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Review

A Systematic Review and Quality Evaluation of Studies on Long-Term Sequelae of COVID-19

Jorge Vásconez González [1*], Juan S. Izquierdo-Condoy [1,2], Raul Fernandez-Naranjo [1] and Esteban Ortiz-Prado [1,3*],

[1] One Health Research Group, Faculty of Health Science, Universidad de Las Américas, Quito, Ecuador
[2] Health Management and Research Area, Universidad Internacional Iberoamericana, Arecibo, Puerto Rico
[3] Facultad de Ciencias de la Salud, Universidad Latina de Costa Rica, San José, CR.
* Correspondence authors: Esteban Ortiz-Prado and Jorge Vásconez González One Health Research Group, Universidad de las Américas, Quito, Ecuador Calle de los Colimes y Avenida Granados: e.ortiz-prado@gmail.com and jorge.vasconez@udla.edu.ec

Abstract: Background: COVID-19 made its debut as a pandemic in 2020; since then, more than 607 million cases and at least 6.5 million deaths have been reported worldwide. While the burden of disease has been described, the long-term effects or chronic sequelae are still being described. **Objective:** To describe the findings of a current systematic review of the long-term effects related to post-COVID-19 sequelae. **Design:** A systematic review was carried out in which cohort studies, case series, clinical case reports were included, and the PubMed, Scielo, SCOPUS and Web of Science databases were extracted. Information published 2020 to June 1, 2022, was sought. **Results:** We reviewed 300 manuscripts during the first step of the literature review process. Then 260 abstracts were analyzed. In the end, we included 32 manuscripts: 9 for pulmonary, 6 for cardiac, 2 for renal, 9 for neurological and psychiatric, and 8 for cutaneous sequelae**. Conclusion:** Studies show that the most common sequelae are those linked to the lungs, followed by skin, cutaneous and psychiatric alterations. Women report a higher incidence of the sequelae, as well as those with comorbidities and severer COVID-19 history. The COVID-19 pandemic has not only caused death and disease since its apparition but has also sickened millions of people around the globe who potentially suffer from serious illnesses that will continue to add to the list of health problems and further burden healthcare systems around the world.

Keywords: sequelae; COVID-19; SARS-COV-2; long-COVID; systematic review

1. Introduction

More than two years have passed since the emergence of a new zoonotic coronavirus[1]. This disease emerged in China after close contact with mammals from a wet market in Wuhan[2]. The rapid spread of the SARS-CoV-2 virus took the planet by surprise, causing a severe flu-like illness that affected more than 670 million and killed more than 6.7 million worldwide[3].

The impact of SARS-CoV-2 should not be attributed to severe pneumonia alone and the direct burden of diseases due to acute COVID-19, but also to the sequelae and complications that the disease can leave among survivors[4, 5]. COVID-19, like a long list of bacterial, viral, or parasitic infectious diseases, can leave sequelae in virtually every body organ[6–9].

It has been reported in multiple studies that most infectious diseases can cause post-acute, chronic, or long-term sequelae, lasting for weeks, months, or years, increasing the impact of this disease on individuals, communities, as well as on health systems around the globe[10]. The acute clinical manifestations of COVID-19 have been well characterized and involve both pulmonary and extrapulmonary systemic manifestations, but for some people, symptoms of COVID-19 persist beyond the acute setting [11]. These COVID-19-related sequelae can be attributed directly to the viral SARS-CoV-2 infection or the severe inflammatory response the body creates in response to the acute infection[4, 12] .

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Among the most frequent long-COVID-19 consequences, we have fatigue, extreme tiredness, and dyspnea. It is essential to point out that even though the severity of the disease is a significant risk factor, several patients with milder and asymptomatic processes can develop long-lasting and disabling sequelae, such as brain fog, paresthesia, muscle weakness, and others[13]. Despite advancing treatments for COVID-19 , the long-term sequelae of this disease are expected to endure in survivors[14].

Studying, analyzing, and identifying the central sequelae related to COVID-19 is fundamental to understanding the real burden of COVID-19. Furthermore, we have the economic and productive impact long COVID-19 can generate among the indirect consequences. This new condition will undoubtedly generate new doctor visits, higher out-of-pocket expenses, and more medication-related expenditures, affecting countrywide economies and patients' quality of life[15, 16].

The aim of this study was o present an overview of the information available on the sequelae of COVID-19 in people who have suffered from the infection.

2. Materials and Methods

2.1. Study design

A systematic review was carried out in which observational descriptive, cohort studies, case series, and clinical case reports were included. The Prisma methodology was used, which is recommended for carrying out meta-analyses and systematic reviews.

2.2. Search strategies

The search for information was carried out in both English and Spanish to obtain the maximum amount of information available. Google search engine was used to access PubMed and Scielo databases, as well as the library system of the International University. of Valencia to access SCOPUS and Web of Science databases. Information published from 2020 to June 1, 2022, was sought. The following terms were used to carry out said search:

"COVID-19 " "Sars-Cov-2" "Post-COVID-19"	AND	"Sequelae" "Cardiac sequelae" "Neurological sequelae" "Psychological sequelae" "Renal sequelae" "Pulmonar sequelae" "Dermatological sequelae"
"Post-COVID-19"	AND	"Manifestations" "Symdrome" "Charactersitcs"
In title (TI), or abstract (AB)		In title (TI) or abstract (AB)

2.3. Inclusion criteria

-Studies including COVID-19 recovered patients, either children or adults.

2.4. Exclusion criteria

- We excluded systematic, literature and narrative reviews, letters to the editor, editorials, and meta-analyses. We also excluded those studies related to SARS or MERS.

-Animal studies and those investigations not reporting long-COVID-19 sequelae were also excluded.

2.5. Data synthesis

In this section, a complete and exhaustive review was carried out of all the manuscripts that met the inclusion criteria. With the information obtained from the cohort studies, a quantitative analysis was carried out, for which the NEWCASTLE - OTTAWA

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QUALITY ASSESSMENT SCALE was used (Table S1), to analyze the cross-sectional studies the JBI critical appraisal checklist for analytical cross-sectional studies was used (Table S2), in the case of the clinical cases (case reports) used the JBI Critical Appraisal Checklist for Case Reports (Table S3), and for case series the JBI Critical Appraisal Checklist for Case Series was used (Table S4). At the end of this process, the information from the manuscripts was organized and synthesized in tables.

3. Results

3.1. Literature review

During the first step of the literature review process, 300 manuscripts were included and appraised for compliance with the inclusion criteria. After this process, we obtained a remainder of 260 articles, in which we performed an analysis of the information provided within the abstracts. Finally, we selected 32 manuscripts for this literature review (Figure 1).

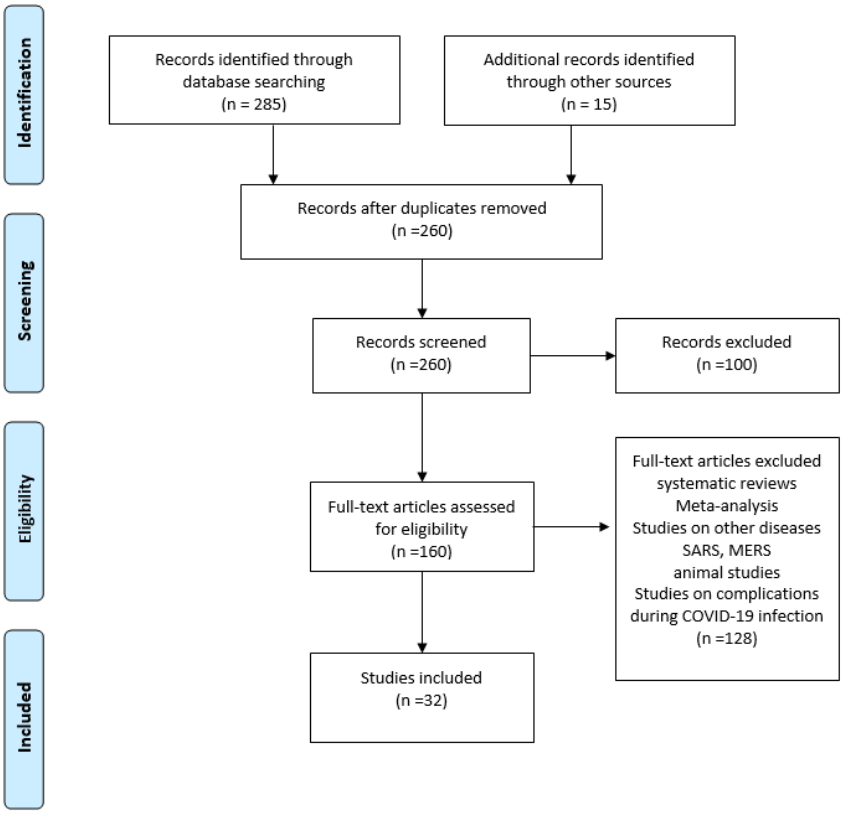

Figure 1. PRISMA Flowchart.

3.2. Specific studies

3.2.1. Pulmonary sequelae

We included nine studies for this section (Table 1). Patients' ages ranged from 3 to 12 months from this cohort after having recovered from COVID-19 infection. The study of the effects on lung function was assessed in 55 patients who had recovered from COVID-19 at least three months prior to the spirometry analysis [17, 18]. The results demonstrated that 10.91% of patients had a decreased respiratory function as determined by a reduced Forced expiratory volume in the first second (FEV1) and by a reduced Forced Vital Capacity (FVC) [17, 18]. In the same context, Huang et al. classified the severity of the disease into 7 categories through the "severity scale", 13% of those in category 5-6 presented FEV1<80% and 13% of patients in category 4 presented FEV1 / FVC <70% [19], alterations in the diffusion of carbon monoxide (DLCO) were also reported, which was

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decreased by 59% compared to its normal value, it is believed that the level of D-dimer at admission was a important factor for DLCO [20, 21].

Pulmonary radiological alterations were also described by employing computed tomography scans (CT). Radiologic evidence demonstrated the presence of fibrosis affecting different lung sections, consolidating in certain lung lobes, mainly the right lower lobe, and the left upper and lower lobes [20, 21]. Pan et al. conducted a study with 209 patients after one year of being diagnosed with COVID-19. The study reported the presence of multifocal reticular or cystic lesions in 13% of patients and evidence of residual linear opacities in 12% of them. Ground glass pattern, bronchial dilation, and parenchymal bands were the more common lesion during the acute and post-acute phases of the COVID-19 infection. The study also showed that 75% of patients did not show radiological alterations after one year [22].

It is essential to highlight the role of the severity of the infection. All the available studies showed that the more severe the infection was, the greatest the lung capacity alteration [19]. Although earlier mechanical ventilation has been associated with better survival among severely ill COVID-19 patients, it also behaves as a predictor of radiological and spirometric abnormalities [21, 23, 24].

Six studies highlight the persistence of respiratory symptoms in patients 1 to 3 months after overcoming COVID-19 infection; 68% of patients had at least one symptom 30 days after infection and 66% at 60 days; overall, 65.6% of patients had persistent symptoms post COVID-19. [25]. The most reported persistent symptom was dyspnea[20, 25–29]. At least 65.6% of patients in the intensive care unit (ICU) and 42% of those hospitalized in general wards presented difficulty breathing after discharge [26]. Women and afro-descendants reported higher dyspnea rates (42.1%) than white populations (25%). Lastly, patients with body mass index (BMI) higher than 30 have more severe dyspnea than those with a BMI below 30 [26]. On top of dyspnea, other symptoms such as cough, runny nose, sneezing, rhinitis, burning sensation in the lungs and trachea, fatigue, and chest pain have been reported [20, 25, 28].

Comorbidities and the severity of COVID-19 are associated with more significant respiratory impact. For example, having diabetes mellitus or hypertension increases the risk of developing pulmonary sequelae [19, 22, 25–27]. Young adults are also at greater risk of developing long-term pulmonary sequelae. For instance, people from 40 to 60 years of age are twice as likely to present sequelae compared to younger patients [22, 25].

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Table 1. Summary of the literature mentioning pulmonary sequelae.

Author	Objetive	Type of Study	Participants	Results	Score
Carvalho. S et al. 2021	To describe the clinical evolution and predictors of persistence of symptoms during 2 months of follow-up in adults with non-critical illness due to coronavirus 2019 (COVID-19).[25].	Cohort study	150 participants 84 women 66 men Middle Ages 49 ± 15 years 2-month follow-up after hospital discharge.	One third of the patients had dyspnea and one sixth chest pain.	7
Huang. Ch et al. 2021	Describe the long-term consequences of COVID-19 in patients after hospital discharge and identify potential risk factors, including disease severity, associated with these consequences cribir las consecuencias a largo plazo de COVID-19 en pacientes después del alta hospitalaria e identificar los posibles factores de riesgo, incluida la gravedad de la enfermedad, asociados con estas consecuencias [19].	Cohort study	1733 participants 897 men 836 women Age 47-65 years 6-month follow-up after hospital discharge.	They classified the severity of the disease they had was classified into 7 categories through the severity scale, 13% of those in category 5-6 presented FEV1<80% and 13% of patients in category 4 presented FEV1/FVC < 70%	8
Halpin. S et al. 2020	Describe post-discharge symptoms and rehabilitation needs in COVID-19 survivors after hospital discharge [26].	Cross-sectional study	100 participants 32 patients in ICU 68 patients in hospital 33 women 35 men Age 20-93 years Follow-up 4 to 6 weeks after hospital discharge.	-72% of patients in the ICU and 60.3% hospitalized presented fatigue. - 65.6% of patients in the ICU and 42.6% hospitalized had dyspnea	5
Zhao. Y et al.2020	To describe the long-term effects on changes in both lung function and CT images in patients with COVID-19 3 months after hospital discharge. [20].	Cohort study	55 Participants 23 women 32 men Mean age 47.74 ± 15.49 Follow-up was 3 months after hospital discharge.	16.36% of the patients presented exertional dyspnea and 1.81% cough.	8
Compagnone. N et al. 2019	Assess the pulmonary status of COVID-19 survivors after ICU discharge [21].	Cohort study	49 participants who were admitted to the ICU 5 women 44 men Age 52-65	-46% of the patients presented a restrictive pattern after spirometry. -28% presented radiological characteristics of pulmonary fibrosis.	7

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			Follow-up at 4, 12 and 24 weeks after hospital discharge.		
Pan. F et al. 2021	To assess chest CT manifestations of COVID-19 up to 1 year after symptom onset.[22].	Cohort study	209 participants 116 women 93 men Age 20-82 years 1-year follow-up after hospital discharge.	-53 patients presented alteration in pulmonary CT -77% of patients presented reticular lesions -74% of the patients presented bronchial dilation.	8
Goërtz. Y et al. 2020	To assess whether multiple relevant symptoms recover after symptom onset in hospitalized and non-hospitalized patients with COVID-19 . [28].	Cohort study	2113 participants 102 hospitalized 2001 not hospitalized 1803 women 310 men Age 39-54 years Follow-up 3 months after recovery from COVID-19 .	71% reported dyspnea and 24% pain in the lungs.	8
Walsh. M et al. 2020	To investigate the prevalence and characteristics of prolonged symptoms in non-hospitalized college students experiencing mild to moderate acute illness. [29].	Cohort study	148 male and female students Follow-up ≥28 days.	43% presented dyspnea.	7
Kamal. M et al. 2020	Investigate and characterize the manifestations that appear after the eradication of coronavirus infection and their relationship with the severity of the disease [27].	Cohort study	287 participants 184 women 103 men Age 20 to 60 years Follow-up does not specify how many days after having overcome the COVID-19 infection.	28% presented dyspnea and 4.9% pulmonary fibrosis.	7

3.2.2. Cardiac sequelae

In this section, we included six studies (Table 2). The cohort of long-term cardiological sequelae was evaluated in recovered patients after one to six months post-COVID-19 infection. Puntman et al. found that after 71 days post SARS-CoV-2 infection, 78% of the patients had some evidence of cardiac compromise. For example, they had a lower ejection fraction in both the left and right ventricles, as well as higher pre-cardiac stroke volume and higher levels of anti-troponin T1, T2, and troponin T [30]. Likewise, Huang et al. performed magnetic resonance (MRI) imaging on 36 patients who recovered from COVID-19 infection. They found significant alterations around native values of T1 and T2 with a significant reduction in the left ventricle's ejection fraction [31]. These

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studies also reported the presence of focal myocardial fibrosis and the presence of active lymphocytic inflammation without evidence of another viral genome [30, 31].

The most common cardiological symptoms after recovering from COVID-19 were palpitations [17, 19, 30–32] Dyspneic patients, women, young adults (20 to 60 y/o), and those with heart rates≥ 90 beats per minute are at higher risk of prolonging palpitations at resting [17]. In addition, chest pain, tightness, and thoracic distress were reported [17, 19, 31–33]. Newly diagnosed hypertension was reported among seven patients after 97 days post-infection, and stroke risk increased among longhaulers [17, 33, 34].

Table 2. Summary of literture mentioning cardiac sequelae.

Author	Objetive	Type of Study	Participants	Results	Score
Huang. Ch et al. 2021	Describe the long-term consequences of COVID-19 in patients after hospital discharge and identify potential risk factors, including disease severity, associated with these consequences [19].	Cohort study	1733 participants, 897 men, 836 women, Age 47-65 years. 6-month follow-up after hospital discharge.	9% presented palpitations and the 5% chest pain.	8
Puntmann. V et al 2020	Evaluate the presence of myocardial damage in unselected patients recently recovered from COVID-19 disease.. [30].	Cohort study	100 participants, 47 women, 53 men. Average age 49 years Follow-up from 64 to 92 days after recovery from COVID-19 infection.	60% myocardial inflammation 17 patients reported chest pain 20 reported palpitations.	7
Xiong. Q et al. 2021	To describe the prevalence, nature and risk factors of the main clinical sequelae in survivors of coronavirus disease 2019 (COVID-19) with more than 3 months of hospital discharge. (38).	Longitudinal study	538 participants, 293 women, 245 men. Age 41-62 years The time from hospital discharge was 95 to 102 days.	12.3% presented pain in the chest and 11.2% tachycardia at rest.	7
Wang. X et al 2020	Investigate clinical outcomes, distribution of quarantine locations, and infection status of contacts of COVID-19 patients after discharge [32].	Cohort study	131 participants, 72 women, 59 men. Age 36-62 years 4-week follow-up from hospital discharge.	6.11% presented chest tightness, the 3.05% chest pain and the 1.53% palpitations.	7
Iqbal. A et al.2021	To assess the prevalence and characteristics of post-COVID-19 manifestations and their effect on the quality of life of people recovered from COVID-19 [33].	Corss-sectional study	158 participants, 87 women, 71 men. 132 Urban and 26 Rural. Age 19-80 years. The mean time since recovery from COVID-19 infection was 38.10 ± 20.00 days.	35.4% presented chest pain	6
Huang. L et al. 2020	Evaluate cardiac involvement in patients recovered from coronavirus disease-2019 by cardiac magnetic resonance imaging [31].	Retrospective observational	26 participants, 16 women, 10 men. Age 35-45 years There was a median of 47 days from the onset of COVID-19 symptoms to the MRI.	12% presented chest pain and the 88% palpitations.	7

3.2.3. Renal sequelae

In this section, we inluded two studies (Table 3); Bowe et al. 2022, showed that after 30 days after recovery from COVID-19, patients had a significant reduction in the glomerular filtration rate of more than 30%, an estimated glomerular filtration reduction of ≤ 50% and a higher risk of suffering from any urogenital and renal disease in the

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following months [35]. Huang et al . analyzed 1,733 patients who recovered from COVID-19 infection. Their results showed that 35% had an estimated glomerular filtration rate of 90 mL/min per 1 73 m2, a lower rate than expected [19]. Although the lengthy hospitalizations and comorbidities may cause adverse effects on the kidneys, we cannot rule out that SARS-CoV-2 has some direct deleterious effect on the kidney[35].

Table 3. Summary of literature mentioning renal sequelae.

Author	Objetive	Type of Study	Participants	Results	Score
Bowe. B et al. 2021	Characterize the risks of post-acute renal outcomes according to the severity of acute COVID-19 infection.[35].	Cohort Study	89,216 participants 8817 women 80,399 men Age 53-73 years Follow-up 127-268 days after COVID-19 infection	Acute kidney injury, decreased estimated glomerular filtration rate.	9
Huang. CH et al. 2021	Describe the long-term consequences of COVID-19 in patients after hospital discharge and identify potential risk factors, including disease severity, associated with these consequences [19].	Cohort Study	1733 participants 897 men 836 women Age 47-65 years 6-month follow-up after hospital discharge.	35% presented decreased glomerular filtration rate.	8

3.2.4. Neuro-psychiatric sequelae

We included nine studies in which participants were followed for up to 9 months post-infection(Table 4).

COVID-19 infection can cause neurological and psychiatric sequelae, including depression, insomnia, anxiety, and other disorders like dementia and post-traumatic stress disorder [36–40]. In addition, Mazza et al. observed that lengthy hospital stays, the presence of comorbidities, and being women have higher scores for mental disorders [36]. Among the least frequent neurological sequelae, parkinsonism was reported on some occasions. An MRI performed on a patient with this sequela revealed that the periventricular white matter presented ischemic changes [37, 41]. Additional long-term sequelae, including frequent headaches, paresthesias, disorientation, anosmia, and ageusia, were reported; nevertheless, more severe complications such as intracranial hemorrhages and ischemic cerebrovascular events have been reported [37, 39, 42]. Mattioli et al. observed that recovered severely ill patients have significantly reduced tendon reflexes, areflexia, essential tremors, and affected tactile sensation [40]. In the same context, Mohmood et al. reported a case of a man whose physical examination revealed 2/5 left ankle strength at dorsiflexion and absent left and right knee reflexes. They also reported altered nerve conduction, active denervation and axonal mononeuropathies [43]. Finally, Needham et al. reported a case series of 11 patients suffering from severe COVID-19, diagnosed with focal axonal loss and multiple mononeuritis [44].

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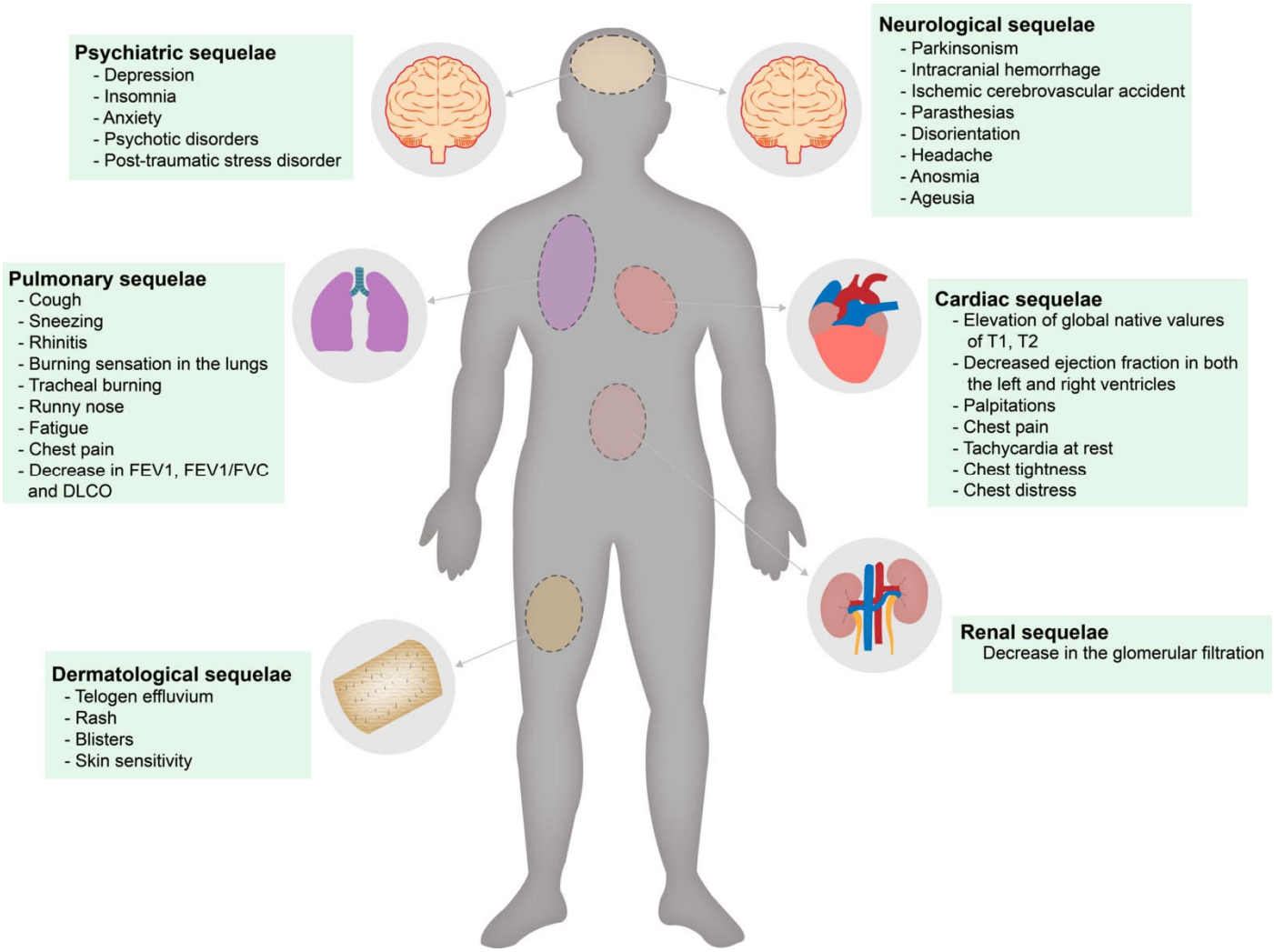

Figure 2. The main reported post-COVID-19 sequelae and long-term symptoms atributted to Long-COVID.

In terms of ethnicity, little is known about epidemiological differences among populations. For instance, Asians were more prone to develop intracranial hemorrhages, African Americans were more likely to report parkinsonism, and white populations had a higher risk of developing dementia and insomnia. In addition, the elderly (> 65 years) have a higher risk of developing neurological and psychiatric sequelae [37]. As for the other organs and systems, the most severe COVID-19 comorbidities and infectious conditions were positively associated with neurological sequelae [39]. In contrast, sex differences were evidenced by women developing more headaches, paresthesias, paresthesias, anosmia, disorientation, confusion, and sleep disorders, while men reported more frequent paresthesias, anosmia, disorientation, confusion, and sleep disorders [39].

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Table 4. Summary of literature mentioning neurological and psychiatric.

Author	Objetive	Type of Study	Participants	Results	Score
Rajaram.R et al. 2022	To present three cases of patients with COVID-19 who developed parkinsonism and responded to levodopa [41].	Case report	3 patients 1 case: 72-year-old male without comorbidities. 2 case: 66-year-old male with diagnoses of high blood pressure, diabetes mellitus and seizure disorder 3 male case of 74 years.	Parkinsonism	6
Mahmood. S et al. 2022	To describe a rare presentation of bilateral lower limb axonal mononeuropathies 2 weeks after recovery from COVID-19 pneumonia.[43].	Case report	1 61-year-old male patient with a history of diabetes mellitus and arterial hypertension.	Axonal mononeuropathies of the lower limbs.	8
Taquet. M et al. 2021	Provide robust estimates of the incidence rates and relative risks of neurological and psychiatric diagnoses in patients within 6 months of a COVID-19 diagnosis[37].	Cohort study	236 379 participantes 131 460 mujeres 104 015 hombres Edad media de 49 años Seguimiento de 6 meses tras la recuperación de la infección por COVID-19 .	2.44%Hemorragia intracraneal. 1.97% Accidente cerebrovascular isquémico. 1.42% Parkinsonismo. 2.33% Demencia. 1.48% Insomnio.	9
Mazza. M et al. 2020	To investigate the psychopathological impact of COVID-19 in survivors at one month of follow-up, also considering the effect of possible risk factors. [36].	Cohort study	402 participants 137 women 265 men Age 18-87 years Evaluation at 31.29 ± 15.7 after hospital discharge.	28% Post-traumatic stress disorder 31% Depression 42% Anxiety 40% Insomnia	7
Furlan. D et al. 2020	To investigate the occurrence of psychiatric and cognitive impairments in a cohort of survivors of moderate or severe forms of COVID-19 .[38].	Cohort study	425 participants 205 women 220 men Average age of 55 years Follow-up 6 to 9 months after recovery from COVID-19 infection.	8% Depression 15.5%Anxiety 13.6% Post-traumatic Stress Disorder	7
Romero. D et al. 2021	Identify and quantify the frequency and outcomes associated with the presence of sequelae or persistent symptoms during the 6 months after discharge for COVID-19 .[39].	Cohort study	797 participants 369 women 428 men Average age 63 years Follow-up 6 months after hospital discharge.	6.8% Anxiety 4.9% Sleep disturbance 4.4% Depression 7.2% Anosmia 3.4% Paresthesia	7
Mattioli. F et al. 2022	To compare neurological and cognitive functions at four months follow-up in	Cohort study	215 participants 135 women	Neurological deficits in 1.2% of patients not	7

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	patients with mild to moderate COVID-19 versus patients requiring ICU admission. [40].		80 men 52 in ICU 163 not admitted to the ICU Mean ICU age 60 years Mean non-ICU age 46.9 years Follow-up at 4 months after COVID-19 infection.	admitted to the ICU and 13.5% of those admitted to the ICU.	
Mattioli. F et al. 2021	To investigate the presence of focal neurological deficits as well as cognitive impairment in a group of patients with COVID-19 , who were examined 4 months after diagnosis. [42].	Cohort study	120 participants 90 women 20 men Age 26-65 years Follow-up 4 months after COVID-19 infection.	6.6% Insomnia 19.1% Anosmia 10.8% Ageusia 1.6% Tremor	9
Needham. E et al. 2020	Presentation of 11 cases of patients with COVID-19 who developed mononeuritis multiplex after being discharged from the ICU [44].	Case serie	11 patients 8 men 11 women Age 21-53 years.	Mononeuritis multiplex	10

3.2.5. Dermatological sequelae

We included eight studies in the dermatological section (Table 5). The most common affection reported was telogen effluvium, often reported between 1 to 3 months post infection [45–51]. Other clinical findings are low hair density and softer hair, which marks positive to the traction test, and empty follicles using trichoscopy and Trichogramma [45–51]. The least common hair-loss pattern was the bitemporal-frontal in 5.12% of cases, followed by front vertical in 7.69% and occipital in 12.82%; the most common pattern was the bitemporal and diffuse affection in 30.76% and 43.58%, respectively [46].

As telogen effluvium is the most common dermo-capillary complaint, it also is more often described by women. For example, Aksoy et al. observed that after COVID-19 recovery, 42.3% of women and 6.2% of men reported telogen effluvium[47]. Monari et al. reported similar proportions with 73.3% and 26.7% respectively [49]. A study including 204 patients observed that telogen effluvium developed in 57 patients, from which 31.7% had a hospitalization history and 24.3% were outpatients [47]. It is still unclear the physiopathological mechanism behind hair loss; however, a proinflammatory cascade with high levels of cytokines was postulated as the main reason, followed by the use of a multidrug regimen during the acute phase of COVID-19 [49, 52]. Anya. J et al. reported a case series of 100 patients who recovered from COVID-19, 143 to 258 days ago. The results revealed that 26% had a rash, 8% had blistering, 15% had high skin sensitivity, and 13% reported alopecia[53].

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Table 5. Summary of literature mentioning skin sequelae.

Author	Objetive	Type of Study	Participants	Results	Score
Arenas. C y Diaz. M 2021	Present 2 patients who presented telogen effluvium as a manifestation of post-COVID-19 syndrome[45].	Case report	2 cases First 56-year-old female case with no pathological history. Second case of a 16-year-old female with no pathological history.	Telogen effluvium	8
Sharquie. K and Jabbar.R 2021	Study the possible effects of COVID-19 on the hair growth cycle and the relationship between COVID-19 and acute telogen effluvium [46].	Cross-sectional study	39 patients 36 women 3 men Age 22-67 years Follow-up 2 to 3 months after COVID-19 infection.	Telogen effluvium	6
Anaya. J et al. 2021	Report a series of patients with post-Covid19 syndrome who attend a Post-COVID Unit and offer a comprehensive review on the subject [53].	Case series and comprehensive review	100 patients 53 women 47 men Age 37-58 years Follow-up at 143-258 days after COVID-19 infection	26% Rash 8% Ampoules 15% Skin sensitivity 13% Alopecia	10
Aksoy. H et al. 2021	To assess the incidence of telogen effluvium developed after COVID - 19 and the correlation between the development of telogen effluvium and the severity of the infection [47].	Cohort study	204 patients 123 women 81 men Mean age 47.23 ±16.471 years 3-month follow-up of positive PCR for COVID-19 .	27.9% Telogen effluvium	8
Rizzetto. G et al. 2020	To report three cases of telogen effluvium occurring after a severe infection by Sars-Cov-2 [48].	Case report	3 patients First female patient 62 years old, 3 months after recovery from infection. Second female case, 74 years old, 3 months after hospital discharge. Third female case, 58 years old, 3 months after hospital discharge.	Telogen effluvium	8
Otsuka. Y et al. 2022	To present the case of a patient with post-COVID-19 alopecia who improved and recovered almost to the level prior to infection [51].	Case report	1 64-year-old male patient Follow-up 1 month after hospital discharge.	Telogen effluvium	8
Rossi. A et al. 2021	Evaluate hair loss that occurs after SARS-CoV-2 infection using trichoscopy and trichogram to investigate possible patterns related to COVID-19 [50].	Case Serie	14 patients 12 women 3 men Age 23-64 years	Telogen effluvium	10

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			Follow-up from 1 to 3 after COVID-19 infection.		
Monari. P et al. 2022	To study the incidence of telogen effluvium after COVID-19 infection[49].	Cross-sectional study	96 patients 34 women 62 men Age 54 to 65 years Mean time of 68.43 days from COVID-19 infection to the onset of symptoms.	30% Telogen effluvium	8

4. Discussion

The arrival of the SARS-CoV-2 virus and the COVID-19 disease cause disease and deaths worldwide. This topic of global reach is not only relevant for the acute burden of the disease but for the long-term sequelae that have been reported[19, 31, 37, 39]. We still do not know which factors are associated with the appearance of long-COVID or post-acute sequelae; however, it is known that more severe infections, as well as younger age, could be conditions that favor its appearance[54]. COVID-19 has caused a significant burden on the overstretched health systems. COVID-19 comes with dramatic and severe sequelae (cardio-respiratory, neurological, and psychiatric conditions), urging us to prioritize its attention globally. The fact that the disease is more common in young and young adult populations and is primarily reported by women suggests that the impact of the disease will be more significant than expected. Considering the expense related to medical care and health care services, the low productivity of individuals due to chronic fatigue, over-the-counter medication abuse, and unnecessary out-of-pocket spending, the importance of long-COVID within our societies is predominant.

To improve our understanding of long-term-COVID-19 sequelae, it is recommended that future research be carried out globally in low and middle-income countries.

The greatest the number of studies, the greater our ability to counteract and prevent further impact. Although comorbidities have been linked to the natural history of COVID-19, very few studies have addressed this aspect. In a worldwide population, hypertension, obesity, diabetes, and other chronic illnesses such as asthma are becoming very common, as well as COVID-19, which does not seem to slow down in its transmission. A pandemic is not near an end, and younger populations are getting more and more infected. If we do not act rapidly, Long-COVID can take a toll more significantly than expected [27, 33, 43]. In this same context, another prevalent factor to consider is overweight and obesity. In these already affected and service-consuming populations, long-COVID is more frequent [26].Ethnicity must also be taken into account; Tachet et al. observed that Asian patients were more likely to suffer from intracranial hemorrhage problems, while African Americans were more affected by parkinsonism, and white participants had more cases of dementia and insomnia [37].

In addition, longer follow-up studies are suggested, this is supported by Pan et al. who observed that patients 1 year after overcoming the acute infection still presented alterations in lung imaging studies, opening the possibility of several sequelae of COVID-19 with a long duration (greater than 12 months) [22].

The evaluation of the quality of the studies showed that the manuscripts that evaluated the development of dermatological sequelae have weaknesses since of the 8 studies analyzed in this work, 5 corresponded to study designs with limited utility such as clinical cases and case series [45, 48, 50, 51, 53], on the other hand, regarding the study of renal sequelae, we consider that the available information is limited, since only 2 studies evaluated this aspect [19, 35]; When comparing the strengths and weaknesses of these studies, it can be seen that the study conducted by Bowe et al. it had 89,216 patients recovered from COVID-19 infection, considered a sufficient sample, but which only

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carried out a 30-day follow-up period; while the study by Huang et al. with a more limited sample of 1733 patients, a follow-up of 6 months after the acute infection was carried out. details that reveal the wide differences and limitations of the studies on sequelae of COVID-19 infection currently available.

This study had several limitations, among which is that some of the symptoms that have been evaluated so far are subjective, such as chest pain or the sensation of palpitations. In addition, when analyzing the studies, care must be taken due to the heterogeneity between the populations studied, marked mainly by important differences in the follow-up period. On the other hand, within the studies included in this investigation, no studies were found that have reported on the variant of the SARS-CoV-2 virus that affected the participants, limiting the possibility of associating this characteristic with the sequelae of the infection. acute, however, through the publication date and the follow-up period, it can be speculated that it will be variants such as Alpha, but the new variants that have emerged during the final stage of 2021 and 2022 must be considered, such as the Delta, Omicron or the XE, of which, as mentioned, no information was available in this regard.

5. Conclusions

Studies have shown that the main long-term sequelae produced by COVID-19 are those of pulmonary origin, especially fatigue and tiredness. In addition, the characteristics of the patients, such as being women, represented a higher incidence of sequelae, especially dermatological and psychiatric sequelae, likewise, several studies concluded that age, the presence of comorbidities, high BMI, and the severity of the acute COVID infection -19 predisposes to the appearance of sequelae of COVID-19. However, studies with more robust methodologies and longer follow-up periods are needed to better understand the behavior of the sequelae of acute COVID-19 infection.

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Supplementary Materials

Table S1: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Study	1	2	3	4	5	6	7	8	Score
Carvalho. S et al. 2021	*		*	*	*	*	*	*	7
Huang. Ch et al. 2021	*		*	*	**	*	*	*	8
Zhao. Y et al.2020	*		*	*	**	*	*	*	8
Compagnone. N et al. 2019	*		*	*	*	*	*	*	7
Pan. F et al. 2021	*		*	*	**	*	*	*	8
Goërtz. Y et al. 2020	*		*	*	**	*	*	*	8
Walsh. M et al. 2020	*		*	*	*	*	*	*	7
Kamal. M et al. 2020	*		*	*	*	*	*	*	7
Puntmann. V et al. 2020	*		*	*	*	*	*	*	7
Wang. X et al. 2020	*		*	*	*	*	*	*	7
Xiong. Q et al. 2021	*		*	*	*	*	*	*	7
Huang. L et al. 2020	*		*	*	*	*	*	*	7
Bowe. B et al. 2021	*	*	*	*	**	*	*	*	9
Taquet. M et al. 2021	*	*	*	*	**	*	*	*	9
Mazza. M et al. 2020	*		*	*	*	*	*	*	7
Romero. D et al. 2021	*		*	*	*	*	*	*	7
Mattioli. F et al. 2021	*	*	*	*	**	*	*	*	9
Furlan. D et al. 2020	*		*	*	*	*	*	*	7
Mattioli. F et al. 2022	*		*	*	*	*	*	*	7
Aksoy. H et al. 2021	*		*	*	**	*	*	*	8

Note: A study can receive a maximum of one star for each item numbered within the Selection and Result categories. A maximum of two stars can be awarded for comparability.

Selection

1. Representativeness of the exposed court.
2. Selection of the unexposed court.
3. Exposure determination.
4. Demonstration that the current outcome of interest was not present at baseline.

Comparability

5. Cohort comparability based on design or analysis.

Results

6. Evaluation of the result.
7. Was the follow-up long enough for the results to occur?
8. Adequacy of cohort follow-up.

Interpretation

Good quality: 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.

Acceptable quality: 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.

Poor quality: 0 or 1 star in the selection domain or 0 stars in the comparability domain or 0 or 1 stars In the outcome/exposure domain

Table S2: JBI Critical Appraisal Checklist for Case Reports

Study	1	2	3	4	5	6	7	8	Score
Rajaram. R et al. 2022	YES	YES	YES	YES	YES	NO	NO	YES	6
Mahmood. S et al. 2022	YES	YES	YES	YES	YES	YES	YES	YES	8
Arenas. C y Diaz. M 2021	YES	YES	YES	YES	YES	YES	YES	YES	8
Rizzetto. G et al. 2020	YES	YES	YES	YES	YES	YES	YES	YES	8
Otsuka. Y et al. 2022	YES	YES	YES	YES	YES	YES	YES	YES	8

1. Were patient demographics clearly described?
2. Was the patient's history clearly described and presented as a timeline?

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3. Was the patient's current clinical condition clearly described at the time of presentation?
4. Were diagnostic tests or evaluation methods and results clearly described?
5. Were interventions or treatment procedures clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse (harm) or unforeseen events identified and described?
8. Does the case report provide lessons to take away?

Table S3: JBI Critical Appraisal Checklist for Case Series

Study	1	2	3	4	5	6	7	8	9	10	Score
Needham. E et al. 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	10
Anaya. J et al. 2021	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	10
Rossi. A et al. 2021	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	10

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard and reliable way for all participants included in the case series?
3. Were valid methods of condition identification used for all participants included in the case series?
4. Did the case series include consecutive participants?
5. Did the case series have complete inclusion of participants?
6. Were there clear reports on the demographics of the study participants?
7. Was there a clear reporting of the clinical information of the participants?
8. Were outcomes or case follow-up results clearly reported?
9. Was there clear reporting of demographic information from the presenting sites/clinics?
10. Was the statistical analysis appropriate?

Table S4: JBI critical appraisal checklist for analytical cross-sectional studies

Study	1	2	3	4	5	6	7	8	Score
Halpin. S et al. 2020	YES	YES	YES	NO	NO	NO	YES	YES	5
Iqbal. A et al.2021	YES	YES	YES	YES	NO	NO	YES	YES	6
Sharquie. K y Jabbar. R 2021	YES	YES	YES	YES	NO	NO	YES	YES	6
Monari. P et al. 2022	YES	YES	YES	YES	YES	YES	YES	YES	8

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were standard and objective criteria used to measure the condition?
5. Were confounding factors identified?
6. Were strategies established to deal with confounding factors?
7. Were the outcomes measured in a valid and reliable way?
8. Was an appropriate statistical analysis used?