Persisting Symptoms and Medical Findings after Acute Covid-19 Illness– a Literature Review

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Abstract

Long-lasting symptoms potentially related to Covid-19 have been recognized by medical practitioners and through peer support groups on social media platforms. Currently there is no consensus on detailed clinical picture or prevalence of these symptoms and their underlying pathophysiologies remain largely unexplored.

This is a literature review exploring firstly what kind of research has been conducted thus far on post Covid-19 symptoms and medical findings. Secondly, we portray, what is known about the symptom prevalence and medical findings based on the current literature.

This thesis includes a structured search on Pubmed looking for three kinds of studies: 1. Symptom prevalence, 2. Medical examination findings and 3. Case studies on rare manifestations. Only studies with PCR/antibody confirmed subjects were included and the symptomatology or medical findings was set only to comprise reports covering the time period at least three weeks after biological confirmation of acute Covid-19.

Symptom prevalence across the studies was found very heterogenous. In order to get a deeper insight into this notion, we grouped the studies according to acute illness severity and time point of inquiry/questionnaire after initial illness. However, also this grouping resulted in great variations in the findings within groups, further confirming the initial impression of great variability across study results. In many studies, the inclusion criteria were set only to prior Covid-19 illness and cohort characteristics were poorly described. For these reasons, comparisons across the studies were impaired and it became clear that controlled, more stratified research is warranted in the future. Studies on symptoms lacked control groups further hindering the analysis.

Fatigue and dyspnea were most prevalent symptoms in our review. Prevalence of some symptoms such as anosmia and hair loss appeared to be increased compared to our clinical experience on prevalence in population. However, as control groups were lacking, even these observations remained unreliable.

With regards to medical examinations, various kinds of abnormal findings were reported. However, control groups were mostly lacking. The impression was that the rate of abnormal findings appeared to be increased. They included e.g. the following:

There were signs of pulmonary impairment in a large proportion of chest CT's with ground glass opacity being the most common finding. In pulmonary function tests, a decreased diffusion capacity was common. Vascular pathologies were explored through large vessel PET, brain PET exploring metabolic rate as an indirect measure of vascular function, nailfold videocapillaroscopy and retinal angiography. Results were suggestive of large vessel vasculitis and brain hypometabolism with varying findings on microvasculature. Cardiac MRIs and echocardiography showed high prevalence of abnormal findings. There were observations of long-lasting dermatologic symptoms. Lowered cognition and psychiatric symptoms were also observed post-acute Covid-19.

The key finding was that the disease entity calls for more stratified and defined cohort studies with controls. Organ dysfunction findings seem prevalent and are a good starting point for studies looking into pathophysiologies of post Covid-19 disease entities.

Tiivistelmä

Covid-19-tautiin mahdolisesti liittyvät pitkäkestoiset oireet on pantu merkille niin terveydenhuollon ammattilaisten kuin sosiaalisen median potilasryhmien keskuudessa. Tällä hetkellä ilmiön laajuus ja kliininen kuva ovat epäselviä ja taudinkuvan patofysiologia on tuntematon

Tässä kirjallisuuskatsauksessa kartoitetaan ensiksi, millaista tutkimusta aiheesta on tehty koskien toisaalta subjektiivisia oireita ja toisaalta objektiivisempia lääketieteellisiä löydöksiä Covid-19 taudin aiemmin sairastaneilla. Sen jälkeen kuvataan oireiden prevalenssia ja raportoituja lääketieteellisistä löydöksistä.

Kirjallisuuskatsaus perustuu Pubmed-tietokannassa tehtyyn strukturoituun hakuun, joka kattoi: 1. Oireprevalennsitutkimuksia, 2. Lääketieteellisiä löydöksiä kartoittavia tutkimuksia, 3. Tapausselostuksia harvinaisista tautimuodoista. Mukaan hyväksyttiin vain tutkimukset,

joissa Covid-19-tapaukset oli varmennettu PCR- tai vasta-ainetutkimuksilla, ja jotka kattoivat ajanjakson, jossa Covid-19 diagnoosista oli kulunut vähintään kolme viikkoa.

Oireprevalenssia koskevat havainnot eri tutkimuksissa olivat hyvin heterogeenisiä. Varmistaaksemme tätä havaintoa, lajittelimme tutkimukset suhteessa akuutin taudin vaikeusasteeseen ja kyselyn ajankohtaan suhteessa akuuttiin tautiin. Vaikka pyrimme näin tuottamaan homogeenisempiä ryhmiä, havaitut prevalenssit näiden ryhmien sisällä vaihtelivat paljon. Päätelmä on, että nämä muodostamamme ryhmät eroavat toisistaan tai niiden oireiden kyselyssä käytetyt tutkimusasetelmat. Identifioimissamme tutkimuksissa inkluusiokriteeri oli usein ainoastaan aiempi Covid-19 tauti ja kohorttien ominaisuudet olivat suhteellisen heikosti kuvattuja. Tämän takia tutkimukset eivät ole vertailukelpoisia. Tutkimuksissa ei ollut kontrolliryhmiä, joka myös haittaa analyysiä.

Väsymys ja hengenahdistus olivat yleisimmät raportoidut oireet. Kliinisen tuntumamme perusteella jotkin oireet vaikuttavat yleisemmiltä kuin väestössä yleensä. Näitä olivat hiustenlähtö ja hajuaistin menetys. Kuitenkin ilman kontrolliryhmää arvio on epävarma.

Lääketieteellisiä löydöksiä kartoittaneissa tutkimuksissa epänormaalien löydösten osuus oli kohtalaisen suuri koskien monia eri elimiä. Tutkimuksissa ei usein ollut kontrolliryhmää, mutta kliinisen käsityksemme mukaan monien löydösten suhteen poikkeavien osuus oli suurempi kuin väestössä yleensä.

Keuhkojen CT-kuvissa poikkeavat löydökset olivat yleisiä mattalasimuutosten ollessa yleisin löydös. Keuhkojen toimintakokeissa diffuusiokapasiteetin alenema oli yleisin löydös.

Vaskulaaripatologioita tutkittiin suurten suonten PET-kuvantamisella, aivojen PET-kuvantamisella, joka kuvastaa metabolista astetta, jolle vaskulaarinen etiologia on mahdollinen, kynsipedin videokapillaroskopialla ja retinan angiografialla Löydökset viittasivat suurten suonten vaskuliittiin, aivojen hypometaboliaan, mikroverenkierron osalta löydökset olivat vaihtelevia.

Sydämen MRI:ssä ja echokardiografiassa poikkeavien löydösten osuus oli suuri. Ihomuutosten suhteen oli havaintoja pitkittyneistä iho-oireista. Tutkimuksissa havaittiin myös viitteitä alentuneesta kognitiosta ja psykiatrisesta sairastavuudesta.

Yhteenvetona voidaan todeta, että Covid-19 jälkeisten oirekuvien ymmärtämiseksi tarvitaan kohorttitutkimuksia joissa potilasryhmät ovat homogeenisempia, kohortin ominaisuudet on kuvattu selkeämmin ja tutkimusasetelmassa on asianmukaiset kontrolliryhmät. Eri elimiä koskevat poikkeavat löydökset vaikuttavat yleisiltä. Nämä löydökset ovat hyvä lähtökohta sairausentiteettien patofysiologioiden kartoittamiseen tähtäävien tutkimusten suunnitteluun.

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1 Introduction

As of 9/5/2021 the accumulated number of PCR-confirmed cases of Covid-19 in the world has reached 158,7 million [1]. Out of these 158,7 million 3,3 million have died, 136,3 million recovered and 19,2 million are currently active [1].

While most people recover fairly quickly back to their pre-Covid-19 health status, some subgroups seem to have persisting symptoms. Long-lasting symptoms potentially related to SARS-CoV-2 infection have been recognized by medical practitioners and through peer support groups on social media platforms. Currently there is no a consensus on the spectrum or prevalence of these symptoms nor of their underlying pathophysiology.

The clinical picture of the acute Covid-19 varies greatly in terms of severity, organ system involvement and the duration of illness [3][4][5]. The pathophysiology appears more complex than simple direct viral toxicity; activation of inflammatory and thromboembolic mechanisms have been described [3]. The severity spans from asymptomatic to severe or even fatal conditions. In terms of organ involvement, respiratory symptoms are usually predominant, however, the clinical picture encompasses a variety of extrapulmonary manifestations such as neurologic, renal, hepatic, gastrointestinal, thromboembolic, cardiac, endocrine and dermatological [6].

Similar to the acute disease, the post-acute Covid-19 manifestations and pathophysiologies are varied. It seems that there are multiple disease entities. Some patients experience symptoms as a continuum of the acute illness, while other patients report worsening or even new symptoms [2]. The number of symptoms possibly linked to previous covid-19 illness is extensive. However, actual risk of developing certain post covid-19 symptoms remains unknown and the descriptions in the literature are diverse. Knowledge on the timespan of these symptoms is limited since the pandemic has only been ongoing for less than18 months (starting 12/2019). Most studies are cross sections made at a certain time point, which limits the understanding of the progression and oscillations of symptoms over time. Also, most studies on symptom epidemiology have not expressed the severity of symptoms, which thus remains poorly characterized.

2 Study objectives

The aim of this review is to shed light on what is currently known about the spectrum of symptoms and medical findings in patients previously ill with SARS-CoV-2 PCR/antibody confirmed Covid-19. We searched three types of studies: 1. Studies into symptom prevalence, 2. Studies looking into any type of measurable medical findings and 3. Case studies about phenomena that are too rare for epidemiologic analyses. We only included studies performed at least three weeks after biological confirmation of Covid-19.

Firstly, we portray a picture of what type of study designs have been used and how common these designs have been. Secondly, we present findings on symptom prevalence in studies reviewed. All in all, the rates of the various symptoms seem to be very heterogenous. In order to confirm this notion, we tried to make a more stratified analysis by sorting cohorts into more homogenous groups. We hypothesized acute disease severity and timespan since acute illness to be most probable and easily accessible explaining factors for post covid-19 symptom prevalence. We performed the grouping of identified prevalence studies accordingly.

Secondly, we looked for findings in medical examinations in patients previously ill with Covid-19. We also reviewed case studies in order to gain insight into more rare manifestations.

We organized the results from studies reviewed according to organ system involved. We present findings from studies looking into symptom prevalence numbers as well as findings on measurable medical findings post Covid-19 illness, case study findings under organ system in question. In this regard we try to shed light on what is currently known both in terms of symptom prevalence and measurable findings giving insight into current knowledge on pathophysiologies. By organizing findings according to organ system, we try to gain understanding of which ones are affected.

3 Methods

For this review of post Covid-19 symptomatology and medical findings we collected three types of studies

1. Prospective or retrospective cohort studies on prevalence of self-reported subjective symptoms at least three weeks after PCR confirmation of Covid-19 in both inpatients and outpatients. Antibody-confirmed cases were also included. We excluded studies without clear expression of follow-up time and with markedly varied patient base across inquired symptoms within the study.
2. Studies on measurable medical findings in any organ system at least three weeks after PCR confirmation of Covid-19 in inpatients and outpatients. Antibody-confirmed cases were also included
3. Case studies about phenomena that are too rare for epidemiologic analyses in patients with PCR/antibody confirmed Covid-19.

We conducted a PubMed search with following types of search entries

1. Established terms referring to prolonged course of Covid-19 illness such as “long covid” (See Table 1)

2. Combinations of often used terms describing prolonged course of illness with covid*

3. MeSH-term post-acute covid-19 syndrome and combining MeSH-term covid 19/complications with often used terms describing prolonged course of illness.

Among these articles, we picked those that met the inclusion criteria for any of the three inclusion criteria described above. In Table 1 we present the search structure, the number of search hits and number of selected articles for this review. Search was performed 31/01/2021.

Table 1 – Search structure, number of hits and number of selected articles

Covid* + term describing prolonged course of illness	
"persistent symptoms" AND covid*	38
"prolonged course" AND covid*	14
post-acute AND covid*	95
post-discharge AND covid*	63
Established terms	
"long covid"	59
"long covid-19"	2
MeSHterms + terms describing prolonged course of illness	
post acute covid-19 syndrome[MeSH Terms]	1
post* AND covid-19/complications[MeSH Terms]	196
"persistent symptoms" AND covid-19/complications[MeSH Terms]	4
Total of reviewed articles	472
Included articles	
Symptom epidemiology	11
Medical examination findings	16
Case studies	3

4 Results

4.1 Overview of articles included

4.1.1. Overview of cohort studies on subjective symptoms

Eleven studies met the inclusion criteria for our review on epidemiology of subjective self-reported symptoms. These were all cohort studies with PCR/antibody confirmed subjects. Time of inquiry of these studies was from 3 weeks to 6 months post acute illness. Studies express timeline counting from symptom onset, time of diagnosis or hospital admission. This is marked, when discussing findings. None of the studies looking into subjective symptoms had control groups.

Nineteen symptoms were studied in more than 1 study and these symptoms were included in our analysis. The number of publications looking at each individual symptom by organ system affected is presented in Table 2.

Table 2 - Number of Cohort studies looking into Subjective Symptoms divided by Organ system affected

Respiratory system	Dyspnea (10), cough (6), chest pain (6), throat pain (2)
Cardiology	Resting heart rate increase or palpitations (3)
Skin	Cutaneous signs (2)
Neurology	Anosmia or dysgeusia (7)
Neuropsychiatry and Psychiatry	Anxiety or depression (3), PTSD symptoms (2)
Gastrointestinal	Nausea, vomiting or diarrhea (4)
Non-specific symptoms	Fatigue (8), sleep disorder (5) myalgia (5), arthralgia (5), fever (4), headache (3), hair loss (3), dizziness (2), poor appetite (2)

The findings on symptom prevalence were very heterogenous. In order to confirm this observation, we tried to make a more stratified analysis by sorting cohorts into more homogenous groups. We hypothesized acute disease severity and timespan since acute illness to be most probable and easily accessible explaining factors and grouped the epidemiological studies accordingly. Studies on symptom epidemiology were found to look into diverse groups of patients, many of them including both inpatients (ICU and non-ICU) and outpatients in same cohorts. This complicated our efforts to perform a more stratified review. Our guidelines for grouping are prescribed below.

The type of treatment facility (ICU/ward/outpatient) can be seen as a correlate for acute illness severity. For most studies we were able to find this information, but for some the definition was only described as critical versus non-critical. We grouped studies into two categories. 1. Studies looking into hospitalized patients including critical and ICU-treated subjects, 2. Studies looking into subjects containing marked proportions of outpatients and excluding critical or ICU-treated patients. Grouping according to time of follow-up portrays the timewise distribution of studies. Categories chosen were 1. Less than a month, 2. 1,5-2,5 months, 3. 3-4 months 4. 6 months.

4.1.2 Overview of studies looking into measurable findings in medical examinations

Fourteen studies met the criteria for studies for measurable findings in medical examinations. These include both cohort studies including patients unsampled according to symptom presence and studies looking into sampled symptomatic subjects. All studies look into PCR/antibody confirmed subjects. Time span was from 3 weeks to 6 months post discharge. Some studies had control groups. There were three case studies that met our inclusion criteria for rare manifestations hard to assess in epidemiologic study settings. Table 3 shows these studies by organ system.

Table 3 - Types and number of studies of medical examination modalities used in assessment of Post Covid-19 illness

Respiratory system	chest x-ray (2), chest ct (4), pulmonary function tests (6)
Vasculature	nailfold videocapillaroscopy (1), retinal angiography (1) and [18 F]FDG-PET/CT vasculitis imaging (1), a case study on Kawasaki-like multisystem inflammatory disease(1), a study on brain metabolic pattern and rate with 18F-FDG brain PET-TT (1), pernio type of dermatologic lesions (1)
Cardiology	cardiac MRI(1) and echography(1)
Skin	dermatologic status(1)
Neurology	18F-FDG brain PET-TT (1), a case study on Guillan-Barre syndrome (1) a case study on Miller-Fisher syndrome (1)
Neuropsychiatry and psychiatry	comprehensive cognitive test (1), HADSA/D questionnaire (1)
Laboratory markers	studies looking into current established laboratory markers (2), a study looking into novel pathways of inflammation and inflammatory markers in Covid-19 (1)

4.2 Respiratory system

Respiratory system was the most studied organ system. We found 10 cohort studies looking into experienced dyspnea [7]-[16], 6 into cough [9],[10],[13],[15],[16][17], six into chest pain [11],[12],[14],[15],[16],[17] and two into throat pain [14,[15]. Two studies looked into chest x-rays [10],[18], two studies into chest CT's in populations unsampled by symptom presence and 1 one study into chest CT's in a sampled symptomatic patient group [16],[19],[20]. Four studies looked into pulmonary function tests in populations unsampled by symptom presence [16],[19],[21],[22].

4.2.1 Self-reported respiratory symptoms

Subjective respiratory symptoms studied were dyspnea (10 cohort studies), chest pain (6), cough (5) and throat pain (2). Findings are presented in Table 4 with information on prevalence numbers, sample size and treatment facility in the acute phase of illness of each study. We show prevalence intervals of subgroups of studies based on 1. time of follow-up and 2. severity of illness.

The most commonly experienced respiratory symptom in post-acute Covid-19 illness was dyspnea. De Lorenzo R & al studied dyspnea prevalence 3 weeks post discharge in subjects including also ICU-treated patients, which showed 31.3% prevalence [7]. There are no studies looking into outpatients and mild hospitalized cases for this time interval. The range of dyspnoea prevalence among patients (most of them hospitalized, part of them in ICU) at around 1.5-2.5 months was 42.6%-61% [8],[9],[10],[12]. Carvalho-Schneider C & al looked into milder cases during the same time period and found a prevalence of 7.7% [11]. At 3-4 months prevalence among studies on severe disease was 5,5%-41,7% [13],[14],[15]. A study presenting data after 6 months follow-up among hospitalized subjects reported a dyspnea prevalence of 26% [16].

Overall, we saw a declining trend of dyspnea over time across the studies.
However, the range of dyspnea prevalence appeared to be substantial within our groups with similar studies. Based on these data, prevalence of dyspnea seems lower in patients with less severe acute illness.

The prevalence of chest pain was markedly lower than that of dyspnea, but still substantial. Carfì A & al looked into chest pain at 1.5-2.5 months and reported a prevalence of 21.7% among hospitalized patients [12. For non-severe inpatients and outpatients at the same time interval of 1.5-2.5 months the prevalence was 6%-13.3%[10],[11]. The prevalence of chest pain for hospitalized patients at 3-4 months was 4%-14.4% [13],[14],[15], and at 6 months 5% [16]. No studies assessing mild disease at respective time points were found.

Based on these data, there seems to be a trend of declining prevalence for chest pain over time.

Studies looking into cough at 1.5-2.5 months among hospitalized patients (including severe cases) reported prevalence of 5%-3.2% [9],[10], and one study looking into milder cases found a rate of 14% [17]. At 3-4 months there were only studies looking into more severe cases with prevalence of 2.5%-16.7% [13,[14]. Based on this data, the progression of experienced cough over time is unclear, even though a slight decline can be seen.

Throat pain was rare and only reported by 0%-3.2% of hospitalized patients including severe cases at 3-4 months [14],[15].

Table 4 – Experienced respiratory symptoms

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Dyspnea							
Less than 1 month	D23 from discharge	[7]	31.3%	31.3%	NA	2.2% ICU, 68.1% ward, 31.9% discharged from ED	185
1.5-2.5 months	D 59.7 from symptom onset	[11]	7.7%	42.6%-61%	7.7%	35.3% non-critically hospitalised, 64.7% outpatients	130
	D60.3 from symptom onset	[12]	43.4%			12.6% ICU, 87.4% ward	143
	D 48 from discharge	[8]	42.6%			32% ICU, 68% ward	100
	D50.8 from discharge	[9]	61 %			7.6% ICU, 92.4% ward	118
	D 54 from discharge	[10]	54.8%			14.5% ICU, 85.5% ward	384
3-4 months	D110 from admission to hospital	[13]	41.7%	5.5%-41.7%	NA	20% ICU, 80% ward	120
	D97 from discharge	[15]	21.4%			5% critical, 95% non-critical hospitalised	538
	3-4 months from discharge	[14]	5.5%			11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	26 %	26 %	NA	4% ICU, 96% ward	1733-1617
Chest pain							
1.5-2.5 months	D 59.7 from symptom onset	[11]	13.1%	21.7%	6%-13.1%	35.3% non-critically hospitalised, 64.7% outpatients	130
	D60.3 from symptom onset	[12]	21.7%			12.6% ICU, 87.4% ward	143
	D54 from discharge	[10]	6 %			91% outpatient, 8% ward, 1% ICU	246
3-4 months	D97 from discharge	[15]	14.1%	4%-14.1%	NA	5% critical, 95 non-critical hospitalised	538
	3-4 months from discharge	[14]	4 %			11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	5 %	5 %	NA	4% ICU, 96% ward	1733-1617
Cough							
1.5-2.5 months	D50.8 from discharge	[9]	5 %	5%-32.2%	14 %	7.6% ICU, 92.4% ward	118
	D54 from discharge	[10]	32.2%			14.5% ICU, 85.5% ward	384
	D68 from infection onset	[17]	14 %			91% outpatient, 8% ward, 1% ICU	246
3-4 months	D110 from admission to hospital	[13]	16.7%	2.5%-16.7%	NA	20% ICU, 80% ward	120
	3-4 months from discharge	[14]	2.5%			11.8% ICU, 88.2% ward	238
Throat pain							
3-4 months	D97 from discharge	[15]	3.2%	0%-3.2%	NA	5% critical, 95 non-critical hospitalised	538
	3-4 months from discharge	[14]	0 %			11.8% ICU, 88.2% ward	238

4.2.2 Pulmonary imaging

Respiratory system was assessed through imaging with chest x-rays and chest CT's. Findings on chest x-rays are presented in Table 5 and on chest CT's in Table 6. Two cohort studies looked into chest x-rays [10],[18], and two into chest CT's in populations non-selected by symptom presence [16],[19], and one study into chest CT's in a cohort sampled to include only symptomatic patients [20].

One study looked into chest x-rays at a mean of 54 days post discharge in hospitalized patients. In this patient population 38% showed abnormalities [10]. It was seen that on a subgroup level within these abnormal chest x-rays 27% (of totals) were significantly improved, 2% unchanged, but 9% were deteriorating. In one study looking into hospitalized patients at a mean of 77 days post symptom onset 18.9% chest x-rays proved abnormal [18].

Table 5 – Chest x-rays

Chest x-ray	Ref.	Abnormal x-rays	Significantly improved (% of totals)	Unchanged (% of totals)	Deteriorating (% of totals)		N
D54 from discharge	[10]	38 %	27 %	2 %	9 %	14.5% ICU, 85.5% ward	244
D77 from symptom onset	[18]	18.9%				8.7% iCU, 49.5% ward, 41.8% outpatient	269

Chest CT scans were examined in two cohort studies in non-selected populations unsampled by symptoms[16],[19]. One of these studies included both inpatients and outpatients, 75% hospitalized (20% of whole cohort needed invasive ventilation) and 25% outpatients. Evaluations were performed at a mean of 63 days and 103 days post diagnosis. 145 patients were examined at first follow-up and 133 of them at the second [19].

The other cohort study looking at chest CT's at 6 months after diagnosis divided patients into 3 subgroups according to acute illness severity. These subgroups were: 1. Patients not requiring oxygen (WHO pneumonia severity grade 3), 2. Patients requiring supplemental oxygen (WHO pneumonia severity grade 4), 3. Patients requiring high-flow nasal cannula

(HFNC)/ non-invasive mechanical ventilation (NIV)/invasive mechanical ventilation (IMV) (WHO pneumonia severity grade 5-6) [16].

In the cohort study looking at time points 63 days and 103 days post diagnosis, 77% and 63% of CT's were found abnormal [19]. The most common types of abnormal findings were:

1. Ground glass opacities, which was observed in 72% of all patients at first and in 52% at second examination
2. Reticulation in 58% at first and 51% at second examination
3. Consolidation in 64% at first and 7% at second examination
4. Bronchial dilation in 32% at first and 6% second examination.

It seems clear that ground glass opacities were markedly improved from day 63 to day 103 post diagnosis and consolidations and bronchial dilations even more so. However, reticulations showed only minor improvement.

In the cohort study looking into chest CT at 6 months post diagnosis, the proportions of abnormal findings were 52% (severity grade 3), 54% (grade 4) and 54% (grade 5-6). Ground glass opacity was found in 41% (grade 3), 48% (grade 4) and 45% (grade 5-6). Irregular lines were detected in 11% (grade 3) and 14% (grade 4) and 24% (grade 5-6). The volume of lesions increased from 1.6 cm^3 (grade 3), to 3.3 cm^3 (grade 4) and 29.1 cm^3 (grade 5-6)[16].

The proportion of abnormalities of any type showed no difference in prevalence across groups divided according to initial illness severity. Also, the most common finding ground glass opacity was equally common across groups. Irregular lines were more common in the more severe acute illness group 5-6. A clear increase of volume of the lesion is seen in accordance with acute illness severity.

In addition to these cohort studies unsampled by symptom presence, we found a study by Myall KJ & al looking into chest CT's at 4 weeks after discharge [20], where subjects were selected by a two-step inclusion process. The first step was to select only symptomatic patients by a phone call screening. In the second step patients with persistent chest x-ray

changes were selected for evaluation with CT. Interstitial lung disease (ILD) was found in 4,8% of all patients screened and 10,8% of symptomatic patients. 59% of ILD were assessed as organizing pneumonia, which was the most prevalent form of ILD in the study group.

Table 6 – Chest CT's

Chest ct	Ref.	Abnormal ct:s	Types of abnormalties in all subjects		N
D63 from diagnosis	[19]	77 %	Ground glass opacity 72%, reticulation 58%, consolidation 64%, bronchial dilation 32%	Invasive ventilation 20%, hospitalized without invasive ventilation 55%, outpatients 25%	145
D103 from diagnosis	[19]	63 %	Ground glass opacity 52%. reticulation 51%. consolidation 7%. bronchial dilation 6%	Invasive ventilation 20%, hospitalized without invasive ventilation 55%, outpatients 25%	133
D186 from symptom onset	[16]	52%(patients not requiring oxygen (group3)), 54% (requiring supplemental oxygen (group 4)) and 54% (requiring high-flow nasal cannula (HFNC)/ non-invasive mechanical ventilation (NIV)/invasive mechanical ventilation (IMV) (group 5-6))	Ground glass opacity 41%, 48% and 45%, average volume of lung lesions 1.6cm3, 3.3cm3 and 29.1cm3, irregular lines 11%, 15% and 24%	Severity of acute illness in the study described on subgroup level	353

4.2.3 Pulmonary function tests

Pulmonary function was assessed in 4 cohort studies. The time point of the evaluation were for study 1. 6 weeks after discharge [21], study 2. a mean of 63 days and 103 days post diagnosis [19], study 3. 3-4 months post discharge [22] and study 4. 6 months post diagnosis [16]. The markers assessed were proportion of patients with abnormal diffusion capacity (DLCO), restriction (TLC) and obstruction (FEV1/FVC). Three of these cohort studies were looking into all of these values and study 3. at only diffusion capacity. We present these findings in Table 7. In this table we also describe the severity of acute illness in terms of treatment facility. The second study with follow-up times at 63 days and 103 consisted of both inpatients and outpatients. Rest of the studies looked into hospitalized patients.

4.2.3.1 Diffusion capacity

Van der Sar-van der Brugge S & al assessed patients 6 weeks after discharge [21]. The study comprised patients with WHO pneumonia grade 3 (27.7% of the patients) and 4 (73.3% of the patients). DLCO<80% was found in 55.6% of grade 3 and 78.5% of grade 4 patients. A more severe abnormality of diffusion capacity, DLCO<60%, was observed in 18.5% (grade 3) and 27.7% (grade 4).

Sonnweber T & al DLCO assessed DLCO at 63 days and 103 days after diagnosis [19]. Of the subjects 75% were hospitalized (20% of whole cohort needed invasive ventilation) and 25% were outpatients. DLCO<80% was found in 31% at 63 days and in 21% at 103 days.

Bellan M & al studied hospitalized patient, part of them treated at ICU [22]. They found DLCO<80% in 51.6% and DLCO<60% 34.4% 3-4 months after diagnosis.

Huang C & al found at 6 months after diagnosis DLCO<80% in 22% of grade 3 pneumonia patients, 29% grade 4 pneumonia patients and 56% grade 5-6 pneumonia patients [16].

Overall, our study found a clear correlation between declining diffusion capacity and acute illness severity. A slight trend of improving diffusion capacity was seen over time.

4.2.3.2 Restriction and obstruction

Restriction and obstruction were assessed in three of the cohort studies looking into pulmonary function. At 6 weeks after discharge TLC<80% was observed in 14.8% (grade 3) and 23.6% (grade 4) [21]. Sonnweber T & al looked at two time points 63 days and 103 days, the prevalence numbers were 11% at both follow ups. The study by Huang C & al found at 6

months after diagnosis TLC<80% in 11% of grade 3, in 10% of grade 4 and in 35% of grade 5-6 patients [16].

Restriction at 6 weeks and 6 months after diagnosis correlated with severe initial illness. Also, the study looking into subjects with less severe illness at 63 days and 103 days from diagnosis shows slightly lower prevalence compared. There is no clear pattern of restriction improving or getting worse over time.

Looking into obstruction, FEV1/FVC<70% was found at 6 weeks after discharge in 21.4% (grade 3) and 27.4% (grade 4) [21]. At 63 days and at 103 days this was observed in 4%, in 8% respectively in a cohort of which 75% were hospitalized (20% of whole cohort needed invasive ventilation) and 25% were outpatients [19]. At 6 months after diagnosis in 8% (grade 3), in 8% (grade 4) and in 2% (grade 5-6) [16].

Obstruction appeared not to show a clear correlation with acute illness severity. The study looking into time point 6 weeks post discharge shows highest prevalence of obstruction. Prevalence 3-4 months and 6 months are similar.

Table 7 – Pulmonary function tests

PFTs	Ref.		N	DLCO<80%	DLCO<60%	TLC<80%	FEV/FVC1<70%
6 weeks from discharge	[21]	27.7% pneumonia grade 3, 72.3% pneumonia grade 4	101	55.6% (grade 3), 78.5% (grade 4)	18.5% (grade 3), 27.7% (grade 4)	14.8% (grade 3), 23.6%(grade 4)	21.4% (grade 3), 27.4%(grade 4)
D63 from diagnosis	[19]	Invasive ventilation 20%, hospitalised without invasive ventilation 55%, outpatients 25%	145	31 %	NA	11 %	4 %
D103 from diagnosis	[19]	Invasive ventilation 20%, hospitalised without invasive ventilation 55%, outpatients 25%	133	21 %	NA	11 %	8 %
3-4 months from discharge	[22]	11.8% ICU, 88.2% ward	219	51.6%	34.4%	NA	NA
D186 from symptom onset	[16]	Severity of acute illness in the study described on subgroup level	353	22% (grade 3), 29% (grade 4) and 56% (grade 5-6)	NA	11%, 10%, 35%	8%, 8%, 2%

4.3 Vasculature

Vascular pathologies have been described in acute Covid-19 illness. In this section we present the spectrum of studies looking into manifestations of vascular origin post-acute Covid-19. We found no studies with similar designs across articles, but only one study of each category was identified. Types of studies gathered were:

1. Vasculitis changes in 18F-FDG-PET/CT examination looking into large vessels [23]
2. Nailfold videocapillaroscopy looking into microvasculature [24]
3. Retinal angiography looking into microvasculature [25]
4. A case study describing a Kawasaki-like multisystem inflammatory disease post Covid-19 [26]
5. A study looking into brain hypometabolism with 18F-FDG-PET/CT suggestive of pathology possibly of vascular origin [27]
6. Pernio findings in a study looking into dermatologic manifestations post Covid-19 (see section 4.5 Results skin) [28]

We could not find any studies on macrothromboembolic complications post-acute Covid-19. However, in the studies looking at laboratory markers post Covid-19 (see section 4.10 Results Laboratory markers) a substantial proportion of patients with abnormal D-dimer values was reported [10],[19]. Vascular findings are presented in Table 8.

Table 8 – Vascular findings

Modality of Vascular examination	Ref.	Key findings	Type of study	N	Timing	Vessel size studied
18F-FDG-PET/CT examination looking vasculitis changes	[23]	Vascular scores similar in patients and controls. Target-to-pool ratio significantly higher in patients in three regions: : 1. thoracic aorta, 2. right iliac artery and 3. femoral arteries. The vascular uptake pattern of [18F]FDG was linear and suggestive of large vessel vasculitis.	Symptomatic patients compared to controls	10	More than 30 days post discharge	Large
Assessment of microvasculature with Nailfold videocapillaroscopy	[24]	Findings in more than two fingers were enlarged capillaries (85.2%), meandering capillaries (81.4%), pericapillary edema (70.4%) and capillary density below 9 capillaries per linear millimeter (63.0%). For findings with more than 33% involvement of the analyzed capillaries the prevalence numbers were meandering capillaries (18.5%), enlarged capillaries (5.6%), capillary density below 9 capillaries per linear millimeter (5.6%), microvascular derangement (3.7%). Hemosiderin deposits suggestive of micro-hemorrhage or micro-thrombosis were found at least in one digit in 31.5% and in more than one finger in 11.1%. Giant capillaries and avascular areas were both found in 5.6%.	Random selection of 82 subjects hospitalized with Sars-Cov-2 PCR/antibody-confirmed pneumonia. Of these subjects 54 were studied after acute phase of illness	54	A mean of 31.6 days post discharge	Micro
Assessment of microvasculature with Retinal angiography	[25]	Vessel density and vessel perfusion were assessed in superficial capillary plexus (SCP) and deep capillary plexus (DCP). No statistical difference was found between cohort and controls. Cotton wool spots were detected in 12.9% of cohort vs. 0% of controls. Predisposing underlying illnesses were more common in the cohort group.	A cohort study of 70 patients randomly selected from PCR-confirmed Covid-19 subjects at a university hospital 1 month after discharge and in 22 controls	70	1 month after discharge	Micro
Brain metabolism examined with 18F-FDG-PET/CT	[27]	Significant hypometabolism in 4 brain regions: 1. bilateral rectal/orbital gyrus including the olfactory gyrus, 2. the right temporal lobe. including the amygdala and the hippocampus. extending to the right thalamus, 3. the bilateral pons/medulla brainstem, 4. the bilateral cerebellum compared with controls	Symptomatic patients compared to controls	35	At least 3 weeks post discharge	Metabolic rate as an indirect measure

4.3.1 Vasculitis changes in 18F-FDG-PET/CT examination looking into large vessels

Vasculitis changes were evaluated in 10 patients recovered from Covid-19, who were experiencing persisting symptoms for more than 30 days post discharge. Examination was executed with [18F]FDG-PET/CT and compared with normal controls. Of the study subjects 5 were hospitalized during acute illness. The total vascular score was similar in both groups. The target-to-pool ratio was significantly higher in Covid-19 survivors in three regions: 1. thoracic aorta, 2. right iliac artery and 3. femoral arteries. The vascular uptake pattern of [18F]FDG was linear and suggestive of large vessel vasculitis. [23]

4.3.2 Nailfold videocapillaroscopy looking into microvasculature

Microvasculature was assessed with nailfold videocapillaroscopy in a random selection of 82 subjects hospitalized with Sars-Cov-2 PCR/antibody-confirmed pneumonia. A total of 28 were assessed during hospitalization and 54 a mean of 31,6 days post discharge. Of the patients assessed post discharge 9.3% were treated in an ICU, 5.6% had pulmonary thromboembolism during acute treatment and none had DIC. No control group was examined in this study. [24]

The prevalence of abnormalities in the patient group counting those with findings in more than two fingers were enlarged capillaries (85.2%), meandering capillaries (81.4%), pericapillary edema (70.4%) and capillary density below 9 capillaries per linear millimeter (63.0%). If we look at findings with more than 33% involvement of the analyzed capillaries, the prevalence numbers were meandering capillaries (18.5%), enlarged capillaries (5.6%), capillary density below 9 capillaries per linear millimeter (5.6%), microvascular derangement (3.7%). Hemosiderin deposits suggestive of micro-hemorrhage or micro-thrombosis were found at least in one digit in 31.5% and in more than one finger in 11.1%. Giant capillaries and avascular areas were both found in 5.6%. [24]

4.3.3 Retinal angiography looking into microvasculature

In this study microvasculature was assessed with OCT angiography in a cohort of 70 patients randomly selected from PCR-confirmed Covid-19 subjects at a university hospital 1 month after discharge and in 22 controls. Vessel density and vessel perfusion were assessed in superficial capillary plexus (SCP) and deep capillary plexus (DCP). No statistical difference was found between cohort and controls. Cotton wool spots were detected in 12.9% of cohort vs. 0% of controls. However, predisposing underlying illnesses were more common in the cohort group. [25]

4.3.4 A Case-study on Kawasaki-like multisystem inflammatory disease post Covid-19

A case study describes a 36-year-old female with a classic presentation of Kawasaki disease with non-exudative conjunctivitis, cracked lips, edema of the hands and feet, palmar erythema, a diffuse maculopapular rash and cervical lymphadenopathy. She was found Sars-Cov-2 IgG positive, which raises suspicion of this manifestation being a post Covid-19 postinfectious phenomenon. The etiology of classic Kawasaki disease is unknown, but post-infectious pathology has been suspected. [26]

4.3.5 Brain metabolism examined with 18F-FDG-PET/CT

35 previously Sars-Cov-2-PCR-confirmed subjects experiencing at least 3 weeks of persistent fatigue and some symptoms of possible neurological origin (dyspnea, hyposmia/anosmia, dysgeusia/ageusia, memory/cognitive impairment, insomnia, pain) were compared with 44 healthy subjects using brain PET scans. Subjects were matched for age and sex. [27]

Patients experiencing symptoms post Covid-19 had significant hypometabolism in 4 brain regions: 1. bilateral rectal/orbital gyrus, including the olfactory gyrus; 2. the right temporal

lobe, including the amygdala and the hippocampus, extending to the right thalamus; 3. the bilateral pons/medulla brainstem; 4, the bilateral cerebellum compared to controls. [27]

4.4 Heart

Cardiological post-acute Covid-19 was studied in 3 cohort studies looking into self-reported subjective symptoms [11],[15],[16], in 1 cohort study looking into cardiac echocardiography [19], and in 1 cohort study looking into cardiac MRI [29].

4.4.1 Self-reported symptoms of cardiac origin

Self-reported symptoms of cardiac origin were studied in 3 cohort studies. Findings are presented in Table 9. The studied symptoms were palpitations in 2 studies and resting heart rate increase in 1 study. Carvalho-Schneider C & al found that at a mean of 59.7 days post symptom onset in subjects containing non-critical hospitalized inpatients and outpatients the prevalence of palpitations was 10.9% [11]. At 6 months post diagnosis Huang C & al observed 9% prevalence of palpitations in hospitalized subjects [16].

Analysis on heart palpitation progression over time is difficult to do based on this data. Studies at 59.7 days and 186 days post symptom onset show similar prevalence numbers. However, the first study contains non-critical hospitalized and non-hospitalized subjects, whereas the second contains only hospitalized subjects.

Xiong Q & al studied self-reported resting heart rate increase at a mean of 97 days post discharge in a study population of hospitalized patients and found a prevalence of 11.2% [15].

Table 9 – Self-reported symptoms of cardiac origin

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Palpitations							
1.5-2.5 months	D 59.7 from symptom onset	[11]	10.9%	NA	10.9%	35.3% non-critically hospitalised, 64.7% outpatients	130
6 months	D186 from symptom onset	[16]	3 %	3 %	NA	4% ICU, 96% ward	1733-1617
Resting heart rate increase							
3-4 months	D97 from discharge	[15]	11.2%	11.2%	NA	5% critical, 95% non-critical hospitalised	538

4.4.2 Cardiac imaging

Cardiac imaging was applied in 2 cohort studies. 1 study examined patients with echocardiography [19] and 1 with cardiac MRI [29]. Findings are presented in Table 10.

Table 10 - Cardiac Imaging

Modality of Cardiac imaging	Ref.	Key findings	Type of study	N	Timing
Echocardiography	[19]	At 60 days 60% showed diastolic dysfunction and at 100 days 55%. Only 4 patients had reduced LVEF, with same prevalence at both follow ups	A cohort study with transthoracic echocardiography with 145 patients 60 days post discharge and 133 of these also 100 post discharge. 22% of patients were treated in an ICU, 75% were hospitalized and 25% outpatients	145 and 133	60 days and 100 days post discharge
MRI	[29]	78% had abnormal findings of any type and 60% ongoing cardiac inflammation	A cohort of 100 Covid-19 patients containing both inpatients (33%) and outpatients (67%)	100	71 days post discharge

145 Sars-Cov-2 patients were examined in a cohort study with transthoracic echocardiography 60 days post discharge and 133 of these also 100 days post discharge. 22% of patients were treated in an ICU, 75% were hospitalized and 25% outpatients. At 60 days 60% showed diastolic dysfunction and at 100 days 55%. Only 4 patients had reduced

LVEF, with same prevalence at both follow ups. There was no control group in this study. [19]

A cohort of 100 Covid-19 patients containing both inpatients (33%) and outpatients (67%) were assessed with cardiac MRI a median of 71 days post discharge.
Of these 78% had abnormal findings of any type and 60% ongoing cardiac inflammation. [29]

4.5 Skin

Dermatologic symptoms were studied in 2 cohort studies looking into subjective self-reported symptoms [11],[16], and 1 study looking into Covid-19 dermatologic symptom duration with data gathered via an international online registry [28].

4.5.1 Self-reported dermatologic symptoms

Self-reported cutaneous symptoms were looked into in 2 cohort studies. Findings are presented in table 11. At 59.7 days post symptom onset Carvalho-Schneider C & al found that in a patient population of non-critical hospitalized inpatients and outpatients 11.5% were experiencing dermatological symptoms [11]. At 6 months post symptom onset in a study by Huang C & al with hospitalized subjects, the prevalence was 3 % [16]. Experienced cutaneous symptoms seem fairly rare based on this data.

Table 11- Self-reported dermatologic symptoms

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Cutaneous signs							
1.5-2.5 months	D 59.7 from symptom onset	[11]	11.5%	NA	11.5%	35.3% non-critically hospitalised, 64.7% outpatients	130
							246
6 months	D186 from symptom onset	[16]	3 %	3 %	NA	4% ICU, 96% ward	1733-1617

4.5.2 International online register study on dermatological symptom duration and type

McMahon DE & al studied persistent dermatological symptoms post Covid-19 in a study, where data was collected through international online register both for PCR confirmed and clinically suspected covid-19 patients. They report findings of 96 patients with PCR confirmed disease. Information collected contained dermatological symptom duration and type of lesions. Findings are presented in table 12. [28]

Sars-cov-2-PCR confirmed subjects showed a median duration of 7 days for all kinds of dermatological manifestations, 7 days for morbilliform, 4 days for urticarial, 20 days for papulosquamous and 12 days for pernio type of lesions. Pernio is a dermatological lesion affecting acral sites following exposure to cold and damp. It is a localized form of vasculitis. [28]

Of the Sars-Cov-2-PCR confirmed patients 2 patients had pernio for more than 60 days. There was 1 subject with pernio and fatigue for 133 days, 1 subject with pernio and livedo reticularis for 150 days. With regards to other types of skin lesions in PCR-confirmed subjects, there was 1 subject with papulosquamous type of lesions for 70 days. [28]

Full time- course of the manifestations in this study may have not been captured because cases might have been reported before they were closed.

Table 12- Dermatologic lesion with durations over 60 days

Type of dermatological lesion	Ref.	Duration
Pernio	[28]	133 days
Pernio and livedo reticularis		150 days
Papulosquamous		70 days

4.6 Neurology

Many reported post-acute Covid-19 illness symptoms are non-specific and in only some of them there is a specific and certain organ of origin. The underlying pathophysiologies remain unknown. Under this section we present the findings from 7 cohort studies looking into prevalence for anosmia/ageusia [9],[11],[13],[14],[16][17],[30], which symptoms can be of neurological origin. This kind of symptoms can originate also more peripherally in the respiratory system. Some symptoms such as fatigue, dizziness, anxiety or depression, PTSD symptoms, nausea, poor appetite and sleep disorder can have a neurologic origin. Prevalence of these symptoms is presented under sections 4.7 Results Neuropsychiatry and Psychiatry, 4.8 Results Gastrointestinal, 4.9 Results Non-specific symptoms.

Regarding neurologic symptoms post Covid-19 we found two case studies describing Guillan-Barre manifestations [31],[32]. Of these the other one described a case of Miller-Fisher syndrome, a subtype of Guillan-Barre involving also eye muscles [31].

In our search we found one study looking into brain hypometabolism with PET-scan. This manifestation is most likely of vascular origin and is presented under section 4.3 Results Vasculature [27].

4.6.1 Self-reported neurologic symptoms – Anosmia and Ageusia

6 cohort studies were looking into subjective experience of anosmia [9],[13],[14],[16],[17],[30], 4 into ageusia [9],[13],[14],[16], and 1 into anosmia or ageusia [11]. Findings are presented in Table 13.

At 1.5-2.5 months in a study by Rosales-Castillo A & al looking into hospitalized subjects including ICU-treated patients, anosmia was experienced by only 1.7% [9]. In the same time interval, in studies looking into mostly outpatients or non-severe hospitalized subjects the

prevalence was 4%-37% [17],[30]. At 3-4 months there were only studies looking into hospitalized subjects including ICU-treated patients. The prevalence of anosmia ranged from 4.6%-13.3% [13],[14]. At 6 months in a study by Huang C & al the prevalence in hospitalized subjects was 11% [16].

Carvalho-Schneider C & al inquired non-critical hospitalized and ambulatory patients on experienced anosmia or dysgeusia at a mean of 59.7 days from symptom onset and found a prevalence of 22.7% [11].

The progression of anosmia over time post Covid-19 based on this data seem controversial. Both highest and lowest prevalence numbers are reported in first time interval 1.5-2.5 months with higher prevalence in studies looking into less severe cases. At 6 months anosmia prevalence was still 11% and clear decline of prevalence cannot be seen.

Ageusia was inquired in 4 cohort studies, which all were looking into hospitalized subjects including ICU-treated patients. At 1.5-2.5 months a study by Rosales-Castillo A & al found a prevalence of 1% [9]. At 3-4 months prevalence interval was 5%-10.8% [13,[14], and at 6 months a study by Huang C & al found a prevalence of 7% [16].

Based on these data, ageusia seems to be less common than anosmia. There is no clear pattern of declining symptoms over time. In these data lowest prevalence (1%) was found at the earliest interval, while also the prevalence numbers later on are fairly low with a maximum rate of 10.8%.

Table 13 – Self-reported anosmia and ageusia

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Anosmia							
1.5-2.5 months	D47 from diagnosis	[30]	37 %	1.7%	4%-37%	4% non-ICU hospitalized, 96% outpatients	1231
	D 50.8 from discharge	[9]	1.7%			7.6% ICU, 92.4% ward	118
	D 68 from infection onset	[17]	4 %			91% outpatient, 8% ward, 1% ICU	246
3-4 months	D110 from admission to hospital	[13]	13.3%	4.6%-13.3%	NA	20% ICU, 80% ward	120
	3-4 months from discharge	[14]	4.6%			11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	11,00 %	11 %	NA	4% ICU, 96% ward	1733-1617
Ageusia							
1.5-2.5 months	D 50.8 from discharge	[9]	1,00 %	1 %	NA	7.6% ICU, 92.4% ward	118
3-4 months	D110 from admission to hospital	[13]	10.8%	5%-10.8%	NA	20% ICU, 80% ward	120
	3-4 months from discharge	[14]	5,00 %			11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	7,00 %	7 %	NA	4% ICU, 96% ward	1733-1617
Anosmia or dysgeusia							
1.5-2.5 months	D 59.7 from symptom onset	[11]	22.7%	NA	22.7%	35.3% non-critically hospitalised, 64.7% outpatients	130

4.6.2 Guillan-Barré case studies

Guillan-Barré syndrome has been reported as an acute complication of Covid-19. In our research we found case studies on post-acute presentation of 1. Guillan-Barre syndrome [31] and 2. Miller-Fisher Syndrome (a variant of Guillan-Barre involving also eye muscles resulting in diplopia) [32]. The presentations manifested 53 days post admission to hospital and 2 weeks after acute symptom onset respectively. Both patients showed classical presentations of the neurologic illnesses and Covid-19 diagnosis was either PCR or antibody confirmed. These findings raise suspicion of Guillan-Barre syndrome being a postinfectious manifestation of Covid-19.

4.7 Neuropsychiatry and psychiatry

We found 2 cohort studies looking into subjective feelings of anxiety [7],[15], 1 into depression [15], 1 into either anxiety or depression [16]. Two cohort studies looked into prevalence of PTSD symptoms [7],[8]. Some symptoms inquired in post Covid-19 symptom studies do not unambiguously represent a certain organ system. Fatigue, sleep disorder, headache and dizziness are represented in the section 4.9 Results Non-specific symptoms.

With regards to more structured assessment of psychiatric disorders, we found one cohort study on hospitalized subjects looking into anxiety and depression with Hospital Anxiety and Depression Scale (HADSA/D) questionnaire [33]. With regards to neuropsychiatric symptoms, we found one study looking into cognitive performance through an online questionnaire [34].

4.7.1 Self-reported psychiatric symptoms

Subjective symptoms of anxiety or depression post Covid-19 were studied in three cohort studies. Findings are presented in Table 14. All studies were looking into hospitalized subjects including ICU-treated patients. At a mean of 23 days post discharge anxiety prevalence was found 29.7% in a study by De Lorenzo R & al [7]. At 97 days post discharge anxiety and depression were 6.5% and 4.3% respectively in a study by Xiong Q & al [15]. At 6 months in a study by Huang C & al prevalence of either anxiety or depression was 23% [16]. Our data shows controversial progression of these symptoms as the prevalence found less than 1 month post discharge and at 6 months show similar results, whereas in between at 3-4 months prevalence is markedly lower.

PTSD symptoms were studied in two cohort studies looking both into hospitalized subjects including ICU-treated patient. At a mean of 23 days post discharge prevalence found in a study by De Lorenzo R & al was 22.2% [7]. At a mean of 48 days post discharge Halpin SJ & al found a prevalence of 23.5% [8]. PTSD symptom prevalence seems fairly high based on this data.

Table 14 – Self-reported psychiatric symptoms

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Anxiety							
Less than 1 month	D23 from discharge	[7]	29.7%	29.7%	NA	2.2% ICU, 68.1% ward, 31.9% discharged from ED	185
3-4 months	D97 from discharge	[15]	6.5%	6.5%	NA	5% critical, 95% non-critical hospitalised	538
Depression							
3-4 months	D97 from discharge	[15]	4.3%	4.3%	NA	5% critical, 95% non-critical hospitalised	538
Anxiety or depression							
6 months	D186 from symptom onset	[16]	23 %	23 %	NA	4% ICU, 96% ward	1733-1617
PTSD Symptoms							
Less than 1 month	D23 from discharge	[7]	22.2%	22.2%	NA	2.2% ICU, 68.1% ward, 31.9% discharged from ED	185
1.5-2.5 months	D48 from discharge	[8]	23.5%	23.5%	NA	32% ICU, 68% ward	100

4.7.2 A cohort study assessing Anxiety and Depression with Hospital Anxiety and Depression Scale (HADSA/D)

A cohort of 100 patients with a PCR-confirmed Covid-19 interstitial pneumonia were evaluated with Hospital Anxiety and Depression Scale (HADSA/D) questionnaire a median of 46 days past viral clearance. Findings are presented in table 14. In the acute phase of illness all patients were hospitalized, 72.4% with low-flow oxygen therapy or no oxygen therapy and 27.6% with CPAP, NIV or mechanical invasive ventilation. 5.7% and 2.8% were treated with antidepressants and anxiolytics respectively before Covid-19 illness. [33]

At the follow up 29% had an abnormal score (>=8) on the anxiety scale, 11% on the depression scale. At least one of these two scales was pathological in 30% of subjects. Patients with abnormal HADSA/D showed more physical symptoms at follow up: 77% vs 43%. There was no control group in this study and comparison to symptom prevalence in population in general cannot be done. [33]

Table 15- Anxiety and Depression with Hospital Anxiety and Depression Scale (HADSA/D)

Type of study	Ref.	N	Timing	Abrnomal anxiety scale	Abnormal depression scale	Abnormal anxiety/depression scale	Somatic symptoms in subject with abnormal scales vs. normal
A cohort study assessing Anxiety and Depression with Hospital Anxiety and Depression Scale (HADSA/D) looking into hopitalized patients	[33]	100	A median of 46 days post viral clearance	29 %	11 %	30 %	77% vs. 43%

4.7.3 Cognitive assessment through an online test comparing population to Covid-19 survivors

Cognition was assessed with an online test in a population of 84285 subjects of whom 361 had a PCR-confirmed Covid-19 anamnesis. The results don't present how long since diagnosis patients have run the test. Test participation was promoted through a documentary project and did not include references to Covid-19 in order to avoid sample bias to people who suspect having post Covid-19 cognition deficits. The Covid-19 survivor subjects were matched for age, race, gender, pre-existing medical conditions and education level. [34]

Based on this data cognitive deficits correlated with the severity of respiratory symptoms in the acute phase. In milder cases consisting of outpatients with or without breathing difficulties PCR-confirmation of Covid-19 showed bigger deficits in cognition compared to suspected cases. The deficits were especially substantial in the ventilator-treated group, where the reduction was 0.57 global composite score, which compares to an average decline of cognition in 10 years in subjects aged 20 to 70. Also, this decline was more

substantial than in 512 subjects with a history of stroke (-0.40SDs) and in 1016 subjects, who reported learning disabilities (-0.49SDs). [34]

4.8 Gastrointestinal

There were 4 cohort studies looking into prevalence of experienced nausea, vomiting or diarrhea post Covid-19 [11],[14],[16],[17]. These findings are presented in table 15. At a mean of 59.7 days from symptom onset Carvalho-Schneider C & al found a prevalence of 11.,7% in subjects either hospitalized non-critically or outpatients [11]. At a mean of 68 days from symptom onset prevalence was found to be less than 1% in a study population consisting of 91% outpatients, 8% ward-patients and 1% ICU-treated patients [17]. At 3-4 months Bellan M & al found a prevalence of 1.3% in a study population of hospitalized patients including also ICU-treated subjects [14]. At 6 months Huang C & al found a prevalence of 5% in a study population of hospitalized subjects including also ICU patients [16].

The prevalence numbers for gastrointestinal symptoms were overall fairly low. There is no clear pattern of decline of symptoms over time. We can't see correlation of prevalence with severity of acute illness based on this data.

Table 16 – Self-reported gastrointestinal symptoms

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Nausea. vomiting or diarrhea							
1.5-2.5 months	D 59.7 from symptom onset	[11]	11.5%	11.5%	<1%	35.3% non-critically hospitalised, 64.7% outpatients	130
	D68 infection onset	[17]	<1%			91% outpatient, 8% ward, 1% ICU	246
3-4 months	3-4 months	[14]	1.3%	1.3%	NA	11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	5,0 %	5,0 %	NA	4% ICU, 96% ward	1733-1617

4.9 Non-specific symptoms

Of the self-reported symptoms studied in cohort studies we classified fatigue, sleep disorder, myalgia, arthralgia, fever, headache, hair loss, dizziness and poor appetite as non-specific. Findings are presented in Table 17. Below we describe findings for each of the symptom inquired.

4.9.1 Fatigue

Fatigue was inquired in 8 cohort studies [8],[9],[10],[12],[13],[15],[16],[17]. At 1.5-2.5 months the prevalence for hospitalized subjects including ICU-treated patients was 30.5%-67.3% [8],[9],[10],[12]. At this same time interval, we found one study by Trinkmann F & al looking into fatigue in mostly outpatient population with a prevalence of 1% [17]. At 3-4 months in hospitalized patients the prevalence interval was 28.3%-55% [13],[15]. At 6 months Huang C & al found a prevalence of 63% in hospitalized subjects [16].

Fatigue was overall the most common experienced symptom in patients post Covid-19. Based on this data, there is no trend of declining fatigue over time. However, inquiries have not looked into grade of fatigue but have been looking for prevalence of any level of fatigue. In this data, it would seem fatigue is markedly less common in non-hospitalized patients. However, more data would be needed to confirm this finding as there is only one study looking into mostly outpatients.

4.9.2 Sleep disorder

Sleep disorder, insomnia or poor quality of sleep was inquired in 5 cohort studies all of which consisted of subjects hospitalized including ICU-treated patients [7],[10],[13],[15],[16]. In a study by De Lorenzo R & al a mean of 23 days post discharge prevalence was found to be 27.6% [7]. In a study by Mandal S & al at a mean of 54 days post discharge it was found to be 61.1% [10]. At 3-4 months prevalence interval was 17.7%-31.0% [13],[15], and at 6 months in a study by Huang C & al it was 26% [16].

A fairly high prevalence of insomnia was reported at all time points studied. However, there are no control groups included. As insomnia is a common symptom in general public the causality of prior Covid-19 illness remain unclear. Based on these data it is not possible to draw a conclusion of any clear trend of declining prevalence of sleep disorder prevalence over time post Covid-19.

4.9.3 Myalgia

Myalgia was studied in five cohort studies [9],[14],[15],[16],[17]. At a mean of 50.8 post discharge Rosales-Castillo A & al found a prevalence of 13% in a cohort of hospitalized patients [9]. At a mean of 68 days post symptom onset Trinkmann F & al found a prevalence of 1% in a study containing mostly outpatients [17]. At 3-4 months interval we found only studies looking into hospitalized patients for which the prevalence was 4.5%-5.9%[14],[15]. At 6 months in a study by Huang C & al in hospitalized patients the prevalence was 2% [16].

Prevalence for myalgia over time post Covid-19 does not show a clear pattern based on this data. Prevalence numbers both early after and 6 months after acute illness have found very low prevalence, whereas in between these studies have reported somewhat higher numbers. Based on this data it would seem that myalgia is rarer in cases less severe in acute phase, but the data is limited as there is only one study looking into mostly outpatients.

4.9.4 Arthralgia

Arthralgia was studied in five cohort studies [11],[12],[14],[15],[16]. In a study by Carvalho-Schneider C & al looking into hospitalized subjects (including ICU patients), a prevalence of 27.3% was reported at 59.7 days (mean) post symptom onset [11]. Carfì A & al only included non-critical inpatients and outpatients and reported a prevalence of 16.3% at 60.3 days (mean) post symptom onset [12]. During the time interval of 3-4 months wesonly found studies looking into hospitalized subjects; these reported a prevalence of 5.9%-7.6% [14],[15]. At 6 months Huang C & al found a prevalence of 9% in hospitalized subjects [16].

Overall, the data we collected appeared to show a trend of declining experienced arthralgia over time. Based on these data it would also seem that arthralgia is more common in hospitalized subjects.

4.9.5 Fever

Four cohort studies looked into post-acute fever [11],[14],[16],[17]. At 1,5-2,5 months for outpatients and non-critical inpatients the prevalence was 0% - <1% [11],[17]. Bellan M & al studied fever at 3-4 months post discharge in a hospitalized cohort and found a prevalence of 0% [14]. At 6 months Huang C & al found a prevalence of <1% in hospitalized subjects [16].

Based on this data post-acute fever prevalence seems negligible.

4.9.6 Headache

Headache was studied in three cohort studies [14],[16],[17]. Trinkmann F & al looked into mostly outpatients at a mean of 68 days post infection onset and observed a prevalence of <1% [17]. Bellan M & al studied headache at 3-4 months post discharge in a hospitalized cohort and found a prevalence of 0% [14]. At 6 months Huang C & al found a prevalence of 2% in hospitalized subjects [16].

In this data headache seems very rare in post-acute Covid-19.

4.9.7 Hair loss

Hair loss was studied in three cohort studies [13],[15],[16]. All these studies were looking into hospitalized subjects including also ICU-treated subjects. At 3-4 months post-acute illness prevalence interval was 20.0%-28.6% [13],[15]. At 6 months in a study by Huang C &al hair loss prevalence was 22% [16].

Hair loss was found to be a common reported symptom. In the data collected, there was no clear decline of the prevalence over time. Even at 6 months 22% of patients report this symptom. The data included only studies looking into hospitalized subjects and therefore it is not known whether this symptom would only be associated with severe acute illness.

4.9.8 Dizziness

Dizziness was studied in two cohort studies both looking into hospitalized subjects [15],[16]. At a mean of 97 days post discharge Xiong Q & al found a prevalence of 2.6% [15]. At 6 months Huang C &al found a prevalence of 6% [16].

In these studies, dizziness was found to be rare.

4.9.9 Poor appetite

Poor appetite was studied in two cohort studies both looking into hospitalized subjects [8],[16]. At a mean of 48 days post discharge Halpin SJ & al found a prevalence of 8.8% [8]. At 6 months Huang C & al found a prevalence of 8% [16].

Poor appetite as a symptom appears to be present only at a fairly low rate according to these observations.

Table 17 – Self-reported non-specific symptoms

	Follow up time	Ref.	Prevalence	Prevalence interval in patients mostly hospitalised and including ICU treated subjects	Prevalence interval in patients excluding ICU treated subject mostly looking into non-severe inpatients and outpatients	Treatment facility	N
Fatigue							
1.5-2.5 months	D48 from discharge	[8]	60.3%	30.5%-67.3%	1 %	32% ICU, 68% ward	100
	D 50.8 from discharge	[9]	30.5%			7.6% ICU, 92.4% ward	118
	D54 from discharge	[10]	67.3%			14.5% ICU, 85.5% ward	246
	D60.3 from symptom onset	[12]	53.1%			12.6% ICU, 87.4% ward	143
	D68 infection onset	[17]	1 %			91% outpatient, 8% ward, 1% ICU	246
3-4 months	D97 from discharge	[15]	28.3%	28.3%-55%	NA	5% critical, 95% non-critical hospitalised	538
	D110 from admission to hospital	[13]	55 %			20% ICU, 80% ward	120
6 months	D186 from symptom onset	[16]	63,00 %	63 %	NA	4% ICU, 96% ward	1733-1617
Sleep disorder							
Less than 1 month	D23 from discharge	[7]	27.6%	27.6%	NA	2.2% ICU, 68.1% ward, 31.9% discharged from ED	185
1.5-2.5 months	D54 from discharge	[10]	61.1%	61.1%	NA	14.5% ICU, 85.5% ward	246
3-4 months	D97 from discharge	[15]	17.7%	17.7%-31.0%	NA	5% critical, 95% non-critical hospitalised	538
	D110 from admission to hospital	[13]	30.8%			20% ICU, 80% ward	120
6 months	D186 from symptom onset	[16]	26,00 %	26 %	NA	4% ICU, 96% ward	1733-1617
Myalgia							
1.5-2.5 months	D 50.8 from discharge	[9]	13,00 %	13 %	1 %	7.6% ICU, 92.4% ward	118
	D68 infection onset	[17]	1 %			91% outpatient, 8% ward, 1% ICU	246
3-4 months	D97 from discharge	[15]	4.5%	17.7%-31.0%	NA	5% critical, 95% non-critical hospitalised	538
	3-4 months from discharge	[14]	5.9%			11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	2,00 %	2 %	NA	4% ICU, 96% ward	1733-1617
Arthralgia							
1.5-2.5 months	D 59.7 from symptom onset	[11]	16.3%	27.3%	16.3%	35.3% non-critically hospitalised, 64.7% outpatients	130
	D60.3 from symptom onset	[12]	27.3%			12.6% ICU, 87.4% ward	143
3-4 months	D97 from discharge	[15]	7.6%	5.9%-7.6%	NA	5% critical, 95% non-critical hospitalised	538
	3-4 months from discharge	[14]	5.9%			11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	9,00 %	9 %	NA	4% ICU, 96% ward	1733-1617
Fever							
1.5-2.5 months	D 59.7 from symptom onset	[11]	0 %	0 %	<1%	35.3% non-critically hospitalised, 64.7% outpatients	130
	D68 infection onset	[17]	<1%			91% outpatient, 8% ward, 1% ICU	246
3-4 months	3-4 months from discharge	[14]	0 %	0 %	NA	11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	<1%	<1%	NA	4% ICU, 96% ward	1733-1617
Headache							
1.5-2.5 months	D68 infection onset	[17]	<1%	NA	<1%	91% outpatient, 8% ward, 1% ICU	246
3-4 months	3-4 months	[14]	0 %	0 %	NA	11.8% ICU, 88.2% ward	238
6 months	D186 from symptom onset	[16]	2 %	2 %	NA	4% ICU, 96% ward	1733-1617
Hair loss							
3-4 months	D97 from discharge	[15]	28.6%	20.0-28.6%	NA	5% critical, 95% non-critical hospitalised	538
	D110 from admission to hospital	[13]	20 %			20% ICU, 80% ward	120
6 months	D186 from symptom onset	[16]	22 %	22 %	NA	4% ICU, 96% ward	1733-1617
Dizziness							
3-4 months	D97 from discharge	[15]	2.6%	2.6%	NA	5% critical, 95% non-critical hospitalised	538
6 months	D186 from symptom onset	[16]	6 %	6 %	NA	4% ICU, 96% ward	1733-1617
Poor appetite							
1.5-2.5 months	D48 from discharge	[8]	8.8%	8.8%	NA	32% ICU, 68% ward	100
6 months	D186 from symptom onset	[16]	8,0 %	8,0 %	NA	4% ICU, 96% ward	1733-1617

4.10 Laboratory markers

We found two cohort studies looking into common venous blood laboratory markers [10,[19]. One study had identified a panel of 96 inflammatory proteins not commonly used in clinical practice [35]. Concentrations of these were assessed in a random selection of patients with mild acute Covid-19 disease.

4.10.1 Established widely used laboratory markers

Laboratory markers were assessed in two cohort studies post-acute Covid-19 for which findings are presented in Table 18. Both studies contained mostly inpatients including severely ill patients treated in ICU and requiring invasive ventilation. One study was looking into prevalence of abnormal laboratory values at a mean of 54 days post discharge [10], one at a mean of 103 days post diagnosis [19]. In the following we describe proportions of abnormal laboratory values in descending order.

The most common abnormal finding was elevation of D-dimer, which was seen in 18% at 54 days post discharge and in 27% at 103 days post diagnosis. At 103 days post diagnosis NT pro-BNP was observed in 23% and elevated ferritin in 17%. These laboratory markers were not studied at the study 54 days post discharge. The fourth most common abnormal laboratory value was elevated CRP at 4.7% 54 days post discharge and at 12% 103 post diagnosis. Procalcitonine and IL-6 were elevated in 9% and 6% respectively at 103 days post discharge. Lymphopenia was seen in 4.5% 54 days post discharge.[10],[19]

At 54 days post discharge it was additionally analyzed, how big proportion of those with abnormal values at discharge remained abnormal. Persistence for elevated D-dimer, elevated CRP and lymphopenia were 30.1% (of 59.6% at discharge), 9.5% (of 49.5%) and 7% (of 64.3%). [10]

The data show no trend of decline in the rates of abnormal laboratory values over time. However, even though both groups contain ICU-treated/invasive ventilation requiring

patients, there might be differences in the severity of acute illness and other characteristics of patients making comparison across studies unreliable. D-dimer seems to be most commonly affected laboratory value in this data and its elevated values are quite prevalent. Significant proportions of patients show abnormalities in other laboratory markers as well, while big majority shows no abnormalities.

Table 18 – Laboratory findings in common laboratory markers

	D54 from discharge [10]	D103 from diagnosis [19]
Treatment facility	14,5% ICU, 85,5% ward	invasive ventilation 20%, hospitalized without invasive ventilation 55%, outpatinets 25%
N	384	133
Abnormal values in all patients		
Lymphpenia	4.5%	NA
Elevated D-dimer	18.0%	27 %
Elevated CRP	4.7%	12.0%
Elevated IL-6	NA	6.0%
Elevated procalcitonine	NA	9.0%
Elevated NT-pro-BNP	NA	13.0%
Elevated ferritin	NA	17.0%
Persisting abnormal values in patients discharged with abnormal values (% of patients discharged with abnormal values)		
Lymphopenia	7% (64.3%)	NA
Elevated D-dimer	30.1% (59.6%)	NA
Elevated CRP	9.5%(49.5%)	NA

4.10.2 Novel markers of inflammation

Ten antibody-confirmed Covid-19 survivors were compared with 10 controls to assess concentrations of 96 proteins of inflammation. Findings are shown in Table 19. This panel was identified by Doykov I & al in their earlier study by mass spectrometry. None of the patients had been hospitalized at acute phase. At the time of follow up at 40-45 days post diagnosis only symptom patients were experiencing was anosmia in 7/10. [35]

Six of the 96 proteins' panel showed marked alterations in concentration. Two of these originate from mitochondria: peroxiredoxin 3 (PRDX3), which is an antioxidant and carbamoyl phosphate synthase (CPS1), which is a major mitochondrial urea cycle enzyme in hepatocytes. N-Myc downstream regulated gene 1 (NDRG1) is cytosolic protein with function in macrophage and mast cell maturation. Collagen triple helix repeat containing 1 (CTHRC1) is anti-inflammatory and regulates various pathways. Cystatin C is a protease inhibitor and is used as a disease prognose estimate in many diseases such as cancer, cardiovascular disease and inflammatory lung disease. Progranulin is a protein, that has role in immune response and neurogenerative disorders. [35]

Table 19 – Novel markers of inflammation

Novel inflammatory marker concentrations altered [35]	Function
Peroxiredoxin 3 (PRDX3)	antioxidant
Carbamoyl phosphate synthase (CPS1)	mitochondrial urea cycle enzyme in hepatocytes
N-Myc downstream regulated gene 1 (NDRG1)	role in macrophage and mast cell maturation
Collagen triple helix repeat containing 1 (CTHRC1)	anti-infalmmatory, reagulation of various pathways
Cystatin C	protease inbitor and is used a disease prognosis estimatie in many disease such as cancer, cardiovascular disease and inflammatory lung disease
Progranulin	immune response, negenerative disease

5 Discussion

Post-acute covid-19 symptoms have been recognized by clinicians and by patient groups on social media platforms. The volume of these notions with manifestations having a timely setting after acute covid-19 supports a view that there exist post-viral disease entities with SARS-Cov-2 as the etiology.

The aim of this review was to give insight firstly on what kind of studies have been conducted on the symptom epidemiology and actual medical examination findings post Covid-19 and secondly portray what has been found in these studies.

Regarding symptom prevalence studies, we found that the results were very heterogenous. The studies conducted thus far have been looking into cohorts often with inclusion criteria being only a PCR-confirmed Covid-19 illness and a pre-determined requirement for the time span since the acute COVID-19 episode. Therefore, the cohorts include both inpatients and outpatients and represent all ages with varied pre covid-19 health status. The characteristics of the cohorts were often either not given or poorly described making comparisons between studies difficult.

The poor characterization of the cohorts made it very challenging to conduct a more stratified analysis. We made an attempt to summarize these heterogenous results on symptom epidemiology by stratification into two groups according to acute disease severity and four groups according to the time of observation after acute illness. Even with this grouping, the results seem diverse, which is portrayed in the varying prevalence numbers within groupings. In addition to varied and unknown patient characteristics in the studies, also differences in symptom inquiry methods pose a challenge in drawing conclusions. Unfortunately, evaluating the actual risk of developing post-viral symptoms proved impossible since the data were insufficient for this purpose.

Another factor impairing the analysis of symptoms relates to lack of control groups in the studies. We identified fatigue and dyspnea as most prevalent symptoms. In addition, the

frequency of symptoms like hair loss, anosmia and ageusia appeared to be increased compared to our clinical experience on prevalence yet these symptoms remained generally rare in the data. Indeed, their actual prevalence can only be evaluated in studies with adequate control groups.

Some symptoms, such as dyspnea, had a likely correlation with more severe acute illness [7]-[16]. However, our stratification into two groups with more and less severe acute illness cohorts proved unsatisfactory, and our analyses were therefore not fully reliable. Likewise, due to variations in the data and its time points and the lack of characteristics of the cohorts, evaluation of symptom progression with time could not be carried out reliably by comparing different cohorts from various studies.

It appears that some post covid-19 manifestations are so rare, that it is not possible to obtain accurate data on them or their frequency with epidemiological methods. Kawasaki-like multisystem inflammatory disease and Guillan-barre syndrome are good examples of this kind of phenomena, but likely not the only [26],[31],[32].

Findings in medical examination are the first steps in understanding the pathophysiology behind post covid-19 symptomatology. Results regarding many organ systems showed quite high rates of abnormalities, such as in cardiac imaging most subjects had abnormal findings [19],[29]. However, many of studies were lacking a control group, which impairs a reliable analysis.

Pulmonary pathology was evaluated by chest x-rays, chest CT's and pulmonary function tests. Chest CT abnormalities proved very common even half a year after acute Covid-19 illness in the hospital treated cohort [16],[19],[20]. Ground glass opacities were most common findings and volume of lesions correlated strongly with acute disease severity. Pulmonary function tests showed abnormalities especially regarding diffusion capacity [16],[19],[21],[22]. Regarding chest x-rays, an interesting finding was, that in a hospitalized cohort most chest x-rays controlled at mean of around 2 months post discharge were normal or significantly improved. However, for 9% deteriorating [10]. It seems probable there are subgroups for which recovery differs markedly from the average.

Vascular complications have been reported in acute Covid-19 disease, both micro and macrothrombi being prevalent manifestations. Post Covid-19 vascular research was fairly limited in number in our research. We found one study suggesting raised prevalence in large vessel vasculitis [23]. Micro vessels were studied in retinal angiography and nailfold videocapillaroscopy study designs. Retinal angiography setting could not find statistical difference between controls and patients [25]. The videocapillaroscopy findings are lacking control, but suggestive of microthrombi and microhemorrhage [24]. A study found hypometabolism in certain brain regions in PET-TT study design compared to controls. Hypometabolism may have a vascular origin [27]. D-dimer was the most common elevated laboratory post Covid-19 suggestive of abnormal coagulation [10],[19]. Kawasaki type multisystem inflammatory disease is a type of vasculitis and has been reported in people previously ill with Covid-19 [26]. These findings raise suspicion of vascular affision post covid-19, but the variability of findings does not portray a clear picture of the mechanism.

Considering dermatologic manifestations, there are patients who have symptoms persisting up to 150 days post-acute illness for which there is no apparent other explaining reason and the time point of the start of symptoms matches with acute Covid-19 illness [28]. At least pernio, livedo reticularis and maculopapular manifestations have been seen post-acutely. Of interest is that pernio is a localized form of vasculitis as vascular pathology has been suspected in post-covid-19 symptomatology.

Cognition was assessed in an online study, where PCR-confirmed covid-19 diagnosis correlated with lower cognition matched for age, race, gender, pre-existing medical conditions and education level in both mild and severe disease forms. Ventilator treated covid-19 correlated more strongly with cognition impairment and was found to be more severe than in patients with previous stroke or learning disabilities.[34]

Other notions regarding nervous system dysfunction in our study were Guillan-Barré cases recorded after Covid-19 [31],[32]. Depression and anxiety were assessed in a study using HADSA/D scale, but there were no controls, which impairs analysis [33].

In most patients, laboratory values return to normal post Covid-19. However, for some changes persist for at least months. Most common abnormal values we found were D-dimer, pro-BNP, CRP and ferritin [10],[19]. Also, a study was looking into untraditional markers of inflammation and found some proteins elevated compared to controls even after mild disease [35].

In our study we found that results from symptom epidemiology studies are very heterogenous. Any reliable estimates for symptom prevalence for certain groups or on aggregate level is hard to make as cohorts have very varied patient bases and cohort characteristics are many times unknown in terms of previous health status, age, sex or other possibly explaining factors.

Many studies found abnormalities in several organs. Many of these studies did not, however, have accurate control groups. It seems that Covid-19 may be followed by a post-infectious syndrome with a greatly variable clinical picture, where at least pulmonary, vascular, cardiac, dermatologic and neurologic systems may be affected.

The results from our review show that more research is needed to understand post-acute Covid-19 symptoms and findings. Epidemiological studies need more defined cohorts and reproducible ways of inquiring symptoms. It seems there are findings of organ dysfunction related to post Covid-19. However, studies with control groups are needed. Understanding pathophysiologies behind these are currently unexplored and ask for more research. Observations on organ dysfunction are good cues, where to start looking for in order to understand the mechanisms underlying the symptoms.

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