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High-resolution chest CT outcomes in post-acute critical and severe COVID-19 pneumonia patients: a systematic review.

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High-resolution chest CT outcomes in post-acute critical and severe COVID-19 pneumonia patients: a systematic review.

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DEDICATORIA

Dedico este trabajo a mis padres Felipe y Nancy, a mi hijo Esteban José, a Rebecca, a mis hermanos y sobrinos, por ser el motor que me impulsó a lograr con este objetivo tan importante dentro de mi vida profesional.

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RESUMEN

ANTECEDENTES: La neumonía por COVID-19 ha mostrado dejar secuelas orgánicas hasta en un 35% de los pacientes recuperados post síndrome de distrés respiratorio agudo (ARDS) por neumonía severa, donde se ha observado que factores como la ventilación mecánica invasiva prolongada, puede jugar un rol importante en el desarrollo de fibrosis pulmonar en controles tomográficos posteriores. OBJETIVO: Describir los hallazgos de tomografía computada de alta resolución del tórax en pacientes de seguimiento que cursaron con neumonía por COVID-19 con grado de afección severa, que recibieron ventilación mecánica invasiva/ no invasiva, admitidos a unidades de cuidados intensivos y correlacionar con grados de fibrosis. MÉTODOS : Se utilizaron bases de datos de Medline vía PubMed y Scopus vía Scopus para la obtención de los artículos, mediante el uso de términos de búsqueda específicos. Se determinaron los criterios de exclusión que fueron aplicados en un primer proceso de selección (screening). En un segundo screening, se realizó una revisión de texto completo. Todo el proceso se registró en el diagrama PRISMA. Con el número final de artículos se realizó la extracción de los datos. RESULTADOS: Se incluyeron 15 artículos, donde se realizaron controles tomográficos en períodos entre 3 a 12 meses, observándose que el sexo masculino, los tiempos prolongados de ventilación mecánica invasiva y algunas comorbilidades predisponen al desarrollo de fibrosis pulmonar en dichos períodos de tiempo.

Palabras clave: Covid-19, adultos, secuelas post neumonía por Covid-19, tomografía computada del tórax/TACAR.

ABSTRACT

BACKGROUND: COVID-19 pneumonia has shown to leave organic sequalae in up to a 35% of severe pneumonia and post-acute respiratory distress syndrome (ARDS) recovered patients, where factors such as prolonged invasive mechanical ventilation can play an important role in the development of pulmonary fibrosis in subsequent tomographic controls. OBJECTIVE: To correlate fibrosis degree with the high-resolution chest CT outcomes in follow-up patients with severe COVID-19 associated pneumonia that received invasive/non-invasive mechanical ventilation and were admitted to ICUs.

METHODS: Medline/PubMed and Scopus/Scopus databases were used to obtain the selected articles by employing specific search terms. Exclusion criteria was determined and applied in a first screening. In a second screening, a full-text review was executed. All the process was registered on the PRISMA diagram. Data extraction was performed from the final number of articles. RESULTS: 15 articles were included, where tomographic controls were carried out in periods between 3 to 12 months, observing that sex (males), prolonged times of invasive mechanical ventilation and some comorbidities predispose to the development of pulmonary fibrosis in said periods of time.

Keywords: Covid-19, post-acute, adult, post-acute COVID-19 syndrome and Chest CT/ HRCT.

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INTRODUCTION

On December 2019, in Wuhan China, a novel SARS-CoV-2 responsible for COVID-19 began spreading worldwide. This event caused a global pandemic and a concerning public health emergency [7].

The SARS-CoV-2 virus can clinically manifest in a versatile way, in which respiratory condition cases are the most frequent, where most of the infected patients had been asymptomatic or have had mild symptoms and a favorable prognosis. However, the SARS-CoV-2 virus can induce to critical illness with accelerated progression in a relevant proportion of hospitalized patients. Consequently, this results in acute respiratory distress syndrome (ARDS), which has conducted a significant number of patients to intensive care units, and therefore, to the collapse of sanitary systems in numerous countries, which have led to the death of millions of patients around the globe [7].

Pneumonia cases are generally considered severe if there is severe respiratory distress, the respiratory frequency is >30 respirations per minute, or oxygen saturation is < 90% while resting, whereas critical pneumonia cases are presented as respiratory insufficiency that requires mechanical ventilation [1].

After acute illness, numerous patients have presented organic deterioration, persistent and residual symptoms. This outcome has been denominated as “long Covid” in order to identify patients with these sequalae. Current evidence shows that the most frequent and persistent symptoms include fatigue, dyspnea, chest pain and coughing. Likewise, these patients tend to present functional respiratory deterioration, even months after the initial disease, as a consequence of capillary and diffuse alveolar damage, hyaline membrane formation, septal fibrous alveolar proliferation and pulmonary consolidation [2].

Current studies show that between 19 up to 35% of patients that recovered from severe illness can present fibrotic outcomes up to 6 months after acute illness. However, L. Gamberini

(2021) that drove his study with a low percentage of subsequent tomographic controls (37 – 21%), found that 70% of patients showed fibrotic sequalae in controls performed between 6-12 months. In this sense, computed tomography is a crucial tool for the diagnosis and monitoring of COVID-19 pneumonia patients (X. Han; 2021).

Taking into consideration the number and percentage of patients with subsequent tomographic controls, the purpose of this systemic review is to assess the correlation between the pulmonary fibrosis development with the aftermath of chest CT outcomes in patients that went through severe disease, needed invasive/non invasive mechanical ventilation or were admitted in ICUs.

METHODS

This systematic review followed the recommendations of PRISMA guidelines. In order to develop the research question (**Table 1**), PICOS framework was established. For article recompilation, we used MEDLINE/PubMed and SCOPUS/SCOPUS bibliographic databases in the years 2021 and 2022. The original languages of the articles were not dismissed, and English represented the main language in the vast majority of articles. The search strategies were adapted to the parameters within the research question. The employed keywords were: "Covid-19", "post-acute", "adult", "post-acute COVID-19 syndrome" and "Chest CT/ HRCT". Search criteria are shown in **Table 2** for PubMed and in **Table 3** for Scopus.

Table 1. PICOS

Item	Definition
Population	Post SARS-CoV2 pneumonia adults
Interventions	Does not apply
Comparisons	Does not apply
Outcomes	Tomographic sequelae
Study type	Observational, prospective and retrospective cohorts, cross-sectional and case control studies with post-acute tomographic follow-up

Eligibility criteria (**Table 4)** was stablished for title review and posterior full-article review. In the first step of the selection process, titles and abstracts were reviewed from all the articles found with the search strategy. In a second step, after careful selection of relevant studies, we executed a full-text review of the papers that filled the inclusion criteria, and excluded patients that showed mild/moderate tomographic severity scores, and those with subsequent tomographic follow-ups three months or less after the acute infection.

From the mentioned process, fifteen studies were included in this investigation (**Table 5).**

Table 2. PubMed research strategy

SEARCH DATE: 22/02/2022		**PUBMED**	
Items	*#*	*Search terms*	*Number of citations*
Population_COVID-19	#1	COVID-19[MeSH] OR SARS-CoV-2[MeSH] OR coronavirus[MeSH]	155.269
	#2	"COVID-19"[TIAB] OR COVID19[TIAB] OR SARSCOV2[TIAB] OR "2019-nCoV"[TIAB] OR "Coronavirus Disease-19"[TIAB] OR "2019 Novel Coronavirus Disease"[TIAB] OR "SARS Coronavirus 2 Infection"[TIAB] OR "SARS-CoV-2"[TIAB] OR "COVID-19 Pandemic"[TIAB]	215.199
	#3	#1 OR #2	237.372
Population_Post-acute	#4	"Subacute Care"[MeSH]	1.313
	#5	post-acute[TIAB] OR postacute[TIAB] OR complicatio*[TIAB] OR sequelae[TIAB] OR "long-haul"[TIAB] OR chronic[TIAB] OR sequel[TIAB] OR sequels[TIAB] OR persistent[TIAB]	2,551,139
	#6	#4 OR #5	2,551,788
Population_Adult	#7	Adult[Mesh]	7.735.971
	#8	Adul*[TIAB] OR "Aged"[TIAB] OR "Middle Age"[TIAB] OR "middle aged"[TIAB]	1,946,804
	#9	#7 OR #8	8.659.994
Population_Post-acute COVID-19	#10	"post-acute COVID-19 syndrome"[Supplementary Concept] OR ("COVID-19"[Mesh] AND complications[Subheading]) OR "COVID-19 sequelae"[TIAB] OR "Postacute Sequelae of SARS-CoV-2 Infection"[TIAB] OR "post-acute COVID-19 syndrome" [TIAB] OR "long-COVID"[TIAB] OR "long-haul COVID"[TIAB] OR "persistent COVID-19"[TIAB] OR "chronic COVID syndrome"[TIAB] OR "COVID-19 sequelae"[TIAB]	16,624
Population_Total	#11	(#3 AND #6 AND #9) OR #10	21,928
Outcomes_Chest CT follow up findings	#12	"Tomography, X-Ray Computed"[Mesh] OR "Multidetector Computed Tomography"[Mesh] OR "Diagnostic imaging"[MeSH]	2,815,844
	#13	"Chest CT" [TIAB] OR HRCT[TIAB] OR "Computed tomography"[TIAB] OR "computed tomographies"[TIAB]	300,091
	#14	#12 OR #13	2.922.705
Total	#15	#11 AND #14	2.414

PubMed research terms used to identify reliable citations on the platform.

Table 3. Scopus research strategy

SEARCH DATE: 22/02/2022		**SCOPUS**	
Items	*#*	*Search terms*	*Number of citations*
Population_COVID-19	#1	TITLE-ABS-KEY ("COVID-19" OR "COVID19" OR "SARSCOV2" OR "2019-nCoV" OR "Coronavirus Disease-19" OR "2019 Novel Coronavirus Disease" OR "SARS Coronavirus 2 Infection" OR "SARS-CoV-2" OR "COVID-19 Pandemic")	
Population_Post-acute	#2	TITLE-ABS-KEY ("post-acute" OR postacute OR complicatio* OR sequelae OR "long-haul" OR chronic OR sequel OR sequels OR persistent)	
Population_Adult	#3	TITLE-ABS-KEY (adul* OR aged OR "middle Age" OR "middle aged")	
Population_Post-acute COVID-19	#4	TITLE-ABS-KEY ("post-acute COVID-19 syndrome" OR "COVID-19 sequelae" OR "Postacute Sequelae of SARS-CoV-2 Infection" OR "post-acute COVID-19 syndrome" OR "long-COVID" OR "long-haul COVID" OR "persistent COVID-19" OR "chronic COVID syndrome" OR "COVID-19 sequelae")	
Outcomes Chest CT follow up findings	#5	TITLE-ABS-KEY ("Chest CT" OR HRCT OR "Computed tomography" OR "computed tomographies")	
Total	#6	((#1 AND #2 AND #3) OR #4) AND #5	2209

Scopus research terms used to identify reliable citations on the platform.

Data extraction from each article was based on the parameters of interests and desired objectives. An Excel spreadsheet included the following criteria: type of study (prospective/retrospective and observational/experimental), total number of subjects, average age, sex, number and percentage of follow-up scans, tomographic findings (normal/resolution of previous tomographic findings, residual/ abnormal tomographic findings, ground-glass opacities, general fibrotic changes), follow-up studies of patients under invasive or non-invasive mechanical ventilation and ICU/non-ICU patients, comorbidities, and tomographic follow-up times.

Table 4. Eligibility criteria

Category	Exclusion criteria	Notes
1. Null entries, duplicates, abstract is reported elsewhere and not in the time period of interest	01 - Null entries	
	02 - Duplicates	
	03 - Abstract that is reported elsewhere	
2 - Nature of study	11 - Not the study type of interest:	Case reports, case series, editorials, clinical guides, expert recommendations, reviews, literature Review. Includes prospective and retrospective cohort studies, cross-sectional, case control studies systematic reviews.
3 - Population	22 - Not COVID-19 pneumonia patients	
	31 - Not post-acute patients with Severe Covid-19 pneumonia or ICU patients exclusively	
	41 - Not adult population	
4. Outcomes	51 - Not including Chest CT follow-up	
5 - Potential	61 - Potential (no exclusion criteria applicable)	

Table 4. reports the eligibility criteria to select the citations during the screening and full text review.

Results

This systematic review compiles data of various studies about tomographic outcomes in post-pneumonia adult patients caused by severe or critical COVID-19, that required invasive/non-invasive mechanical ventilation and/or ICU admission. The search started on the 23rd of February 2022, where a total of 4623 studies were obtained. The selection process is resumed on the PRISMA table (**Figure 1)**.

A total of 3203 papers resulted from the first screening, where title and abstract were reviewed and 55 of them were taken for a full-text review. In a second screening, forty studies that included COVID-19 post-pneumonia tomographic follow-up with mild and moderate severity scores and studies undertaken under 3 months were discarded. Finally, a total of fifteen studies were scrutinized for this systematic review.

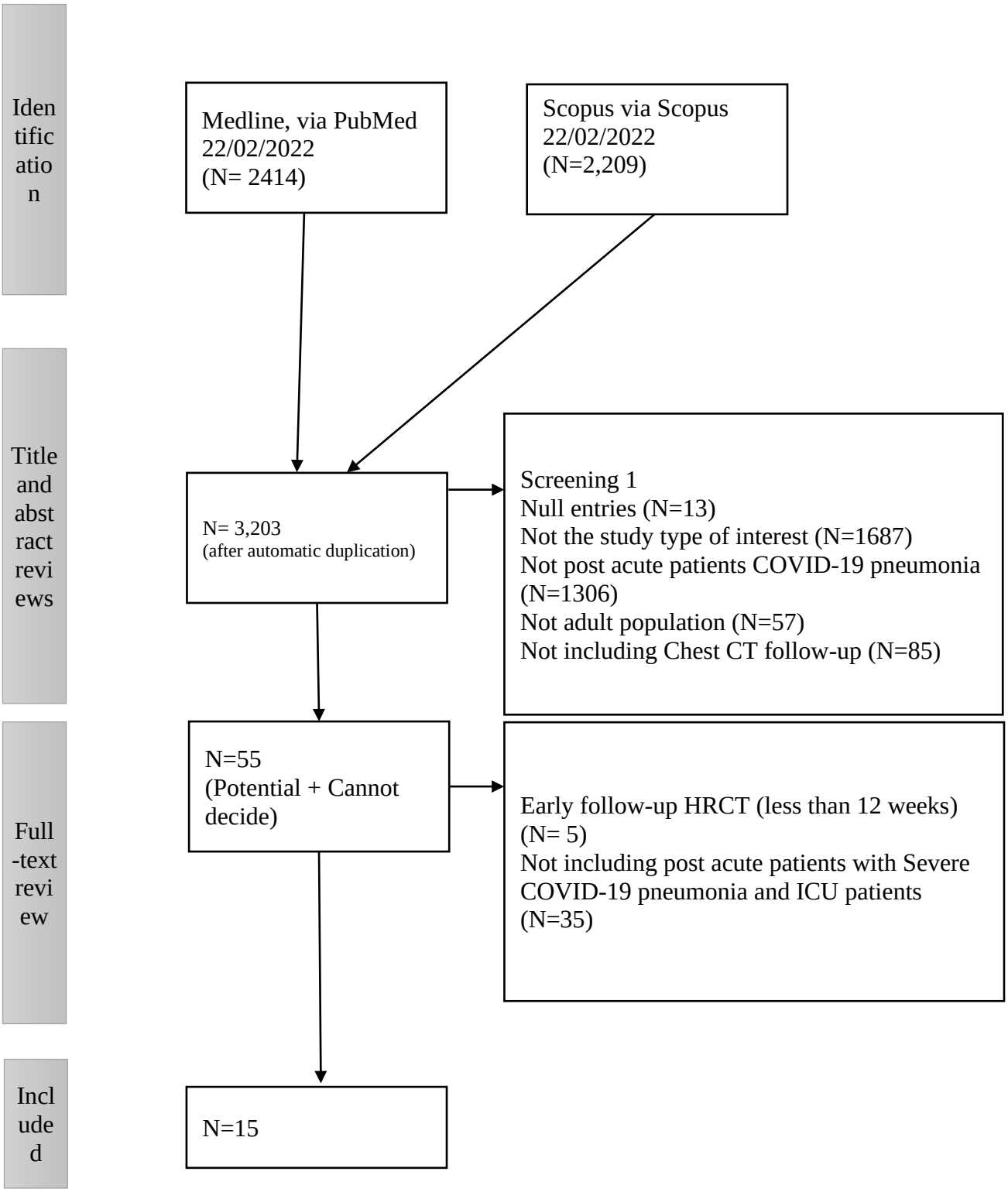
Table 5. Studies included in the systematic review.

Author	Title	Journal	Publication year
M. Baldini et al.	Evaluation of the pulmonary function of patients with severe coronavirus 2019 disease three months after diagnosis	Medicina (Argentina)	2021
D. Giordano et al.	Long-term sequelae are highly prevalent one year after hospitalization for severe COVID-19	Scientific Reports	2021
N. Compagnone et al.	Residual lung damage following ARDS in COVID-19 ICU survivors	Acta Anaesthesiologica Scandinavica	2022
S. Farghaly et al.	Clinical characteristics and outcomes of post-COVID-19 pulmonary fibrosis A case-control study	Medicine (United States)	2022
A. Froidure et al.	Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae	Respiratory Medicine	2021
L. Gamberini et al.	Health-related quality of life profiles, trajectories, persistent symptoms and pulmonary function one year after ICU discharge in invasively ventilated COVID-19 patients, a prospective follow-up study	Respiratory Medicine	2021
J. González et al.	Pulmonary Function and Radiologic Features in Survivors of Critical COVID-19: A 3-Month Prospective Cohort	Chest	2021
X. Han et al.	Six-month follow-up chest CT findings after severe COVID-19 pneumonia	Radiology	2021
G. Hanna et al.	The role of ventilatory support for long-term outcomes after critical infection with COVID-19: A prospective cohort study	Clinical Respiratory Journal	2022

Author	Title	Journal	Publication year
C. Huang et al.	6-month consequences of COVID-19 in patients discharged from hospital: a cohort study	The Lancet	2021
S. Mihaela et al.	Ninety-day outcome of patients with severe COVID-19 treated with tocilizumab - a single centre cohort study	Swiss Medical Weekly	2021
L. Morin et al.	Four-Month Clinical Status of a Cohort of Patients after Hospitalization for COVID-19	JAMA - Journal of the American Medical Association	2021
R. C. Robey et al.	Pulmonary Sequelae at 4 Months After COVID-19 Infection: A Single-Centre Experience of a COVID Follow-Up Service	Advances in Therapy	2021
X. Wu et al.	3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalization: a prospective study	The Lancet Respiratory Medicine	2021
M. Zhou et al	Changes in glomerular filtration rate and metabolomic differences in severely ill coronavirus disease survivors 3 months after discharge	Biochimica et Biophysica Acta - Molecular Basis of Disease	2022

Table 5. shows the studies that were included in this systematic review.

Figure 1. PRISMA diagram



The analyzed studies were entirely observational, where most of them were prospective (8 out of 15), non-specified (4 out 15), and retrospective (3 out of 15). The greater part were cohort studies (10 out of 15), one case control study, one transversal and one observational pilot study. Multiple statistical tests with p= <0.05 values were employed. All of the studies were undertaken between 2021 and 2022.

Selected papers were executed in follow-up periods between 3 and 12 months, where a high-resolution chest computed tomography was not available in all the included patients on each study due to various circumstances like: death, subsequent controls in other health centers, failure reaching out the patients, or refusal to participate in the studies. Articles clustered patients in different groups depending on the needs of the research. For example, C. Huang et al. performed tomographic controls to less than a quarter of the population study, but included an important number of patients (390/1733 – 22%) that were selected based on scales that included: patients who needed or not supplementary oxygen and patients that required high flow nasal cannulas or invasive/non-invasive mechanical ventilation. In several studies, patients were grouped according to their lung compromise. In contrast, Giordano, D. et al. performed tomographic controls on most patients (190 – 95%). Most of the studies included initial tomographic studies for comparative purposes and some of them made various subsequent controls as seen in X. Wu et al., where controls were performed after 3, 6, 9 and 12 months after the acute infection.

Generally, studies included adult patients where average ages ranged between 54 and 64 years. In all the studies, males ranged from 52% to 90% of the population, excluding M. Zhou et al. (**Table 6**).

Table 6. Average Age and Sex according to the studies

Author	Mean Age (years)	Male N°	Male %	Female N°	Female %
M. Baldini et al.	54	40	73%	15	27%
D. Giordano et al.	62	122	61%	78	39%
N. Compagnone et al.	58	44	90%	5	10%
S. Farghaly et al.	59	46	72%	18	28%
A. Froidure et al.	60	79	59%	NR	NR
L. Gamberini et al.	64	129.	73%	NR	NR
J. González et al.	60	46	74.2%	16.	25,80%
X. Han et al.	54	80	70%	34	30%
G. Hanna et al.	59	64	76%	NR	NR
C. Huang et al.	57	897	52%	836	48%
S. Mihaela et al.	60	42	84%	8	16%
L. Morin et al.	57	109	61,60%	68	38,40%
R. C. Robey et al.	58	135	61%	86	39%
X. Wu et al.	59	47	57%	36	43%
M. Zhou et al	61	40	44%	NR	NR

Table 6. shows the mean age, number and percentage of patients according to sex

In order to avoid influencing the factors under investigation, X. Wu et al. monitored patients with severe pneumonia without comorbidities and without the need of invasive mechanical ventilation. The rest of studies included patients with comorbidities, where arterial hypertension was generally the main comorbidity, followed by diabetes mellitus, obesity and heart-related diseases shown in **Table 7**. S. Farghaly et al. showed that mortality doubled in patients with previous pulmonary fibrosis and asthma in comparison to those that presented other comorbidities like diabetes and hypertension. Some studies included smoking as one of the research variables. In L. Morin et al., a high percentage of non-smokers (75,9%), former smokers (18,4%) and a low percentage of smokers (5,8%) was found. Globally, most of the patients in the selected studies reported more than one comorbidity.

Table 7. Comorbidities found in the studies

Author	Comorbidities notes
M. Baldini et al.	Obesity 37 (67%), Arterial hypertension 20 (36%), Diabetes Mellitus 19 (35%), Smoking 16 (29%), Asthma 4 (7%), Coronary disease 3 (5%), Cardiac insufficiency 2 (4%), Hypothyroidism 2 (4%), COPD 1 (2%), Crohn´s disease 1 (2%), Psoriasis 1 (2%), Rheumatoid arthritis 1 (2%), Sjogren disease 1 (2%), Fibromyalgia 1 (2%), Hepatitis C 1 (2%), Chronic renal failure 1 (2%), Active oncological disease 1 (2%), Renal tubular acidosis type-1 1 (2%)
D. Giordano et al.	Arterial hypertension 82 (41%), Diabetes 31 (15.5%), Dyslipidemia 18 (9%), COPD 12 (6%), Obesity 22 (11%), IBD 4 (2%), Chronic liver disease 7 (3.6%), Autoimmune disease 3 (1.5%), Hematological disease 13 (6.5%), Coronary artery disease 18 (9%), Atrial fibrillation 13 (6.5%), Other structural heart disease 3 (1.5%), Other arrhythmogenic heart disease 6 (3%), Endocrinological disease 22 (11%), CKD 12 (6%), Stroke/TIA 5 (2.5%), VTE 4 (2%), Anxiety and depression 8 (4%), Active malignancy 18 (9%)
N. Compagnone et al.	Arterial hypertension (40%), Diabetes mellitus (10%).
S. Farghaly et al.	Arterial hypertension (66%), diabetes mellitus (66%), obesity (42%), asthma (15%), heart disease (10%), kidney disease (3%), tuberculosis (2%), chronic obstructive pulmonary disease (2%).
A. Froidure et al.	Overweight, 84 (63%), obesity 37 (28%), diabetes 29 (22%), hypercholesterolemia 56 (42%) Arterial hypertension 63 (47%). Thirty patients (22%) were current or former smokers and 25 (19%) suffered from a confirmed chronic respiratory condition, namely asthma (N = 12), chronic obstructive pulmonary disease (COPD) with or without emphysema (N = 5), lung cancer (N = 3), interstitial lung disease (N = 2), chronic pulmonary embolism (N = 2) and cystic fibrosis (N = 1)
L. Gamberini et al.	Hypertension: 88 (49.4%), Chronic ischemic heart disease: 13 (7.3%), Chronic kidney disease: 6 (3.4%), COPD: 13 (7.3%)
J. González et al.	Arterial hypertension 37,1%, diabetes mellitus 15,5%, chronic heart disease 9,7%, asthma 4,8%, COPD 4.8%,
X. Han et al.	Diabetes 13 (11%), Hypertension 32 (28%), chronic pulmonary disease 16 (14%)
G. Hanna et al.	Diabetes 15 (17%), Hypertension 38 (44%), Cardiovascular disease 5 (6%), Chronic lung disease 16 (19%), Ever smoker 34 (40%)
C. Huang et al.	Hypertension 505 (29%), Diabetes 207 (12%), Cardiovascular diseases 128/1732 (7%), Cerebrovascular diseases 47/1732 (3%), Malignant tumor 44 (3%), Chronic obstructive pulmonary disorder 31 (2%), Chronic kidney disease 27 (2%)

Author	Comorbilities notes
S. Mihaela et al.	Hypertension 32 (64%), Diabetes 11 (22%), Chronic lung disease 6 (12%), Bronchial asthma 4 (8%), Ichaemic heart disease 10 (20%), Chronic kidney disease 6 (12%), autoinmune disease 2 (4%)
L. Morin et al.	Hypertension 225 (47.1%), Obesity 130 (37%), Diabetes mellitus 128 (26.8%), Chronic heart disease 77 (16.1%), Respiratory disease (other than COPD) 75 (15.7%), Chronic kidney disease 51 (10.7%), Declared psychiatric disorder 42 (8.8%), Neurodegenerative disorder 34 (7.1%), Alcohol abuse, 21 (4.7%), Active cancer 18 (3.8%), Other immunosuppression 18 (3.8%), COPD 17 (3.6%), Chronic dialysis 17 (3.6%), HIV infection 12 (2.5%), Solid organ transplantation 9 (1.9%), Liver disease 7 (1.5%), Pregnancy 5 (1.1%), Bone marrow transplantation 2 (0.4%)
R. C. Robey et al.	Hypertension 74 (33%), asthma 43 (19%), diabetes mellitus 36 (16%), chronic obstructive pulmonary disease 19 (9%) cardiovascular disease 19 (9%).
X. Wu et al.	Study excluded patients with previous comorbidities
M. Zhou et al	Hypertension 30 (33.7%), Diabetes 19 (21.3%), Coronary heart disease 9 (10.1%), Cerebrovascular disease 4 (4.5%), Malignancy 3 (3.4%), Liver disease 8 (9.0%)

Table 7 list of comorbidities found in the included studies.

Within the subsequent tomographic controls, the percentages of patients with normal CT outcomes or complete CT resolution of the initial findings ranged between 10% and 40%, whereas those with abnormal or residual CT outcomes ranged between 60% and 90%. Two prevailing patterns were identified within the follow-up abnormal tomographic outcomes: residual ground glass opacities and general fibrotic changes (which includes reticulations, bronchiectasis and honeycombing). Residual ground glass opacity pattern was mainly observed, and ranged between 23% to 91%, whereas the fibrotic pattern was found in minor percentages that ranged between 19% and 35% of the follow-up patients. However, a single study (L. Gamberini et al) which included a low percentage of follow-ups at 6 and 12 months (37 patients of 178), showed that up to a 70% (26/37) of patients presented fibrotic residual outcomes (**Table 8)**.

Author	Normal (no findings/ complete radiologic resolution) N°	Normal (no findings/ complete radiologic resolution) %	Abrnormal CT scan/Residual Findings N°	Abnormal Ct scan/Residual Findings %	GGO N°	GGO %	General fibrotic Changes N°	General Fibrotic Changes %
M. Baldini et al.	6	10%	NR	90%	40	82%	NR	NR
D. Giordano et al.	NR	NR	NR	NR	NR	NR	NR	NR
N. Compagnone et al.	17	NR	25.	NR	NR	NR	12	28%
S. Farghaly et al.	NR	NR	NR	NR	NR	91%	NR	25%
A. Froidure et al.	30.	33%	NR	NR	73	67%	22	20%
L. Gamberini et al.	NR	NR	NR	NR	15	40%	26	70%
J. González et al.	17	29,80%	NR	NR	34	59,60%	12	21,10%
X. Han et al.	43	38%	NR	NR	71	62%	40	35%
G. Hanna et al.	22/86	26%	64/86	74%	NR	NR	NR	NR
C. Huang et al.	NR	NR	NR	NR	Scale 3: not requiring supplemental oxygen 39, Scale 4: requiring supplemental oxygen 78, Scale 5–6: requiring HFNC, NIV, or IMV: 41	Scale 3: not requiring supplemental oxygen 41%, Scale 4: requiring supplemental oxygen 48%, Scale 5–6: requiring HFNC, NIV, or IMV 45%	NR	NR
S. Mihaela et al.	14	40%	21.	60%	NR	NR	7	33%
L. Morin et al.	NR	NR	108	63%	72	42,20%	33	19,40%
R. C. Robey et al.	25	35%	47	65%	32	44%	15	21%
X. Wu et al.	63	NR	20	NR	19	23%	NR	NR
M. Zhou et al	NR	NR	NR	NR	NR	NR	NR	NR

Table 8. *High resolution Chest CT findings at follow up. (GGO – ground glass opacities. NR – nor reported)*

Generally, it was seen that mechanical ventilation itself or its prolonged use could influence in the development of medium-term fibrotic sequalae; however, X. Wu et al. showed that although its use, as well as the associated comorbidities, are not exclusive from this type of patients. G. Hanna et al. compared patients with high flux nasal oxygen with patients under invasive mechanical ventilation (IMV), and demonstrated that IMV influences in the decrease of the total lung capacity (92% vs 84% respectively) along with a higher probability of developing pulmonary function alterations in comparison to patients that where managed with high flux nasal oxygen. The relationship between fibrotic sequalae with the type of ventilation during hospitalization and patients in ICUs is shown in **Table 9.**

Table 9. Fibrotic-type sequelae and its relation with ventilation during hospitalization

Author	General fibrotic Changes N°	General Fibrotic Changes %	N° Invasive Mechanichal ventilation	% Invasive Mechanichal ventilation	N° Non IMV	% Non IMV	N° ICU PATIENTS	% ICU PATIENTS	N° NON-ICU PATIENTS	% NON-ICU PATIENTS
M. Baldini et al.	NR	NR	25(55)	45%	30	55%	NR	NR	NR	NR
D. Giordano et al.	NR	NR	18	9%	No supplementation 59. Nasal cannulae or venturi mask 82. Non-invasive ventilation 41.	No supplementation 29.5% Nasal cannulae or venturi mask 41% Non-invasive ventilation 20.5%	23	11,50%	NR	NR
N. Compagnone et al.	12	28%	49	100%	NA	NA	49	100%	NA	NA
S. Farghaly et al.	NR	25%	40	63%	14	22%	52.	81%	12.	19%
A. Froidure et al.	22	20%	15	NR	NR	NR	30	22%	NR	NR
L. Gamberini et al.	26	70%	178	100%	NA	NA	178.	100%	NA	NA
J. González et al.	12	21,10%	39	62,90%	30	49,20%	62	100%	NA	NA
X. Han et al.	40	35%	NR	NR	NR	NR	NR	NR	NR	NR
G. Hanna et al.	NR	NR	53/86	NR	33/86	NR	86	100%	NA	NA

Author	General fibrotic Changes N°	General Fibrotic Changes %	N° Invasive Mechanichal ventilation	% Invasive Mechanichal ventilation	N° Non IMV	% Non IMV	N° ICU PATIENTS	% ICU PATIENTS	N° NON-ICU PATIENTS	% NON-ICU PATIENTS
C. Huang et al.	NR	NR	10	1%	Admitted to hospital, requiring supplemental oxygen 1172 Admitted to hospital, requiring HFNC or non-IMV or both 112	Admitted to hospital, requiring supplemental oxygen 68% Admitted to hospital, requiring HFNC or non-IMV or both 6%	76.	4%	NR	NR
S. Mihaela et al.	7	33%	24	NR	24	NR	26	52%	24	48%
L. Morin et al.	33	19,40%	73	NR	405	NR	142	NR	336	NR
R. C. Robey et al.	15	21%	NR	NR	NR	NR	37/44	84%	35/38	92%
X. Wu et al.	NR	NR	NA	NA	83	100%	NA	NA	83	100%
M. Zhou et al	NR	NR	4	4,50%	85	95,50%	NR	NR	NR	NR

Table 9. Fibrotic like changes, patients who underwent IMV/non IMV and patients admitted to ICU. (HFNC – High flow nasal canula, IMV – invasive mechanical ventilation. ICU – intensive care unit. NR – nor reported, NA – Not applicable)

Most of the studies showed that factors like advanced age, acute respiratory distress syndrome development and basal chest CT studies with severe CT scores (≥18/25) are strongly related to the development of fibrotic changes. S. Farghaly et al. associated males as a risk factor for fibrotic sequalae (72% M vs 28% F) as well as X. Han et al. who presented similar findings (70% M vs 30% F). (**Table 10)**. Alternative outcomes observed in all the studies was the alteration of diffusing capacity of the lungs for carbon monoxide (DLCO). X. Han et al. presented a strong association between CT scores ≥ 18 and a more severe pulmonary sequalae in survivors as well as higher mortality rates.

Table 10. Male population and fibrotic-like changes.

Author	Male N°	Male %	General fibrotic Changes N°	General Fibrotic Changes %
M. Baldini et al.	40	73%	NR	NR
D. Giordano et al.	122	61%	NR	NR
N. Compagnone et al.	44	90%	12	28%
S. Farghaly et al.	46	72%	NR	25%
A. Froidure et al.	79	59%	22	20%
L. Gamberini et al.	129.	73%	26	70%
J. González et al.	46	74.2%	12	21,10%
X. Han et al.	80	70%	40	35%
G. Hanna et al.	64	76%	NR	NR
C. Huang et al.	897	52%	NR	NR
S. Mihaela et al.	42	84%	7	33%
L. Morin et al.	109	61,60%	33	19,40%
R. C. Robey et al.	135	61%	15	21%
X. Wu et al.	47	57%	NR	NR
M. Zhou et al	40	44%	NR	NR

Table 10. Relationship between male population and fibrotic like changes during follow-up

Discussion and conclusion

In this systematic review, we have analyzed 15 articles of tomographic outcomes in severe/critical post-pneumonia COVID-19 follow-up patients in periods of 3 to 12 months, where the found data was similar between all the articles.

Currently, there is not enough evidence to exactly predict the long-term sequalae caused by severe COVID-19 pneumonia; however, the present systematic review allows us to identify the outcomes that could correlate to pulmonary sequalae in determined groups of patients. Sex (males), prolonged invasive/non-invasive mechanical ventilation times and comorbidities play an important role in the development of short term pulmonary sequalae.

In this systematic review, most of the analyzed studies that contemplate short follow-up times (3 months) limit the prediction of medium and long-term sequalae. Studies that contemplated serial follow-up times (3, 6 and 12 months) have shown that residual outcomes, like ground glass opacities, usually show complete resolution over time in comparison to the fibrotic type. However, X Han et al. mention that fibrotic changes found in 6 months follow-up, cannot be determined as real fibrosis. Finally, long-term follow-up studies (> 12 months) are necessary to predict more precisely the chance of developing pulmonary sequalae, and if fibrotic sequalae are effectively permanent.

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