 (3.7)
DP	6 (27.3)	5 (22.7)	13 (29.5)	2 (4.5)	20 (40.0)	1 (2.0)	8 (18.6)	1 (2.3)	15 (37.5)	5 (12.5)	8 (29.6)	0 (0.0)
CP	6 (27.3)	4 (18.2)	11 (25.0)	2 (4.5)	12 (24.0)	0 (0.0)	10 (23.3)	2 (4.7)	4 (10.0)	2 (5.0)	6 (22.2)	1 (3.7)
JP	5 (22.7)	4 (18.2)	16 (36.4)	2 (4.5)	23 (46.0)	1 (2.0)	25 (58.1)	2 (4.7)	18 (45.0)	3 (7.5)	15 (55.6)	2 (7.4)
DC	4 (18.2)	4 (18.2)	17 (38.6)	8 (18.2)	27 (54.0)	4 (8.0)	16 (37.2)	3 (7.0)	21 (52.5)	5 (12.5)	16 (59.3)	2 (7.4)
DB	7 (31.8)	4 (18.2)	11 (25.0)	1 (2.3)	19 (38.0)	1 (2.0)	9 (20.9)	0 (0.0)	11 (27.5)	4 (10.0)	9 (33.3)	0 (0.0)
DR	2 (9.1)	3 (13.6)	7 (15.9)	4 (9.1)	13 (26.0)	1 (2.0)	7 (16.3)	2 (4.7)	14 (35.0)	4 (10.0)	8 (29.6)	0 (0.0)
ANX	8 (36.4)	3 (13.6)	17 (38.6)	2 (4.5)	28 (56.0)	3 (6.0)	24 (55.8)	2 (4.7)	21 (52.5)	5 (12.5)	14 (51.9)	0 (0.0)
DIZ	4 (18.2)	1 (4.5)	8 (18.2)	1 (2.3)	19 (38.0)	3 (6.0)	13 (30.2)	1 (2.3)	15 (37.5)	2 (5.0)	12 (44.4)	0 (0.0)
STML ^a	6 (27.3)	2 (9.1)	17 (38.6)	0 (0.0)	27 (54.0)	0 (0.0)	21 (48.8)	1 (2.3)	15 (37.5)	3 (7.5)	11 (40.7)	0 (0.0)
MC	4 (18.2)	1 (4.5)	7 (15.9)	1 (2.3)	10 (20.0)	0 (0.0)	8 (18.6)	0 (0.0)	9 (22.5)	2 (5.0)	5 (18.5)	0 (0.0)
LA	6 (27.3)	1 (4.5)	14 (31.8)	1 (2.3)	22 (44.0)	0 (0.0)	15 (34.9)	1 (2.3)	13 (32.5)	3 (7.5)	8 (29.6)	0 (0.0)
DT ^a	6 (27.3)	0 (0.0)	11 (25.0)	0 (0.0)	15 (30.0)	1 (2.0)	10 (23.3)	2 (4.7)	5 (12.5)	2 (5.0)	5 (18.5)	0 (0.0)
EFD	4 (18.2)	3 (13.6)	12 (27.3)	1 (2.3)	18 (36.0)	2 (4.0)	17 (39.5)	4 (9.3)	5 (12.5)	2 (5.0)	8 (29.6)	1 (3.7)
DSP	3 (13.6)	1 (4.5)	7 (15.9)	1 (2.3)	15 (30.0)	3 (6.0)	8 (18.6)	1 (2.3)	12 (30.0)	3 (7.5)	5 (18.5)	0 (0.0)

Source: author

Abbreviations: LC - Long COVID, FA - fatigue, PEM - post-exertional malaise, ST - sore throat, MP - muscle pain, DP - dyspnea, CP - chest pain, JP - joint pain, DC - dry cough, DB - difficulty breathing, DR - diarrhea, ANX - anxiety, DIZ - dizziness, STML - short-term memory loss, MC - mental confusion, LA - loss of attention, DT - difficulty thinking, EFD - executive functioning difficulties, DSP - difficulty in solving problems,

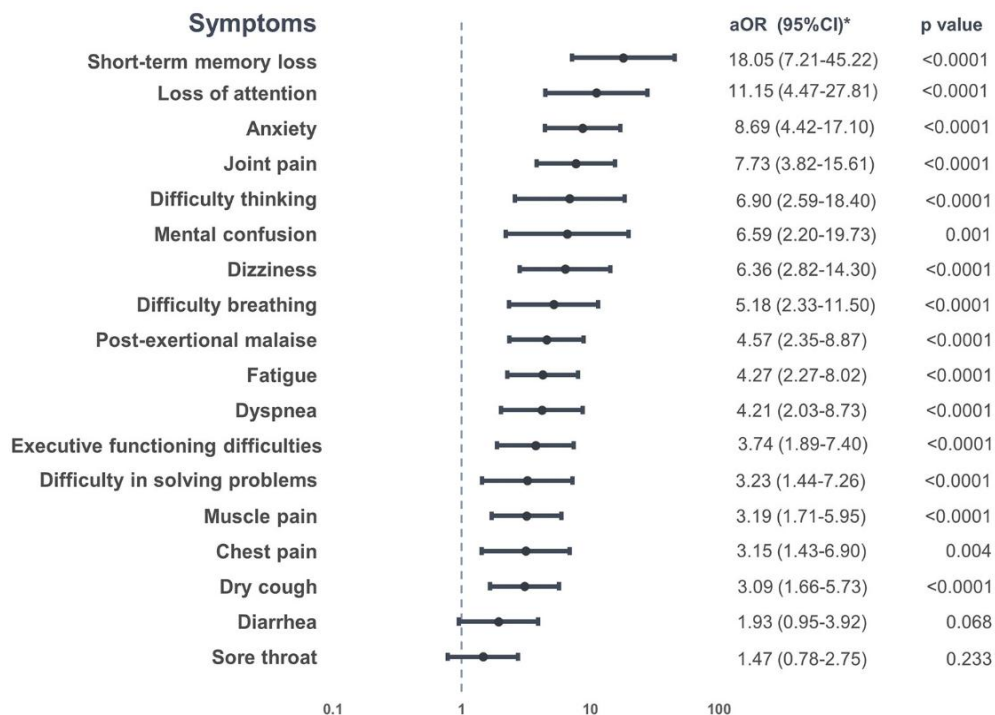
^a - one missing value.

The most frequently reported symptoms by age groups were: fatigue (40.9%) and anxiety (36.4%) by adults aged 18-29 years; fatigue (43.2%), anxiety (38.6%), short-term memory loss (38.6%) and dry cough (38.6%) by adults aged 30-39 years; fatigue (60%), post-exertional malaise (60%) and muscle pain (58%) by adults aged 40-49 years; joint pain (58.1%) and anxiety (55.8%) by adults aged 50-59 years; muscle pain (52.5%), dry cough (52.5%) and anxiety (52.5%) by adults aged 60-69 years; dry cough (59.3%), post-exertional malaise (55.6%), joint pain (55.6%) and anxiety (51.9%) by adults aged 70+ years (Table 30).

Adjusted odds ratios for persistent validated symptoms

Table 31 shows unadjusted odds ratios (OR) after application of a bivariate logistic regression for each validated symptom. In a multivariate logistic regression model adjusted for covariates-sex, age and comorbidities, the largest adjusted odds ratio (aOR) were estimated for short-term memory loss (aOR: 18.05, 95%CI: 7.20 – 45.22), loss of attention (aOR: 11.15, 95%CI: 4.47–27.81), anxiety (aOR: 8.69, 95%CI: 4.42–17.10), and joint pain (aOR: 7.73, 95%CI: 3.82–15.61) (Figure 9).

Figure 8 - Adjusted odds ratios (aOR) for validated symptoms



Source: author

Abbreviations: CI - confidence interval, aOR - adjusted odds ratios, adjusted for sex, age and comorbidities, statistical significance $p < 0.05$

Table 32 - Unadjusted odds ratios (OR) for validated symptoms

Symptoms	With Long COVID N=156	Without Long COVID N=70	Unadjusted OR		
	n (%)	n (%)	OR	95%CI	p-value
Short-term memory loss ^a	50 (32.1)	9 (12.9)	17.84	7.26–43.78	<0.0001
Loss of attention	78 (50.0)	6 (8.6)	10.67	4.36–26.07	<0.0001
Anxiety	112 (71.8)	15 (21.4)	9.33	4.78–18.22	<0.0001
Joint pain	102 (65.4)	14 (20.0)	7.56	3.86–14.79	<0.0001
Difficulty thinking ^a	52 (33.5)	5 (7.1)	6.56	2.49–17.29	<0.0001
Mental confusion	43 (27.6)	4 (5.7)	6.28	2.16–18.28	<0.0001
Dizziness	71 (45.5)	8 (11.4)	6.47	2.91–14.42	<0.0001
Difficulty breathing	66 (42.3)	10 (14.3)	4.4	2.09–9.23	<0.0001
Dyspnea	70 (44.9)	14 (20.0)	3.26	1.67–6.33	<0.0001
Post-exertional malaise	98 (62.8)	19 (27.1)	4.54	2.44–8.42	<0.0001
Fatigue	112 (71.8)	28 (40.0)	3.82	2.11–6.90	<0.0001
Difficulty in solving problems	50 (32.1)	9 (12.9)	3.2	1.47–6.95	0.002
Chest pain	49 (31.4)	11 (15.7)	2.46	1.19–5.08	0.013
Executive functioning difficulties	76 (48.7)	15 (21.4)	3.48	1.81–6.68	<0.0001
Muscle pain	105 (67.3)	29 (41.4)	2.91	1.63–5.21	<0.0001
Dry cough	101 (64.7)	26 (37.1)	3.11	1.73–5.58	<0.0001
Diarrhea	51 (32.7)	14 (20.0)	1.94	0.99–3.81	0.051
Sore throat	65 (41.7)	22 (31.4)	1.56	0.86–2.83	0.144

Source: author

Abbreviations: OR - odds ratios; CI - Confidence Interval, ^a one missing value.

They were followed by difficulty thinking (aOR: 6.90, 95%CI: 2.59–18.40), dizziness (aOR: 6.36, 95%CI: 2.82–14.34), difficulty breathing (aOR: 5.18, 95%CI: 2.33–11.54), post-exertional malaise (aOR: 4.57, 95%CI: 2.35–8.87), fatigue (aOR: 4.27, 95%CI: 2.27–8.02), difficulty in solving problems (aOR: 3.23, 95%CI: 1.44–7.26), chest pain (aOR: 3.15, 95%CI: 1.43–6.90), executive functioning difficulties (aOR: 3.74, 95%CI: 1.89–7.40), muscle pain (aOR: 3.19, 95%CI: 1.71–5.95) and dry cough (aOR: 3.09, 95%CI: 1.66–5.73). Two clinical outcomes didn't showed statistically significant association with Long COVID: diarrhea (aOR: 1.93, 95%CI: 0.95–3.92) and sore throat (aOR: 1.47, 95%CI: 0.78–2.75) (Figure 9).

Self-reported symptoms.

Table 32 presents the results of the bivariate logistic regression, which estimated the unadjusted odds ratios (ORs) for the four self-reported symptoms. The most commonly self-reported symptom experienced by respondents with Long COVID after the acute phase of infection was olfactory or

taste disorders (41.0%), followed by dysphagia (16.0%), hair loss (14.7%), and headache (10.3%). In the multivariate logistic regression analysis—adjusted for sex, age, and comorbidities—none of the symptoms included in the final model showed a significant association with Long COVID. The adjusted odds ratios (aORs) were as follows: headache (aOR: 1.58; 95% CI: 0.52–4.82), olfactory and taste disorders (aOR: 0.99; 95% CI: 0.54–1.81), dysphagia (aOR: 0.85; 95% CI: 0.39–1.87), and hair loss (aOR: 0.56; 95% CI: 0.27–1.16) (Figure 10).

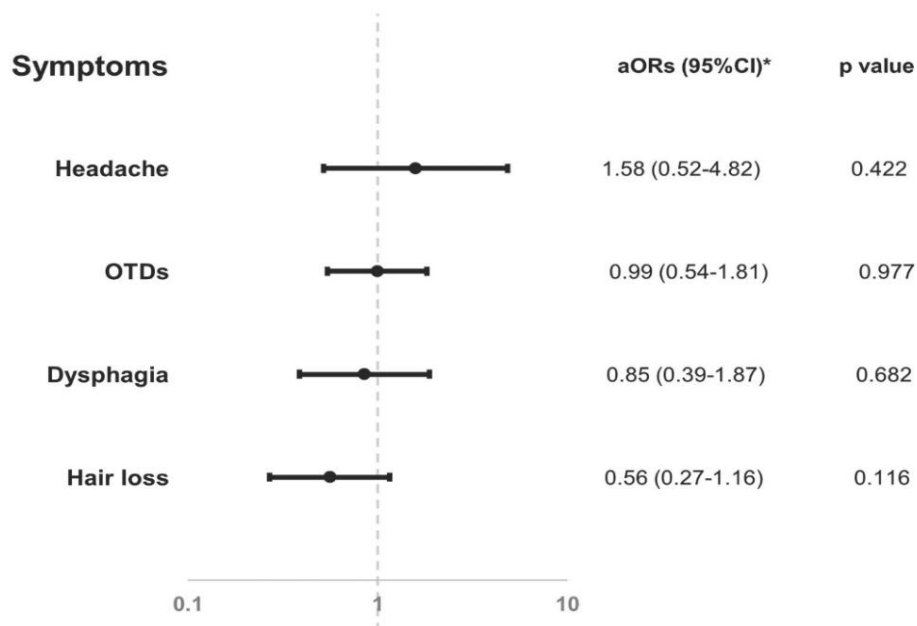
Table 33 - Unadjusted odds ratios (OR) for self-reported symptoms

Symptoms	With Long COVID N=156	Without Long COVID N=70	Unadjusted OR		
	n(%)	n(%)	OR	95%CI	p-value
Headache	16 (10.3)	5 (7.1)	1.49	0.52–4.23	0.458
Olfactory and taste disorder	64 (41.0)	29 (41.4)	0.98	0.56–1.74	0.955
Dysphagia ^a	25 (16.0)	13 (18.6)	0.83	0.39–1.74	0.701
Hair loss	23 (14.7)	17 (24.3)	0.54	0.27–1.09	0.085

Source: author

Abbreviations: OR - odds ratios; CI - Confidence Interval , ^a two missing values

Figure 9 - Adjusted odds ratios (aOR) for self-reported symptoms



Source: author

Abbreviations: CI - confidence interval, OTDs - olfactory and taste disorders, aOR - adjusted odds ratios, adjusted for sex, age and comorbidities, statistical significance $p < 0.05$

4.3 Risk Factors associated with Long COVID

Table 33 summarizes the results of the risk factor analysis, which included several sociodemographic and clinical predictors. In a multivariate logistic regression analysis, a significant association was found between Long COVID and the following predictors: female sex, age 40–49 years, age 70+ years, and the presence of five and more symptoms. Other potential risk factors like ethnicity, education, comorbidities, age 18–29 years, age 50–59 years, and age 60–69 years did not show a statistically significant association with Long COVID.

Compared with men, women were at increased risk of Long COVID (aOR: 1.91, 95% CI: 1.03–3.53, $p=0.032$) (Table 33). Both the 40–49-year-old and 70+-year-old age groups were associated with a higher risk of reporting persistent symptoms in the bivariate analysis. After adjustment for covariates, individuals aged 40–49 years had an approximately 3.5-fold increased risk (aOR: 3.45, 95% CI: 1.14–10.51, $p = 0.029$), and those aged 70+ years had a 4-fold increased risk (aOR: 4.0, 95% CI: 1.03–15.50, $p = 0.045$) compared with adults aged 18–29 years. There was a statistically significant association between Long COVID and the number of validated symptoms. Individuals with SARS-CoV-2 infection who initially reported ≥ 5 symptoms had a 15.8-fold increased risk (aOR: 15.82, 95%CI: 7.33–34.15, $p<0.0001$) of Long COVID, compared with those who reported fewer than 5 symptoms.

4.4 HRQOL among Adults with Long COVID

4.4.1 Results of a Descriptive Analysis of EQ-5D-5L Responses

Table 34 presents the results of the analysis of responses to EQ-5D-5L descriptive system. The proportions of health issues had statistically significant differences between two groups in four of five EQ-5D-5L dimensions- mobility, usual activities, pain/discomfort, and anxiety/depression.

Table 34 - Risk factors associated with Long COVID

Variables	With Long COVID N=156	Without Long COVID N=70	Unadjusted OR		Adjusted OR	
	n (%)	n (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Symptoms						
< 5	28 (17.9)	50 (71.4)	Reference		Reference	
≥ 5	128 (82.1)	20 (28.6)	11.43 (5.90 – 22.12)	<0.0001	15.82 (7.33 – 34.15)	<0.0001
Sex						
Male	42 (26.9)	30 (42.9)	Reference		Reference	
Female	114 (73.1)	40 (57.1)	2.04 (1.13 – 3.68)	0.018	1.91 (1.03 – 3.53)	0.032
Age (years)						
18-29	11 (7.1)	11 (15.7)	Reference		Reference	
30-39	27 (17.3)	17 (24.3)	1.59 (0.57 – 4.46)	0.380	1.56 (0.55 – 4.43)	0.408
40-49	40 (25.6)	10 (14.3)	4.0 (1.35 – 11.84)	0.012	3.45 (1.14 – 10.51)	0.029
50-59	29 (18.6)	14 (20.0)	2.07 (0.72 – 5.93)	0.175	1.75 (0.59 – 5.19)	0.312
60-69	27 (17.3)	13 (18.6)	2.01 (0.72 – 6.03)	0.179	1.81 (0.59 – 5.53)	0.298
70+	22 (14.1)	5 (7.1)	4.4 (1.22 – 15.84)	0.023	4.0 (1.01 – 15.51)	0.045
Ethnicity						
White	42 (26.9)	19 (27.1)	Reference		Reference	
Non-White	114 (73.1)	51 (72.9)	1.01 (0.54 – 1.91)	0.973	1.07 (0.55 – 2.08)	0.843
Education^a (years)						
< 12 ^c	107 (68.6)	55 (78.6)	Reference		Reference	
≥ 12	47 (30.1)	14 (20.0)	1.73 (0.88 – 3.41)	0.116	2.04 (0.99 – 4.21)	0.053
Comorbidities						
none	94 (60.3)	49 (70.0)	Reference		Reference	
any	62 (39.7)	21 (30.0)	1.54 (0.84 – 2.81)	0.161	1.13 (0.57 – 2.23)	0.723
AH	43 (27.6)	14 (20.0)	1.52 (0.77 – 3.01)	0.228	1.21 (0.38 – 3.88)	0.738
Diabetes	17 (10.9)	8 (11.4)	0.95 (0.39 – 2.31)	0.906	0.56 (0.19 – 1.68)	0.303

Source: author

Abbreviations: OR – odds ratio, aOR – adjusted odds ratio, CI – confidence interval, AH - arterial hypertension,

^a- two missing values.

The responses to self-care dimension did not show any statistically significant difference between two groups (Table 34).

Among individuals with Long COVID, the most common observed health issues were slight or moderate (Table 34). The highest proportion of respondents who reported slight problems was for pain/discomfort (27.6%), followed by anxiety/depression (26.9%), mobility (24.4%), and usual activities (17.3%). The common moderate issues followed the same pattern as for slight issues: pain/discomfort (32.1%), anxiety/depression (25.0%), mobility (15.4%), and usual activities (14.7%). The highest proportion of responses with severe problems was observed for anxiety/depression (12.2%), followed by usual activity (5.8%), and mobility (3.8%). Extreme health issues were identified for two EQ-5D-5L dimensions: anxiety/depression (2.6%) and pain/discomfort (1.9%).

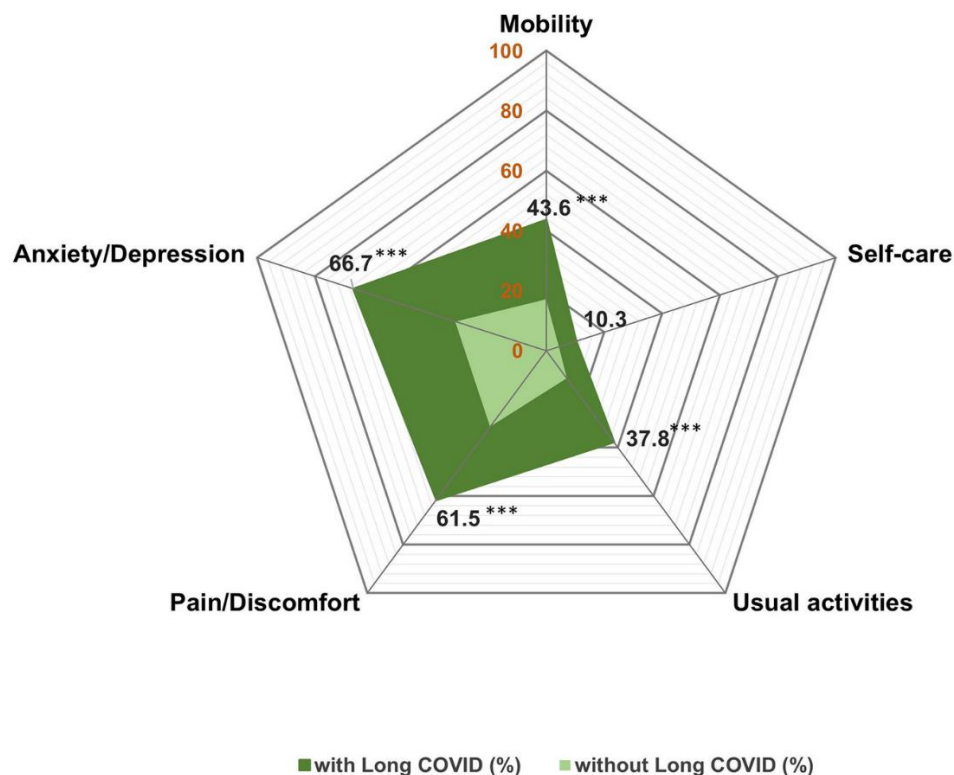
Table 35 - Proportions (%) of respondents to EQ-5D-5L descriptive system

Dimensions		All N=226		With Long COVID N=156		Without Long COVID N=70		p-value
		n	%	n	%	n	%	
Mobility	none	146	64.6	88	56.4	58	82.9	<0.001
	slight	48	21.2	38	24.4	10	14.3	
	moderate	25	11.1	24	15.4	1	1.4	
	severe	7	3.1	6	3.8	1	1.4	
	extreme	0	0	0	0	0	0	
Self-care	none	207	91.6	140	89.7	67	95.7	0.238
	slight	10	4.4	7	4.5	3	4.3	
	moderate	8	3.5	8	5.1	0	0	
	severe	1	0.4	1	0.6	0	0	
	unable	0	0	0	0	0	0	
Usual activities	none	159	70.4	97	62.2	62	88.6	<0.001
	slight	34	15.0	27	17.3	7	10.0	
	moderate	23	10.2	23	14.7	0	0	
	severe	10	4.4	9	5.8	1	1.4	
	unable	0	0	0	0	0	0	
Pain/discomfort	none	108	47.8	60	38.5	48	68.6	<0.001
	slight	58	25.7	43	27.6	15	21.4	
	moderate	57	25.2	50	32.1	7	10.0	
	severe	0	0	0	0	0	0	
	extreme	3	1.3	3	1.9	0	0	
Anxiety/depression	none	100	44.2	52	33.3	48	68.6	<0.001
	slight	56	24.8	42	26.9	14	20.0	
	moderate	47	20.8	39	25.0	8	11.4	
	severe	19	8.4	19	12.2	0	0	
	extreme	4	1.8	4	2.6	0	0	

Source: author

Figure 11 shows the comparison of the proportions of respondents reporting any health issues of EQ-5D-5L descriptive system between individuals with Long COVID and those without persistent illness. There was a significantly higher proportion of respondents with health issues among individuals with Long COVID compared to those without Long COVID in four of the five dimensions. The highest difference was observed for anxiety/depression (66.7% vs. 31.4%, $p<0.001$), followed by pain/discomfort (61.5% vs. 31.4%, $p<0.001$), mobility (43.6% vs. 17.1%, $p<0.001$), and usual activities (37.8% vs. 11.4%, $p<0.001$). There was not a statistically significant difference between two groups for self-care (10.3% vs. 4.3%, $p=0.135$).

Figure 10 - Proportions (%) of respondents reporting any health issues, plotted separately for individuals with Long COVID versus without Long COVID.



Source: author

Abbreviations: MO -mobility, SC -self-care, UA -usual activities, PD - pain/discomfort, AD - anxiety/depression, ***- p-value <0.001

Table 35 shows the most observed self-reported health states on EQ-5D-5L descriptive system, together with the prevalence of the worst health state. Out of all 3,125 possible health states on EQ-5D-5L descriptive system, 85 variations of health states were detected for our study

population. The cumulative frequency of the top thirteen most frequently observed health states was approximately 60 %, the remaining 40% of observations were distributed over 72 health states.

The most frequently observed self-reported health state was the best possible health state, 11111- no health problems in five dimensions, accounting for 23.9 % of observations (Table 35). It was followed by health states representing mild/moderate levels of anxiety/depression, e.g. 11112 and 11113 health states (8.4% and 4.0%, respectively). None of the respondents reported the worst possible health state on EQ-5D-5L descriptive system referent to extreme health issues 55555 on all five health dimensions.

Table 36 - Frequency of the 13 most reported health states and the frequency of the worst health state observed in a study population.

EQ-5D-5L health states	Frequency (%)	Cumulative frequency (%)
11111	54 (23.9)	23.9
11112	19 (8.4)	32.3
11113	9 (4.0)	36.3
11121	8 (3.5)	39.8
11131	8 (3.5)	43.3
11122	7 (3.1)	46.4
21121	7 (3.1)	49.5
11123	6 (2.7)	52.2
21122	6 (2.7)	54.9
11212	4 (1.8)	56.7
21213	3 (1.3)	58.0
21233	3 (1.3)	59.3
31333	3 (1.3)	60.3
...		
55555	0 (0.0)	100

Source: author

4.4.2 Comparison of EQ-5D-5L Index Values

Table 36 summarizes EQ-5D-5L index values for respondents with and without Long COVID, referenced to their sociodemographic and clinical characteristics. As described previously, all observed EQ-5D-5L health states coded as a 5-digit numbers were transformed into index values.

Within a group of individuals with Long COVID, poorer health index values were observed for women compared to men (0.747 vs. 0.902, $p < 0.001$), adults aged ≥ 60 years compared to those aged < 60 years (0.738 vs. 0.943, $p < 0.001$), adults with comorbidities compared to those without coexisting conditions (0.730 vs. 0.817, $p = 0.019$), and individuals with ≥ 5 COVID-19-related symptoms compared to those with < 5 symptoms (0.749 vs. 0.942, $p < 0.001$). HRQOL decreased with age, with the lowest estimated median index value observed among adults aged 50–59 years (0.695, IQR = 0.554 – 0.875). Adults with Long COVID had significantly lower median index values than individuals without Long COVID (0.784 vs. 1.0, $p < 0.001$), regardless of sex, age, ethnicity, education, or comorbidities.

Both males and females in this group had significantly lower median index values compared to individuals without Long COVID (males: 0.902 vs 1.0, $p=0.027$; females: 0.747 vs. 0.972, $p<0.001$). Index values were also significantly lower in adults with Long COVID across all age groups compared to those without Long COVID. Older adults aged ≥ 60 years had significantly lower median index values compared to adults in the same age group without Long COVID (0.738 vs. 0.943, $p < 0.001$) (Table 36).

Symptomatic adults with persistent symptoms had a lower estimated median index value compared to those without Long COVID (0.784 vs. 0.943, $p < 0.001$). The lowest median index value was estimated for adults with ≥ 15 symptoms (0.749 vs. 0.880, $p = 0.012$). Non-White adults with Long COVID had lower median value index value than Non-White adults without Long COVID (0.780 vs. 1.0, $p < 0.001$) (Table 36).

Table 37 - EQ-5D-5L median index values comparing adults with versus without Long COVID

Variables	All N=226			With Long COVID N=156			Without Long COVID N=70			
	median	IQR	p ^a	median	IQR	p ^a	median	IQR	p ^a	p ^b
COVID-19	0.874	0.700-1.000	-	0.784	0.633-0.902	-	1.000	0.877-1.000	-	<0.001
Sex										
Male	0.942	0.782-1.000	<0.001	0.902	0.734-0.957	<0.001	1.000	0.876-1.000	0.985	0.027
Female	0.817	0.673-0.943		0.747	0.604-0.877		0.972	0.879-1.000		<0.001
Symptoms										
none	1.000	1.000-1.000	<0.001	0	0	NA	1.000	1.000-1.000	0.013	NA
any	0.844	0.690-0.943		0.784	0.633-0.902		0.943	0.865-1.000		<0.001
< 5	1.000	0.882-1.000	<0.001	0.942	0.838-1.000	<0.001	1.000	0.942-1.000	<0.001	0.023
≥ 5	0.773	0.615-0.902		0.749	0.603-0.882		0.880	0.721-0.986		0.012
Age (years)										
< 60	0.877	0.705-1.000	0.089	0.817	0.641-0.940	0.185	1.000	0.887-1.000	0.427	<0.001
≥ 60	0.787	0.641-0.943		0.738	0.610-0.862		0.943	0.830-1.000		<0.001
18-29	0.940	0.877-1.000	0.008	0.877	0.776-0.943	0.033	1.000	0.940-1.000	0.528	0.007
30-39	0.902	0.794-1.000		0.875	0.701-0.940		1.000	0.921-1.000		0.002
40-49	0.861	0.652-0.957		0.831	0.629-0.943		1.000	0.812-1.000		0.039
50-59	0.809	0.603-0.902		0.695	0.554-0.875		0.972	0.804-1.000		0.001
60-69	0.780	0.656-0.942		0.738	0.602-0.847		0.943	0.816-1.000		0.001
70+	0.844	0.640-1.000		0.731	0.624-0.950		0.953	0.894-1.000		0.028
Race										
White	0.876	0.667-0.972	0.780	0.844	0.619-0.943	0.627	0.944	0.844-1.000	0.662	0.002
Non-White	0.845	0.701-1.000		0.780	0.641-0.902		1.000	0.883-1.000		<0.001
Education* (years)										
< 12	0.861	0.700-1.000	0.617	0.770	0.630-0.902	0.452	1.000	0.883-1.000	0.325	<0.001
≥ 12	0.875	0.703-0.943		0.844	0.648-0.940		0.943	0.865-1.000		0.009
Comorbidities										
none	0.883	0.717-1.000	<0.002	0.817	0.695-0.941	0.019	1.000	0.921-1.000	0.156	<0.001
any	0.780	0.604-0.940		0.730	0.585-0.879		0.943	0.802-1.000		<0.001

Source: author

Abbreviations: IQR-interquartile range; NA- not applicable,

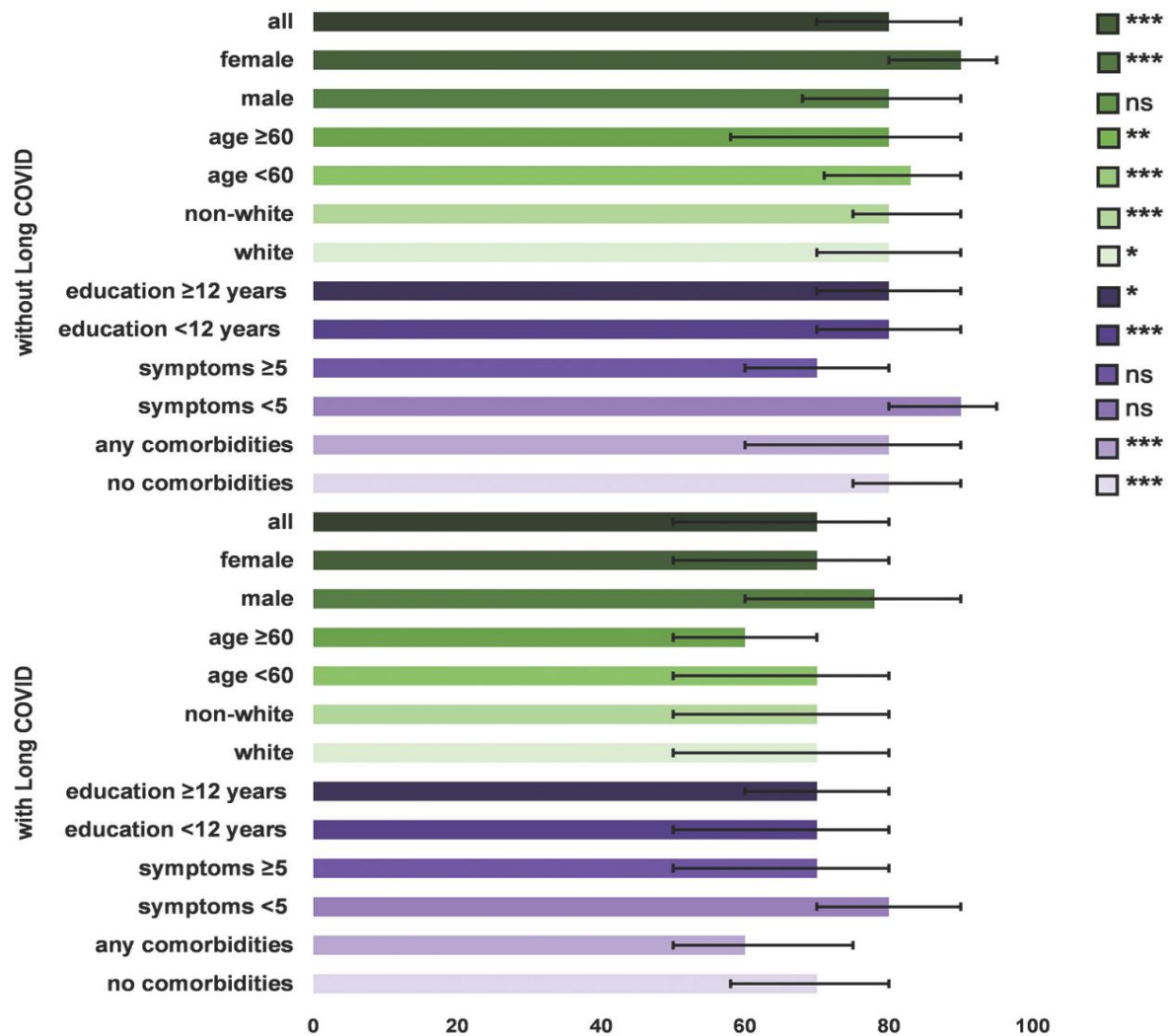
^a- statistical differences withing the groups,^b- statistical differences between groups (Long COVID vs without Long COVID),

*- three missing values.

4.4.3 Comparison of VAS Scores

Figure 12 presents result of a visual analogue scale (VAS) median scores comparison between two groups- individuals with Long COVID and those without persistent post-COVID illness.

Figure 11 - VAS median scores comparing adults with versus without Long COVID



Source: author

Abbreviations: VAS median score with respective interquartile range (IQR); ns-not statistically significant ($p>0.05$),

*- $p<0.05$, **- $p<0.01$, ***- $p<0.001$

Individuals with Long COVID had significantly lower median scores compared to those without Long COVID (70 vs. 80, $p<0.001$). The comparison of EQ-VAS scores between those two groups showed similar trend as with EQ-5D-5L index values, except for males and number of symptoms. The most significant differences between two groups with estimated lower VAS median scores in individuals with Long COVID compared to those without Long COVID were observed for: females (70 vs. 90, $p<0.001$), age <60 years (70 vs. 80, $p<0.001$), non-White individuals (70 vs. 80, $p<0.001$), individuals with <12 years of schooling (70 vs. 80, $p<0.001$), and individuals with comorbidities (60 vs. 80, $p<0.001$). Symptomatic individuals with Long COVID had significantly lower median VAS score compared to symptomatic individuals without Long COVID (70 vs. 80, $p<0.001$), although there was no significant difference between two groups (Figure 12).

4.4.4 Association between Long COVID and HRQOL Outcomes

Table 37 reports estimated unadjusted odds ratios (OR) with respective 95% confidence intervals of the univariate logistic regression for five EQ-5D-5L dimensions- mobility, usual activities, anxiety/depression, pain/discomfort and self-care issues. Figure 13 reports adjusted odds ratios (aOR) for HRQOL dimensions with respective 95% confidence intervals of the multivariate logistic regression.

Table 38 - Unadjusted odds ratios for EQ-5D-5L dimensions with a predicted probability as of Long COVID membership “yes”.

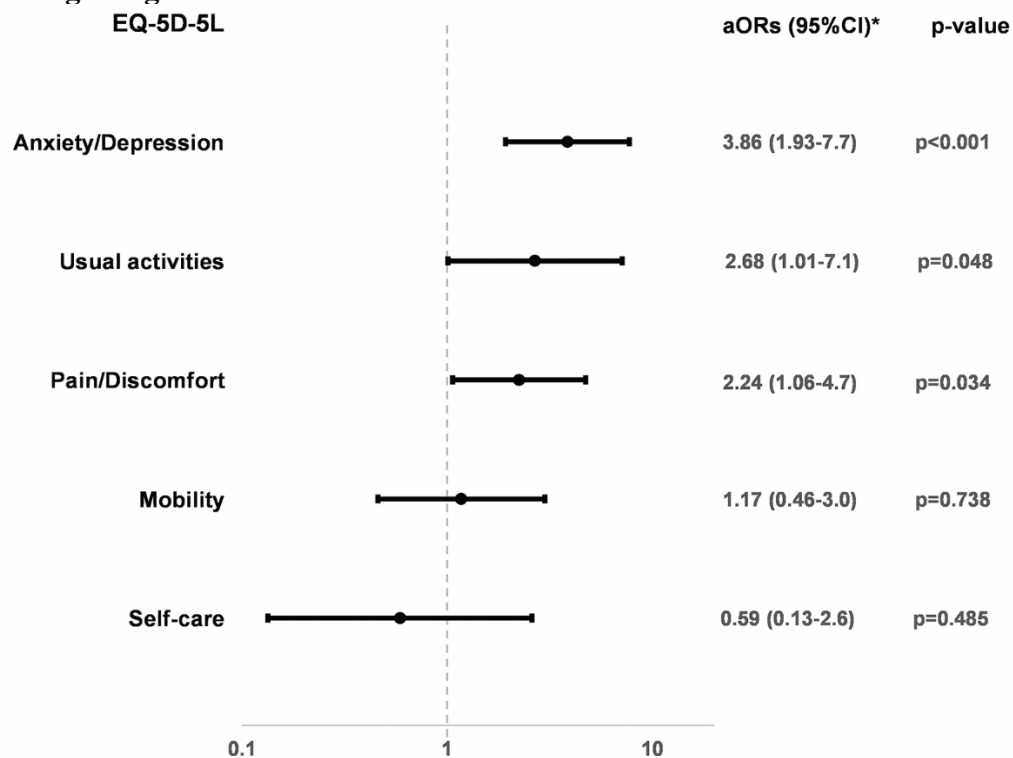
Dimension	All	With Long COVID	Without Long COVID	Unadjusted		
	N=226	N=156	N=70	OR	95%CI	p-value
	n(%)	n(%)	n(%)			
Mobility	80 (35.4)	68 (43.6)	12 (17.1)	1.42	0.585-3.421	0.441
Self-care	19 (8.4)	16 (10.3)	3 (4.3)	0.76	0.187-3.105	0.705
Usual activities	67 (29.6)	59 (37.8)	8 (11.4)	2.25	0.873-5.778	0.093
Pain/discomfort	118 (52.2)	96 (61.5)	22 (31.4)	2.16	1.061-4.385	0.034
Anxiety/depression	125 (55.3)	104 (66.7)	22 (31.4)	3.13	1.641-5.980	<0.001

Source: author

Abbreviations: OR-odds ratios; CI- confidence Interval

Figure 13 presents adjusted odds ratios (aOR) for EQ-5D-5L descriptive system dimensions. The results showed that individuals with Long COVID have about 3.9-fold increased chances of having any issues with anxiety/depression (aOR: 3.86, 95%CI: 1.93-7.75, $p<0.001$); about 2.7 increased chances of having any deterioration with usual activities (aOR: 2.68, 95%CI: 1.01-7.13, $p=0.048$), and 2.2-fold increased chances of having issues with pain/discomfort (aOR: 2.24, 95%CI: 1.06-4.73, $p=0.034$) as compared with individuals without Long COVID (Figure 13). There was no statistically significant association between Long COVID and two of five EQ-5D-5L dimensions: mobility (aOR 1.17, 95%CI: 0.46-3.0, $p=0.738$) and self-care (aOR: 0.59, 95%CI: 0.13-2.6, $p=0.485$).

Figure 12 - Adjusted odds ratios for EQ-5D-5L dimensions with a predicted probability for having Long COVID



Source: author

Abbreviations: aOR- adjusted odds ratio,

*-adjusted for sex, age, and comorbidities.

5 DISCUSSIONS

This PhD thesis studied the prevalence, risk factors, and clinical outcomes of Long COVID, as well as its impact on the health-related quality of life among adults who were diagnosed with mild to moderate COVID-19 in Brazilian primary care during the 2021 pandemic. The analysis was drawn from a cross-sectional survey conducted from May 2023 to July 2024 in six Family Health Care Units, using two instruments—a standardized questionnaire containing a set of eighteen validated clinical outcomes and a generic EQ-5D-5L instrument.

Overall Long COVID prevalence.

In the present thesis, a high proportion of adults had ongoing health problems after non-severe COVID-19 illness. More than two-thirds of the study participants met the definition of Long COVID and reported at least one persistent symptom three months or longer after symptom onset. Only a small number of individuals were completely symptom-free or experienced short-term effects after infection.

This is one of a few studies conducted in primary care in the Northeast region of Brazil to report persistent health issues among nonhospitalized individuals about 3 months after confirmed mild to moderate SARS-CoV-2 infection. This is remarkable for a sample with a median age of 49 years, all of whom received medical care in primary care settings during or after the acute phase of infection. What is even more alarming is that more than two-thirds of the study population who reported persistent illness are women, non-White individuals, individuals who did not complete elementary school, and those who are living in a territory with high and very high risk of socioenvironmental vulnerability. Furthermore, this is one of the few reports on the burden of Long COVID among vulnerable communities.

Several previous studies reported a substantial prevalence of long-lasting post-COVID effects among those adults who experienced non-severe COVID-19 (15-17, 97, 98, 106, 114). However, the estimates of the prevalence of Long COVID after mild-to-moderate infection vary considerably across countries. The reported prevalence of Long COVID depends on disease definition, settings, characteristics of the study population, clinical outcomes that were observed, and instruments for their measurement (4, 5, 14).

A few previous studies from Brazil explored persistent symptoms among COVID-19 survivors (110-118). The studies based on previously hospitalized (110, 112, 113, 115) or mixed cases (114, 117, 118) reported long-lasting symptoms in 41.5% to 100% of adults with COVID-19. Additionally, there are far more studies on Long COVID prevalence among hospitalized adults and from South and South-East regions of Brazil.

In a recent population-based survey from Brazil, that was carried out in 133 large cities and included 33 250 individuals, 65.1% of those individuals with a history of COVID-19 illness experienced persistent symptoms after acute phase, which is in keeping with an estimates in a present thesis (172). However, in a countrywide survey (172) there is no description regarding the severity of COVID-19. Additionally, estimations of the prevalence of Long COVID in a countrywide survey were based on self-reported symptoms.

One previous study of 140 non-hospitalized patients reported Long COVID in 44.3% of adults with confirmed SARS-CoV-2 infection (116), which is lower compared to the estimated prevalence in my study. However, this study used online questionnaires, which may misrepresent those patients who were not able to fill in the online forms. Additionally, the study was conducted in the South region of Brazil (116), which has higher socio-economic indexes as compared to the North-East region, where this thesis study was conducted; hence, it may impact differently the people's health outcomes.

Prevalence of persistent symptoms.

The standardized questionnaire, which included a set of validated clinical outcomes, was used in a survey of the study population with a purpose to avoid potential heterogeneity in self-reported symptoms. The analysis of the prevalence of persistent symptoms in the present thesis showed that individuals with Long COVID following non-severe infection exhibit a wide array of clinical symptoms spanning multiple organ systems.

Among the eighteen validated clinical outcomes explored in this thesis, sixteen were significantly associated with Long COVID. Neurological and neuropsychiatric symptoms stood out as the most prevalent persistent symptoms, which were reported by 98.7% of all the participants in this thesis study. Fatigue was the most frequently reported neurological symptom, which was identified in more than two-third of individuals with Long COVID. Muscle pain, post-exertional

malaise, anxiety, and short-term memory loss were also highly common symptoms and were identified in more than half of adults in this group. Moreover, along with memory issues, about one third of patients with long-haul COVID experienced other cognitive signs such as difficulty thinking, loss of attention and difficulty in solving problems.

Previous studies have identified a wide range of neurological and neuropsychiatric impairments during and after the acute phase of COVID-19 illness (6, 10-11, 15, 98, 173), with few studies in the non-hospitalized cohorts (114, 174, 175). A meta-analysis of over 10 000 individuals from 18 studies describes neurological and neuropsychiatric symptoms both highly common three months after an acute COVID-19 infection (173). The cognitive impairments in this analysis were found to be more prevalent in non-hospitalized patients as compared with previously hospitalized patients (51% vs 32%, respectively). Moreover, fatigue and cognitive symptoms showed a strong tendency to progress over time. The results of a large cross-sectional cognitive performance study of 84 285 survivors of COVID-19 describe significant cognitive deficits in these patients versus controls (174). Cognitive symptoms remained present even in those who had milder COVID-19 cases and those who no longer had other residual symptoms, and could not be explained by differences in age, education, and other sociodemographic characteristics (174).

Fatigue assessment in an international cohort study among 3762 individuals revealed 41% of patients who continued to experience extreme levels of fatigue, which severely impacted their ability to back to work (6). Additionally, a prospective web-based survey suggests that patients may experience both physical and mental fatigue, which does not resolve overtime in all patients, even if they receive healthcare (174). This study also signals that considerable proportion of patients with severe fatigue may progress to chronic fatigue that persists longer than six months. A prospective cohort study based on 6 months follow-up of home isolated patients with mild to moderate COVID-19 reported fatigue in one third of the sample predominantly in young adults aged 16-30 years old (125).

A few previous studies from Brazil, reported fatigue as common feature among the survivors of acute SARS-CoV-2 infection (111-114, 116, 118). The prevalence of fatigue in these studies varies considerably. Cohort studies based on hospitalized cases reported fatigue in 35% to 63% of individuals with Long COVID (111-113), while those studies that followed non-hospitalized cases reported 11% to 54% (114, 116). A cohort study based on an online survey of non-hospitalized

patients revealed that about 43% of patients have continued to experience fatigue 1 year after infection (116). Additionally, cognitive deficit (memory, attention/concentration) along with emotional issues were found common in both previously hospitalized and non-hospitalized COVID-19 survivors in an average of eight months after infection onset (118).

Muscle pain along with fatigue is one of the most frequently reported symptoms by patients with Long COVID, although the prevalence of this symptom varies substantially across the studies (6, 172, 176, 177, 178). A meta-analysis found the muscle pain being present in 27% of non-hospitalized adults (173). Similar findings were reported by other meta-analysis based on 128 studies of Long COVID (177). Interestingly, the presence of muscle pain is found to be associated with prolonged time to clearance of SARS-CoV-2 RNA and/or greater amount or duration of viral antigen burden in the upper respiratory tract (177).

Evidence suggests that patients with COVID-19 may encounter a wide spectrum of cognitive difficulties, ranging from mild to severe symptoms (6, 173, 178). The occurrence of mild cognitive impairment symptoms was highly common in this thesis study. About half of respondents reported post-exertional malaise and short-term memory loss symptoms. More than 20% of respondents reported difficulties in solving problems or difficulties in thinking, loss of attention or mental issues. A wide range of common neurologic and neuropsychiatric symptoms in this PhD study along with other symptoms experienced by patients with Long COVID after non-severe infection may point to larger health issues in the future. This thesis highlights the importance of long-term assistance in primary care not only for previously hospitalized patients who required rehabilitation, but also for those who continue experiencing health problems after milder illness.

Factors associated with Long COVID.

In this thesis study, female sex, age 40–49 years and 70+ years, and five or more initial symptoms were associated with Long COVID. A higher number of COVID-19 related symptoms was the strongest predictor of Long COVID in our cohort.

The presence of multiple symptoms (11, 16, 17, 98) was consistently identified by previous studies as a significant risk factor for Long COVID. Higher symptoms load or wide array of symptoms of initial infection are associated with a greater chance of experiencing long-term post-COVID-19 effects (11, 16).

In this thesis, women had 1.9-fold increased risk of having Long COVID compared to men. Female sex is universally recognized as a risk factor for developing Long COVID identified by many previous studies, irrespective of hospitalization status for acute illness (6, 7, 11, 16, 17, 98, 108, 110, 112, 114, 122). There is growing evidence of a role of dysregulated sex hormones (179) along with other pathophysiological (180, 181, 182) and social factors (119, 130, 183-186) in a multisystem disruption in women with Long COVID. However, the exact mechanisms behind sex differentiation in Long COVID development remain not fully clear.

In this thesis, more than two-third of a group of individuals with Long COVID was comprised by women, who reported multiple symptoms, including neurological impairments and anxiety. According to several previous studies (6, 14, 96, 182), women are more susceptible than men to have post-COVID 19 sequelae in the categories of psychiatric and neurological impairments, including anxiety, depression, and cognitive disorders, which were highly common in this study.

Old age is a known risk factor of poor outcomes in COVID-19 illness. However, there are conflicting findings on the association between Long COVID and age. Some studies reported increased risk with older age (7, 105, 108), while other studies reported increased risk among young and middle-aged adults (9, 98, 101, 106). Moreover, there are reports showing that estimated risk factors for Long COVID by age more likely dependent on initial severity of infection (129), and older adults have a greater risk of morbidity and mortality from COVID-19 than younger adults (187) and are also at risk of Long COVID (188).

Adults aged 70+ years had the highest proportion of comorbidities in this study, including diabetes and hypertension, compared to other age groups, which may contribute to poorer outcomes. Furthermore, the evidence suggests that SARS-CoV-2 infection can exacerbate existing chronic conditions (182, 188). Additionally, the general decline in physiological functions, lower capacity of cell regeneration, and less robust immune responses in elderly may render them more susceptible to tissue-damaging immunity and chronic inflammation (189). Group of adults aged 40-49 years comprises more women and has the highest proportion of symptoms ≥ 5 compared to other age groups, which could double the risk. However, the exact pathophysiological mechanism of Long COVID in middle-aged adults is not fully understood.

Although substantial progress has been made in defining mechanisms of Long COVID development, some questions remain uncovered due to complex human biology and

pathophysiology (190). Several mechanisms have been described, including post-acute virus persistence (191, 192), post-acute inflammation (193), immune dysregulation and autoimmunity (194), reactivation of other pathogens (195), disruption of the gut microbiome (196), mitochondrial dysfunction (197), and microvascular blood clotting with endothelial dysfunction (198). Additionally, microglial reactivity with consequent neural dysregulation was found to play a central role in neurocognitive manifestations of Long COVID (199).

Health-related quality of life of COVID-19 survivors.

More than two-thirds of adults with Long COVID in this PhD study reported continuous health issues two years and beyond after non-severe COVID-19 illness. The results revealed significantly poorer HRQOL outcomes in adults with Long COVID compared to those without Long COVID, regardless of age, sex, ethnicity, education, and pre-existing chronic conditions. The common health issues reported by respondents with Long COVID were anxiety or depression, pain or discomfort, problems with mobility and poorer ability to conduct usual activities. Further, anxiety/depression issues, pain/discomfort issues, and deteriorations of usual activities were strongly associated with Long COVID.

The results of the present thesis add to the evidence of previous findings, which indicate a decrease in health-related quality of life for those who experienced long-lasting effects after COVID-19 (19, 20, 137, 140, 141). In a meta-analysis of seven studies that reported HRQOL out of twenty-four cohort studies, 52% of adults with persistent symptoms had decreased HRQOL (137). Notably, while some studies included in this meta-analysis reported larger declines in HRQOL for those who experienced severe illness (143, 144), there is a study that showed substantially poorer health outcomes in adults who experienced mild infection (145).

A high proportion of adults in my study who had continuing health problems two years and beyond after non-severe infection is particularly alarming. This agrees with the results of a prospective online survey of assessment of HRQOL among adults with persistent symptoms using EQ-5D-5L measures also showed that an individual's HRQOL continued to be affected two years after acute infection (20). Further, in this survey by Kim et al., 2023, the EQ-5D-5L scores had similar distribution at 12 and at 24 months after COVID-19 (20). The proportions of those who reported slight problems two years after infection across five dimensions are in keeping with our findings, although the proportion of those who had experienced moderate to severe health issues is

higher among respondents in our study. However, an online survey did not include adults aged over 70 years, and those who could not fill in online forms; hence, it may impact individuals' health outcomes differently.

In this PhD study, the highest proportion of adults with Long COVID had health issues with anxiety/depression, followed by pain/discomfort, mobility, and usual activities, although the analysis did not identify a statistically significant difference for self-care issues between the two groups. The same tendency was reported in a recent meta-analysis, where pain/discomfort and anxiety/depression were the most common health problems among adults with persistent symptoms one year after acute infection (19). Similarly to my findings, self-care wasn't reported as a common health problem among individuals with Long COVID [19].

More than two-thirds of the participants in my study reported anxiety or depression outcomes, which were also strongly associated with COVID-19 long-lasting effects. In a meta-analysis of HRQOL and psychological problems among COVID-19 survivors, anxiety or depression during the COVID-19 pandemic was strongly associated with a decreased HRQOL (140). Fatigue, pain, post-exertional malaise, difficulties with executive functioning, and memory issues were the most frequent neurological features in my study (200). All these symptoms may potentially lead to problems with pain/discomfort, mobility, and may impact an individual's daily activities. The results of an international cohort study of 3,762 individuals with Long COVID confirmed that the presence of neuropsychiatric symptoms, particularly the presence of fatigue, cognitive disfunctions, and executive functioning problems, may severely impact the individual's daily functioning and their ability to go back to work (6). Further, two systematic reviews reported a decline in daily activities of those with Long COVID with decreasing HRQOL, regardless of the scales applied (139, 141).

Among all respondents with Long COVID in my study, women, older adults, non-white individuals, adults with pre-existing chronic diseases, and those with fewer years of schooling all had significantly decreased HRQOL. Further, symptomatic adults with a higher number of COVID-related symptoms had significantly poorer HRQOL outcomes compared to asymptomatic individuals or those with fewer than five clinical features.

These findings agree with previous research that has shown that women are more susceptible to having Long COVID and have poorer quality of life outcomes compared to men (4,

6, 19, 20, 137). Moreover, women are at the greater risk for major depression, anxiety, and other mental disorders than men globally, which may help explain poorer health outcomes among females in this study (185). Furthermore, as some evidence suggests, females may endure more profound impact during the COVID-19 pandemic than men do, given their specific social roles [184] and existing significant structural inequities faced by women in Brazil (186).

Adults aged ≥ 60 years had the highest proportion of comorbidities in my study, including diabetes and hypertension; hence, this may explain the poorer health outcomes compared to younger age groups. Additionally, SARS-CoV-2 infection can exacerbate existing chronic conditions, which, combined with less robust immune responses in the elderly may render them more susceptible to chronic inflammation (189). Furthermore, a longitudinal study of Long COVID during two epidemic peaks in Brazil described a correlation between pre-existing chronic conditions and the persistence of COVID-19- related symptoms (111).

The analysis in the present thesis shows that non-white adults with Long COVID have lower EQ-5D-5L median index values as compared to non-white adults without Long COVID. Health inequities may put people from racial or ethnic minority groups at greater risk for developing Long COVID (8). A data set based on a retrospective analysis of 62,339 electronic health records of positively tested COVID-19 individuals suggests that racial/ethnic minority groups may experience a higher overall burden of potential Long COVID compared to white individuals (130). There is still a scientific gap regarding the effect of social disadvantages (e.g., ethnic minorities, people with low education, and/or poor living conditions) on Long COVID development and its health outcomes (201). A few studies showed that individuals with lower socioeconomic status, along with poor living environments, may face a higher risk of Long COVID (202, 203). However, the assessment of HRQOL among vulnerable groups with Long COVID is relatively unexplored.

There are a few studies from Brazil that have previously described HRQOL among adults with Long COVID (119, 204). I identified two studies from Brazil that assessed HRQOL using the EQ-5D-5L measures: one study explored the impact of Long COVID in a socially vulnerable community (119), and the other study described persistent symptoms among healthcare workers (120). Neither study provided estimates of utility scores, which prevented me from comparing the results. The study of a Brazilian vulnerable community reported mostly slight to moderate

problems for anxiety/depression, pain/discomfort, mobility, and usual activities, which are in keeping with our findings. Although in the study by Azambuja et al., 2024 (119) HRQOL was assessed among previously hospitalized patients (99.8%), estimates in my study are higher for the population that experienced health issues after mild-to-moderate COVID-19. The previous assessment of HRQOL on long-lasting effects of COVID-19 also reported that patients with mild illness had significantly worse health outcomes compared to previously hospitalized (145).

Strength and limitations.

A strength of this thesis study was the assessment of Long COVID using a standardized questionnaire with a set of predefined validated outcomes, which could be useful for assessing Long COVID in primary care practice, especially in resource-limited settings. Additionally, the list of symptoms that were assessed was narrowed to avoid their excessive heterogeneity. To my knowledge, this is one of a few studies conducted in Brazil that assessed the prevalence and risk factors of Long COVID in primary care and in Northeast region of Brazil. Moreover, this is the first study from Brazil that assessed the health-related quality of life among adults with long-lasting symptoms in primary care, including individuals living in a territories of high risk for socioenvironmental vulnerability, two years after the 2021 COVID-19 pandemic. Moreover, a generic EQ-5D-5L instrument was applied, which is recommended by Delphi consensus for HRQOL measurement of Long COVID among adults in research and clinical practice. The study was conducted in several public ambulatory settings, which varied in terms of the resident population. Additionally, a face-to-face interview permitted to better represent the lived experiences of COVID-19 survivors.

This study has several limitations. Among key limitations is the retrospective nature of a survey, which may introduce potential recall biases. Other limitations are convenience sampling and relatively small sample size. A larger cohort would enhance the statistical power of the findings. Although this PhD study identified potential risk factors associated with Long COVID, cross-sectional design does not allow any inferences regarding causality. The possibility of reverse causality should be also acknowledged. Although most adults in my study were vaccinated within the universal Brazilian COVID-19 vaccination program, we could not be able to track if they were vaccinated before or after infection. More women responded to our questionnaire; thus, it may influence the results. Furthermore, the testing capacity for SARS-CoV-2 infection during the 2021

pandemic was very limited within primary care in Brazil; some individuals may not be tested, or all positive test results may not be routinely coded. The United States population value set was used to estimate EQ-5D-5L utility scores; thus, it may not accurately represent the Brazilian population's values.

6 FINAL CONSIDERATIONS

This thesis contributes to research evidence on the prevalence, risk factors, and the health-related quality of life of adults who experienced long-lasting health issues after mild-to-moderate SARS-CoV-2 infection. The results on the clinical sequelae of Long COVID indicate a high prevalence of persistent symptoms spanning multiple organ systems. This is one of the few studies from Brazil that has been implemented at primary care level. More than half of all individuals with Long COVID in this study reported at least one persistent symptom in primary care three months or longer after infection.

Among eighteen validated clinical outcomes included in a survey, sixteen were significantly associated with Long COVID. The neurological and neuropsychiatric manifestations stood out as the most reported persistent symptoms among individuals who experienced this condition. Such symptoms as fatigue, muscle pain, post-exertional malaise, anxiety, and short-term memory loss were observed in more than two-third of adults with Long COVID, which may point to larger health issues in the future.

In this study, several risk factors were associated with reporting persistent symptoms after non-severe SARS-CoV-2 infection. Reporting five or more symptoms was the strongest predictor of symptoms' persistence beyond 3 months after initial infection. Female sex, presence of comorbidities, age 40-49 years, and age 70 years and older also were significantly associated with Long COVID.

Individuals with Long COVID continued to experience significantly poorer health-related quality of life two years and beyond after mild-to-moderate infection compared to those without persistent illness, regardless of sex, age, ethnicity, education, or comorbidities. Adults with this condition are likely at higher risk for having health issues related to anxiety or depression, pain or discomfort, and deterioration of usual activities.

One of the key contributions of this PhD research is providing insights on scope of the Long COVID problem at primary care level. This thesis highlights the need to target multidisciplinary services in primary care for COVID-19 survivors experiencing long-term health issues after infection. Furthermore, understanding the long-lasting health effects of SARS-CoV-2 infection and

identifying adults at higher risk for enduring health issues can help health professionals, caregivers, and policymakers better address aspects of patients' lives that lack quality and develop a multidisciplinary approach in primary care for managing this condition.

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APPENDIX

Appendix - Long COVID Questionnaire (English version ^{a)})

	Items	Response options
GENERAL INFORMATION.		
Verify the complete name and date of birth of the participant via identification document (CPF-Cadastro de Pessoas Físicas or RG-Registro Geral).		
	Date of interview	DD/MM/YY
	Location	Neighborhood/USF* of reference
	Name of the interviewer	Code name
01	What is your name?	Full name (given name, middle name, family name)
02	What is your phone number?	Code of the state, telephone number
03	What is your address?	Complete address
04	What is your age?	Age/Date of birth
05	What is your gender?	☐ Male ☐ Female ☐ Other ☐ Prefer not to answer
	If other, please specify	
06	What is your level of education?	☐ Primary school incomplete ☐ Primary school complete ☐ Secondary school incomplete ☐ Secondary school complete ☐ Technical/professional course incomplete ☐ Technical/professional course complete ☐ Higher education incomplete ☐ Higher education complete ☐ Post-graduation course incomplete ☐ Post-graduation course complete ☐ NS
07	What is your ethnic origin?	☐ White ☐ Black/African ☐ Asian/Oriental ☐ Mixed ☐ Indigenous ☐ NS
08	Did you have any chronic diseases before COVID-19 illness?	☐ Yes ☐ No <i>If Yes, can you specify disease(s)?</i> <i>Open question</i>
09	Have you received any COVID-19 vaccinations?	☐ Yes ☐ No <i>If Yes, how many doses?</i> ☐ One dose ☐ Two doses ☐ Three or more
10	What type of COVID-19 vaccine(s) you received?	<i>Open question</i>
SYMPTOMS		
Explain to the participant: "I am going to ask you about different symptoms related to COVID-19 illness. It is important that you answer "YES" if these symptoms were new since you were diagnosed with COVID-19 in 2021, or if they occurred within a period of 3 months after infection. If you did not have these symptoms or experienced them before you got COVID-19, answer "NO". Make a note if the respondent does not remember or does not want to answer the question.		
11	Did you feel fatigue?	☐ Yes

		☐ No
12	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
13	Did you feel post-exertional malaise?	☐ Yes ☐ No
14	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
15	Did you had sore throat?	☐ Yes ☐ No
16	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
17	Did you feel muscle pain?	☐ Yes ☐ No
18	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
19	Did you feel dyspnea? (<i>shortness of breath</i>)	☐ Yes ☐ No
20	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
21	Did you feel chest pain?	☐ Yes ☐ No
22	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
23	Did you feel joint pain?	☐ Yes ☐ No
24	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
25	Did you feel dry cough?	☐ Yes ☐ No
26	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
27	Did you feel difficulty breathing?	☐ Yes ☐ No
28	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
29	Did you feel diarrhea?	☐ Yes ☐ No
30	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months

		☐ 2 to 3 months ☐ More than 3 months
31	Did you feel anxiety?	☐ Yes ☐ No
32	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
33	Did you feel dizziness?	☐ Yes ☐ No
34	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
35	Did you feel short-term memory loss?	☐ Yes ☐ No
36	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
37	Did you feel mental confusion?	☐ Yes ☐ No
38	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
39	Did you feel loss of attention?	☐ Yes ☐ No
40	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
41	Did you feel difficulty thinking?	☐ Yes ☐ No
42	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
43	Did you feel difficulty in executive function? (Difficulty performing daily tasks and work)	☐ Yes ☐ No
44	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
45	Did you have difficulty in solving problems?	☐ Yes ☐ No
46	If Yes, how long it lasted?	☐ Less than 1 month ☐ 1 to 2 months ☐ 2 to 3 months ☐ More than 3 months
47	Have you experienced any other symptoms that were not asked about in this questionnaire? If Yes, please specify	Open question

NS- I don't know/can't tell;

^a – The English translation was provided by the author. This translation was not submitted to the formal process of translation and cross-cultural adaptation, followed the validation process.

Appendix - Long COVID Questionnaire (original version in Brazilian Portuguese)

	Questões	Respostas
INFORMAÇÕES GERAIS.		
<i>Verifique o nome completo e a data de nascimento do participante através de documento de identificação (CPF/RG).</i>		
	Data da entrevista	Dia/mes/ano
	Local	Bairro/USF referente
	Nome do entrevistador	Nome codificado
01	Qual seu nome?	Nome completo
02	Qual o seu contato?	Colocar DDD e telefone.
03	Qual o seu endereço?	Endereço completo
04	Qual sua idade?	Idade/Data de nascimento
05	Qual seu gênero?	☐ Masculino
		☐ Feminino
	Se outro, qual?	☐ Outro
		☐ Prefiro não dizer
06	Até que ano você estudou?	☐ Primário Incompleto
		☐ Primário completo
		☐ Secundário incompleto
		☐ Secundário completo
		☐ Curso Técnico/profissionalizante incompleto
		☐ Curso Técnico/profissionalizante
		☐ Curso superior incompleto
		☐ Curso superior completo
		☐ Pós-graduação incompleta
		☐ Pós-graduação
		☐ NS
07	Você se considera?	☐ Branco (a)
		☐ Preto (a)
		☐ Oriental
		☐ Pardo (a)
		☐ Indígena
		☐ NS
08	Você tinha doenças crônicas pré-existentes ao COVID-19?	☐ Sim
		☐ Não
		<i>Se sim, qual/quais?</i>
		Resposta aberta:
09	Você se vacinou?	☐ Sim
		☐ Não
		<i>Se sim, com quantas doses?</i>
		☐ Uma dose
		☐ Duas doses
		☐ Três ou mais doses
10	Quais foram as vacinas que você se vacinou?	Resposta aberta:
SINTOMAS.		
<i>Explique ao participante: "Vou perguntar a você sobre os diferentes sintomas relacionados à doença COVID-19. É importante que você responda "SIM" se esses sintomas eram novos desde que você foi diagnosticado com COVID-19 em ano 2021, ou se os sintomas ocorreram dentro de um período de 3 meses após a infecção. Responda "NÃO" caso você não tinha esses sintomas ou os sentia antes de contrair COVID-19".</i>		
<i>Anota caso o entrevistado não se lembre ou não queira responder à pergunta.</i>		
11	Você sentiu fadiga?	☐ Sim
		☐ Não
12	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês
		☐ De 1 a 2 meses
		☐ De 2 a 3 meses
		☐ Mais de 3 meses
13	Você sentiu mal-estar pós-esforço?	☐ Sim

		☐ Não
14	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
15	Você sentiu dor de garganta?	☐ Sim ☐ Não
16	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
17	Você sentiu dores musculares?	☐ Sim ☐ Não
18	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
19	Você sentiu dispneia? (<i>falta de ar</i>)	☐ Sim ☐ Não
20	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
21	Você sentiu dor no peito?	☐ Sim ☐ Não
22	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
23	Você sentiu dores nas articulações?	☐ Sim ☐ Não
24	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
25	Você sentiu tosse seca?	☐ Sim ☐ Não
26	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
27	Você sentiu dificuldade em respirar?	☐ Sim ☐ Não
28	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
29	Você sentiu diarreia?	☐ Sim ☐ Não
30	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
31	Você sentiu ansiedade?	☐ Sim ☐ Não
32	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês

		☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
33	Você sentiu tontura?	☐ Sim ☐ Não
34	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
35	Você sentiu perda de memória de curto prazo?	☐ Sim ☐ Não
36	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
37	Você sentiu confusão mental?	☐ Sim ☐ Não
38	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
39	Você sentiu perda de atenção?	☐ Sim ☐ Não
40	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
41	Você sentiu dificuldade de pensar?	☐ Sim ☐ Não
42	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
43	Você sentiu dificuldade de funcionamento executivo? (Dificuldade para fazer as tarefas do dia a dia e do trabalho)	☐ Sim ☐ Não
44	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
45	Você sentiu dificuldade em resolver problemas?	☐ Sim ☐ Não
46	Se sim, perdurou por quanto tempo?	☐ Menos de 1 mês ☐ De 1 a 2 meses ☐ De 2 a 3 meses ☐ Mais de 3 meses
47	Você sentiu mais algum sintoma que não foi perguntado neste questionário? Se sim, qual/quais?	Resposta aberta
NS-não sabe dizer		

Appendix – EQ-5D-5L Instrument (Portuguese version for Brazil).

Abaixo de cada título, por favor marque O quadrado que melhor descreve sua saúde HOJE.

MOBILIDADE

- Não tenho problemas em andar ☐
- Tenho problemas leves em andar ☐
- Tenho problemas moderados em andar ☐
- Tenho problemas graves em andar ☐
- Sou incapaz de andar ☐

CUIDADOS PESSOAIS

- Não tenho problemas para me lavar ou me vestir ☐
- Tenho problemas leves para me lavar ou me vestir ☐
- Tenho problemas moderados para me lavar ou me vestir ☐
- Tenho problemas graves para me lavar ou me vestir ☐
- Sou incapaz de me lavar ou vestir sozinho/a ☐

ATIVIDADES HABITUAIS (ex. *trabalho, estudos, atividades domésticas, atividades em família ou de lazer*)

- Não tenho problemas em realizar as minhas atividades habituais ☐
- Tenho problemas leves em realizar as minhas atividades habituais ☐
- Tenho problemas moderados em realizar as minhas atividades habituais ☐
- Tenho problemas graves em realizar as minhas atividades habituais ☐
- Sou incapaz de realizar as minhas atividades habituais ☐

DOR / MAL-ESTAR

- Não tenho dores ou mal-estar ☐
- Tenho dores ou mal-estar leves ☐
- Tenho dores ou mal-estar moderados ☐
- Tenho dores ou mal-estar fortes ☐
- Tenho dores ou mal-estar extremos ☐

ANSIEDADE / DEPRESSÃO

- Não estou ansioso/a ou deprimido/a ☐
- Estou levemente ansioso/a ou deprimido/a ☐
- Estou moderadamente ansioso/a ou deprimido/a ☐
- Estou muito ansioso/a ou deprimido/a ☐
- Estou extremamente ansioso/a ou deprimido/a ☐

Nós gostaríamos de saber o quão boa ou ruim a sua saúde está HOJE.

Esta escala é numerada de 0 a 100.

100 significa a melhor saúde que você possa imaginar.

0 significa a pior saúde que você possa imaginar.

Marque um X na escala para indicar como a sua saúde está HOJE.

Agora, por favor escreva no quadrado abaixo o número que você marcou na escala.

A SUA SAÚDE HOJE =

