Royal Australasian College of Surgeons

Impact of post-COVID-19 conditions (long COVID) on surgery

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IMPACT OF POST-COVID-19 CONDITIONS (LONG COVID) ON SURGERY

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CONFLICTS OF INTEREST None

RACS EVIDENCE SUPPORT SERVICES PROCESS

This literature review involves multiple phases:

1. project protocol
2. initial draft
3. final report.

This document represents the **final report**.

The aim of the protocol is to establish the central research question(s), methodology, target population, appropriate comparator and relevant outcomes. The initial draft contains the results of the literature search and an overview of the results. The final report includes the complete synthesis of the results along with any recommendations. During each stage, the working group will be consulted to ensure the work is fit for purpose.

CONTENTS

Abbreviations	
AE	adverse event
ANZCA	Australian and New Zealand College of Anaesthetists
ARDS	acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CT	computed tomography
DLCO	diffusing capacity of the lungs for carbon monoxide
DVT	deep vein thrombosis
FVC	forced vital capacity
HCP	healthcare practitioner
ICU	intensive care unit
IQR	interquartile range
IRR	incidence risk ratio
IV	intravenous
LFT	liver function test
MA	meta-analysis
MBS	Medicare Benefits Schedule
MI	myocardial infarction
NA	not available
NICE	National Institute for Health and Care Excellence
NR	not reported
NS	not significant
OR	odds ratio
PASC	post-acute sequelae of COVID-19
PCR	polymerase chain reaction
PE	pulmonary embolism
PICO	population, intervention, comparator, outcome

PTSD	post-traumatic stress disorder
RACS	Royal Australasian College of Surgeons
RACGP	Royal Australian College of General Practitioners
RAT	rapid antigen test
RCT	randomised controlled trial
RR	risk ratio
RT-PCR	reverse transcription polymerase chain reaction
SARS	Severe Acute Respiratory Syndrome
SD	standard deviation
SpO2	peripheral blood oxygen saturation
SR	systematic review
TLC	total lung capacity
UK	United Kingdom
USA	United States of America
UTI	urinary tract infection
VTE	venous thromboembolism
WHO	World Health Organization

1 Recommendations and summary

1.1 Recommendations

- The clinical spectrum of acute COVID-19 encompasses the following:
    - asymptomatic: positive test for SAR-CoV-2 without symptoms consistent with COVID-19
    - mild illness: mildly ill with various symptoms of COVID-19 (e.g. fever, cough, fatigue) without shortness of breath
    - moderate illness: evidence of lower respiratory disease (e.g. shortness of breath) during clinical or imaging assessment; peripheral blood oxygen saturation [SpO2] ≥94% on room air
    - severe illness: signs and symptoms of severe lower respiratory disease necessitating hospitalisation and usually oxygen therapy; SpO2 ≤94% on room air.
- The definition of post-COVID-19 condition (long COVID) varies. This report uses the National Institute for Health and Care Excellence (NICE) definition of long COVID: 'signs and symptoms that continue or develop after acute COVID-19, including both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).[1]

Vaccination

- Where possible, patients should be fully vaccinated against SARS-CoV-2, with their most recent dose at least 14 days prior to an elective surgical procedure.

Following acute infection

- The risks of surgery must be balanced against the risks and potential consequences of delay. For major elective surgery following SARS-CoV-2 infection, consider a delay of 2–3 weeks or longer before surgery, with the proviso that the patient had mild COVID-19 symptoms, is asymptomatic at the time of surgery, is vaccinated and has returned to baseline functioning. For minor elective surgery, consider delaying the procedure until after the patient's infectious period ends.
- For patients who had moderate or severe COVID-19 or continue to have persistent COVID-19 symptoms, consider a delay of 7 weeks or longer, while balancing the risks of surgery against the risks and potential consequences of delay. Ensure a formal clinical review is conducted prior to surgery for these patients, with specific questions regarding:
    - history of acute COVID-19
    - presence of risk and protective factors associated with long COVID
    - nature and severity of previous and/or current symptoms
    - timing and duration of symptoms since the onset of acute COVID-19
    - history of COVID-19 vaccination(s)
    - history of other health conditions
    - exacerbations of pre-existing conditions.

Long COVID/persistent symptoms

- For patients with persistent COVID symptoms, consider a delay of 7 weeks or longer, with the proviso that the risks of surgery are balanced against the risks and potential consequences of delay.
- For patients with long COVID, the decision to defer surgery should be based on clinical signs, symptoms, risk factors and context. Where appropriate, surgery should be deferred until the

patient returns to baseline functioning, while balancing the risks of surgery against the risks and potential consequences of delay.

- A preoperative assessment, including evaluation of the cardiorespiratory system, should be performed before surgery can proceed (Table 1). Further evaluation of the renal, hepatic, haematological, immunological, musculoskeletal, neurological and psychological systems may be required, based on patient symptoms.
- Prehabilitation strategies to improve patient operative fitness may be required before surgery occurs.

Table 1 Suggested preoperative assessment tools

Subjective assessment	
All patients	Formal clinical review History of acute COVID-19 Nature and severity of previous and current symptoms, including fatigue/effort intolerance Timing and duration of symptoms since start of acute COVID-19 History of other health conditions Exacerbations of pre-existing conditions
Patients presenting with cognitive symptoms/disorder	History of cognitive symptoms
Patients presenting with respiratory symptoms (cough and/or dyspnoea)	History of dyspnoea (at rest and exertion), cough, discomfort, pleuritic pain, wheezing
Objective assessment	
All patients over age 65 or who required hospitalisation during acute COVID-19 infection	Frailty assessment Sarcopenia assessment
All patients with persisting COVID-19 symptoms	Immune system tests
Patients presenting with effort intolerance/fatigue	Cardiopulmonary exercise testing 6-minute walk test Incremental shuttle walk Stair-climb test Lung function tests Complete blood count with differential chemistries: • renal and hepatic function tests • thyroid stimulating hormone • C-reactive protein • creatine kinase
Patients presenting with cardiac symptoms	Physical examination Postural blood pressure Electrocardiogram Thyroid-stimulating hormone level Transthoracic echocardiogram
Patients presenting with respiratory symptoms	Modified Borg dyspnoea scale SpO2 Presyncope or syncope [a] Postural blood pressure Chest CT Pulmonary function testing Echocardiogram CT pulmonary angiogram [b]
Patients presenting with fatigue	Complete blood count with differential chemistries: • renal and hepatic function tests • thyroid stimulating hormone • C-reactive protein • erythrocyte sedimentation rate • creatine kinase
Patients presenting with cognitive disorders/memory deficit/concentration difficulties	Physical examination determining: • baseline deficits • palsies • asymmetries • cognitive testing

Patients presenting with sleep disorders	Pittsburgh sleep quality index
Musculoskeletal symptoms	
Patients presenting with mobility dysfunction/decline	Cardiopulmonary exercise testing 6-minute walk test Incremental shuttle walk Stair-climb test Muscle strength testing
Patients presenting with pain, discomfort, joint pain, arthralgia	Visual analogue pain scale
Patients presenting with haematologic symptoms	Preoperative D-dimer measurement Venous ultrasound for thrombosis

Abbreviations:
CT = computed tomography, SpO2 = peripheral blood oxygen saturation
Notes:
a = patients with orthostasis
b = if unexplained cardiopulmonary symptoms and/or low SpO2 despite normal chest imaging

1.2 Summary

Introduction

Patients infected with SARS-CoV-2 may experience symptoms that persist for weeks to months after resolution of the initial infection (long COVID or post-COVID condition). The symptoms of long COVID are heterogenous. They may involve multiple organ systems and reflect an ongoing inflammatory condition that can result in significant deconditioning. As the pandemic progresses—albeit in a highly vaccinated community—and elective surgery resumes, it is likely that surgeons and their perioperative teams will encounter patients experiencing long COVID. Given that these patients may be deconditioned and have an ongoing inflammatory response, it is likely they will have increased surgical risks. At present, it is unclear whether long COVID influences postoperative outcomes and if an alteration in treatment approach, including delaying surgery, is required. This report highlights the impact of COVID-19 on surgery, with a particular emphasis on long COVID in adults and children.

Methods

A mixed methodology approach was used, consisting of a rapid review and input from a working group of clinicians. Biomedical and preprint databases and grey literature sources were searched. Eligible studies were selected using a hierarchical approach. In the first instance, studies were limited to systematic reviews and meta-analyses. Where evidence gaps remained, lower levels of evidence were included. Relevant studies were extracted and the results synthesised narratively.

Results

The pooled prevalence of long COVID ranges from 43% (95% CI 39–46%) to 56% (95% CI 45–66%) in adults. The pooled prevalence is 25% (95% CI 18–33%) in children and adolescents. Predominant long COVID symptoms relevant to surgery include effort intolerance, generalised pain/discomfort and mobility dysfunction/decline in adults; and fatigue, dyspnoea, headache, myalgia/arthralgia, abdominal pain and fever in children and adolescents. Clinical signs of long COVID in adults include increased oxygen requirements, chest imaging and/or pulmonary diffusion abnormalities (e.g. ground glass opacification, lung fibrosis and restrictive patterns on spirometry), elevated D-dimer and/or C-reactive protein, persisting lymphopaenia and tachycardia. In adults, common risk factors include more severe initial SARS-CoV-2 infection, female sex, body mass index (BMI) ≥25kg/m^2, comorbidities, poor general health and smoking. In children, significant risk factors include female sex, age 6–18 years, general pre-existing conditions, pre-existing pain, mobility or neurological conditions, ≥7 acute COVID-19 symptoms and hospitalisation for acute COVID-19. Being vaccinated for COVID-19 was a preventative factor for adults (RR 0.71 95% CI 0.58–0.8).

Generally, postoperative mortality and complications in patients with prior SARS-CoV-2 infection decrease with increasing time between the date of the first positive test and surgery. Patients who had mild COVID-19 symptoms had no increased risk of postoperative complications at any timepoint. Patients with moderate or severe COVID-19 had increased postoperative complications, generally persisting beyond 8 and 12 weeks, respectively.

At 7 weeks or longer after testing positive for SARS-CoV-2, patients who underwent surgery had similar odds/risks of postoperative mortality or developing pulmonary, thrombotic, septic or other complications as did patients without prior SARS-CoV-2 infection. Patients with ongoing COVID-19 symptoms at the time of surgery (whether 7 weeks or longer after testing positive for SARS-CoV-2) had increased risk of postoperative mortality, pulmonary complications and venous thromboembolism (VTE) relative to patients who were asymptomatic or those whose symptoms had resolved before surgery. There was no difference in postoperative complications between vaccinated patients undergoing surgery at 0–4, 4–8

and ≥8 weeks after testing positive for SARS-CoV-2 compared to patients who acquired COVID-19 30 days after surgery.

For individuals with persistent symptoms, delaying surgery beyond 7 weeks after testing positive for SARS-CoV-2 should be considered, with the proviso that the risks of surgery are balanced against the risks and potential consequences of delay. It is recommended that all patients with a history of COVID-19 infection have a dedicated clinical review prior to surgery determine any perioperative or postoperative risks, especially those who have not returned to their pre-COVID baseline.

Conclusion

Current advice regarding delaying surgery for individuals with long COVID or persisting COVID-19 symptoms remains uncertain. In patients with prior moderate or severe SARS-CoV-2 infection, there may be a greater risk of morbidity and mortality following surgery, even after a 7-week postponement following the onset of infection. Delaying surgery further can be considered, but this must be weighed against the risk of not proceeding and compromising patient care. It is difficult to draw firm conclusions from the current literature available, especially with lingering uncertainty regarding how long persisting COVID-19 symptoms may last. Tools to accurately determine the risk profile of patients should be considered, as operating on individuals with long COVID may become inevitable as the pandemic continues.

2 Introduction

2.1 Background

COVID-19 was declared a pandemic in March 2020 and has since caused substantive morbidity and mortality worldwide.[2] The disease COVID-19 results from infection with the virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[33] COVID-19 varies from asymptomatic to severe infection necessitating hospitalisation (severe lower respiratory disease, blood oxygen saturation [SpO2] ≤94% on room air).[4, 5] However, most patients experience mild symptoms (fever, cough and fatigue) to moderate symptoms (signs of lower respiratory disease e.g. shortness of breath, SpO2 ≥94% on room air) and recover without specific treatment within 14 days.[4, 5]

Following the resolution of the initial infection, some patients may experience relapsing–remitting or persistent symptoms that last for weeks to months after the initial infection has resolved (long COVID or post-COVID condition).[6] The symptoms of long COVID are heterogenous, involving multiple organ systems, and reflect an ongoing inflammatory condition that can result in significant deconditioning.[7, 8] Risk factors associated with the development of long COVID are still being determined, with preliminary data suggesting it is more common among those who had severe acute COVID-19, older persons, females and those with specific and/or pre-existing comorbidities.[7] There are no specific laboratory diagnostic tests to confirm long COVID, potentially resulting in underdiagnosis or overdiagnosis of this condition. The prevalence and impact of long COVID in children is also uncertain and requires further investigation. Children are of particular concern because they were among the last groups to receive COVID-19 vaccines and owing to their life expectancy they may experience ongoing symptoms for a much greater period of time.

As the pandemic progresses and elective surgery resumes, it is likely surgeons will encounter patients experiencing long COVID. It is presently unclear whether long COVID influences postoperative outcomes and if a delay to surgery is required. Given that these patients may be deconditioned and have an ongoing inflammatory response, it is likely they will have increased surgical risk. RACS completed a report highlighting the potential implications of COVID-19 on surgery in late 2020.[9] There were limited data characterising long COVID and its clinical implications at the time of writing. Since then, the evidence base has increased. Therefore, the current report updates the existing RACS report highlighting the impact of COVID-19 on surgery, with a particular emphasis on long COVID in adults and children.

2.2 Research questions

1. What is the prevalence of long COVID in adults and children?
2. What is the pathogenesis of long COVID in adults and children?
3. What are the symptoms of long COVID in adults and children?
4. What are the risk factors associated with developing long COVID in adults and children?
5. What are the postoperative outcomes in patients with previous SARS-CoV-2 infection?
6. What are the surgical implications of long COVID?

3 Prevalence, symptoms and risk factors associated with long COVID in adults

3.1 Summary

- Twenty-three publications addressed this question. These publications related to the prevalence, symptoms and risk factors associated with long COVID. The included studies varied considerably in their definitions of acute COVID-19 and long COVID, eligibility criteria, location of trial, method of reporting and timepoints assessed. This variability likely contributed to the observed heterogeneity in the results.
- In adults who previously tested positive for SARS-CoV-2, the pooled prevalence of long COVID ranged from 43% (95% CI [confidence interval] 39–46%) at 30–120 days to 56% (95% CI 45–66%) at 21–162 days post-infection in the meta-analyses.
- There was no clear trend in the prevalence of long COVID over time with 37% (95% CI 26–49%) of adults who previously tested for SARS-CoV-2 reporting long COVID at 30 days, 25% (95% CI 15–38%) at 60 days, 32% (95% CI 15–57%) at 90 days and 49% (95% CI 40–59%) at 120 days.
- Factors associated with increased risk of developing long COVID in adults include female sex, acute disease severity, admittance to an intensive care unit (ICU) during acute COVID-19 infection, BMI ≥25 kg/m^2, ≥1 comorbidity, chronic pulmonary disease, asthma, smoking, vaping, being unvaccinated against COVID-19 and contracting the Delta variant of SARS-CoV-2.
- In adults, common symptoms associated with long COVID include diminished general health, effort intolerance, pain/discomfort, mobility dysfunction/decline, fatigue, hindrance in daily function, sleep disorders, physical decline/fatigue and attention disorders.
- There was no clear trend in how symptoms of long COVID change over time. Compared to earlier timepoints, the prevalence increased, decreased or remained unchanged at later timepoints.
- Clinical signs associated with long COVID in adults include increased oxygen requirements, overall chest imaging abnormalities, pulmonary diffusion abnormalities, ground glass opacification, restrictive patterns on spirometry, lung fibrosis, tachycardia, elevated D-dimer and C-reactive protein levels, and persistent lymphopaenia.

3.2 Methodology

To address the aims of this review, a mixed methods approach was used consisting of a rapid review and input from a working group of clinicians. Rapid reviews are streamlined systematic reviews that can be completed in shorter timeframes. The targeted approach is limited in scope, inclusion criteria and resources.[10]

To identify relevant literature, systematic searches were conducted using a combination of medical subject headings and key words relating to the population, intervention, comparator and outcome (PICO) criteria (Table 2). Searches of MEDLINE (PubMed) were performed on 14 April 2022, in addition to searches of grey literature (government agencies and health department websites), preprint servers medRxiv and bioRxiv (monthly through to October 2022), and pearling of reference lists (Table A1, A2 and A3).

The population of interest was adults (≥18 years) with long COVID. At the time of searching, there was no standardised definition of long COVID across the published literature, with studies differing in how they defined the disease. When selecting eligible studies for review, the UK NICE definition of long

COVID was followed where possible, that is, 'signs and symptoms that continue or develop after acute COVID-19, including both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)'.[1] Additional definitions were also eligible for inclusion, including persistent manifestation 21 days after onset of COVID-19 symptoms. Studies providing this definition were used selectively and, where possible, data from later timepoints post-COVID-19 were used (>30 days).[11, 12]

Relevant outcomes included prevalence and symptoms of long COVID and risk factors associated with developing long COVID. Were possible, data relating to the prevalence and symptoms of long COVID were delineated into overall prevalence and prevalence per timepoint (e.g. 3, 6 or 12 months post-positive COVID-19 test). Symptoms of interest were those relevant to surgery and anaesthesia. Studies that focused exclusively on mental health symptoms or a specific symptom (e.g. fatigue only) were excluded.

When selecting eligible study designs a hierarchical approach was used. In the first instance, studies were limited to systematic reviews and meta-analyses. Where evidence gaps remained, lower levels of evidence were searched and selected for (e.g. large cohort, cross-sectional and case-control studies).

Identified citations were imported into Rayyan (Qatar Computing Research Institute, Al-Rayyan, Qatar) and underwent title and abstract screening by 2 researchers. A single researcher screened the full text of articles for inclusion and extracted data into a standardised template. Study selection utilised a data saturation method, preferentially selecting studies based on publication type, recency of publication and sample size. Thus, evidence bases for the prevalence, symptoms and risk factors differed, as reflected by the number and type of included studies addressing each outcome.

Table 2 PICO criteria for research questions 1–4 (adults)

Population	Adults with long COVID, defined as signs and symptoms that continue or develop after acute COVID-19 at ≥ 30 days (as per the minimum follow-up period in the included studies)
Intervention	NA
Comparator	NA
Outcome	Prevalence of long COVID in adults Symptoms of long COVID in adults Risk factors associated with developing long COVID in adults Impact of long COVID on surgery
Study design	Comparative and single-arm studies (systematic reviews, meta-analyses, RCTs, cohort, cross-sectional, case control studies)
Exclusion criteria	Letters, editorials, conference abstracts, literature reviews

Abbreviations:
NA = not applicable, RCT = randomised controlled trial

3.3 Results

Eighteen systematic reviews,[12-21] 9 of which performed meta-analyses;[11, 21-28] 2 cohort studies;[29, 30] 2 cross-sectional studies[31, 32] and one case-control study[33] were included in this section (Table A6). The systematic reviews were published from 2020 to 2022 and the observational studies were published in 2021 and 2022.[29-33] Thus, the systematic reviews and observational studies likely reflect populations that differ in their vaccination status and the strain of SARS-CoV-2 with which they were infected. The extent to which these factors impact the prevalence of long COVID is discussed below and remains uncertain.

Included studies varied with respect to their definition of long COVID. Three studies provided no definition.[26, 30, 31] Two studies provided no specific timeframes but were based around the development or persistence of symptoms after the acute phase.[25, 29] One study defined long COVID as persistent symptoms from 8 weeks after hospital discharge,[24] another defined it as persistent symptoms from 2 weeks after recovery from COVID-19.[16] Two studies defined long COVID as persistent manifestations from 21 days after onset of COVID-19 symptoms.[11, 12] Ten studies had similar definitions based around new or persistent symptoms from 4 weeks after acute COVID-19 infection;[12, 13, 15, 18, 21, 22, 27, 33, 34] 5 studies required 3 months of persistent symptoms.[14, 19, 20, 28, 32] One study defined long COVID as persistent symptoms and evidence of organ damage ≥2 months after hospital discharge for acute COVID-19.[17]

The method of diagnosing COVID-19 (or SARS-CoV-2 infection) also varied. Diagnosis methods were not reported in 4 studies.[13, 17, 21, 28] One study did not require a positive test for COVID-19 as a prerequisite for diagnosis.[12] Three studies had vague diagnostic criteria, including participants who tested positive or were suspected of SARS-CoV-2 infection[15] or those who had 'confirmed SARS-CoV-2 infection'[26] or those with 'confirmed positive test for SARS-CoV-2.'[27] The remainder of the studies used clinical and laboratory methods for confirming COVID-19 or SARS-CoV-2, including nucleic acid testing, RT-PCR (reverse transcription polymerase chain reaction) testing, antibody testing, blood tests or rapid antigen tests.[11, 14, 16, 18-20, 22-25, 29-33]

The number of studies and participants included within the systematic reviews ranged from 9 to 84 studies and 3,000 to 17,256,654 participants, respectively. The included populations were generally older (≥50 years) with equal representation of men and women. Acute COVID-19 hospitalisation status was not reported in 4 studies;[17, 21, 23, 33] 4 studies included only hospitalised patients[24, 28, 29, 31] and 2 included only non-hospitalised patients.[12, 30] The remainder included both hospitalised and non-hospitalised individuals.[11, 13-16, 18-20, 22, 25-27, 32] There was limited information regarding other demographic factors; patient comorbidities[11 12] and BMI[24] was reported in only a couple of systematic reviews. Greater information relating to patient demographics was reported in the observational studies, for instance comorbidities were listed in 4 of the 5 studies.[28-30, 32]

Prevalence of long COVID in adults

The cumulative pooled prevalence of long COVID was reported in 2 meta-analyses and ranged from 43% (95% CI 39–46%)[22] to 56% (95% CI 45–66%)[11] in individuals previously testing positive for SARS-CoV-2 or suspected of having COVID-19 (Table 3). The cumulative pooled prevalence was 49% (95% CI 35–63%) in women and 37% (95% CI 24–51%) in men, but higher in those who were hospitalised during their initial infection (54%, 95% CI 44–63%) compared to non-hospitalised persons (34%, 95% CI 25–46%).[22] Likewise, those admitted to ICU reported greater prevalence compared to those not admitted to ICU during their initial infection (34–84%).[14] The prevalence of long COVID among studies performed in USA, Europe and Asia was similar at 31% (95%CI 23–43%), 44% (95%CI 32–56%) and 51% (95%CI 37–65%), respectively.[22]

Four systematic reviews provided estimates of long COVID at specific timepoints. In one review, the prevalence of long COVID significantly differed over time; however, the direction of effect was inconsistent, with the prevalence of long COVID decreasing from 30 and 60 days and increasing from 90 to 120 days.[22] The authors hypothesised this was due to studies predominantly using hospitalised patient populations from 90 days onwards.[22] In 3 other reviews, the prevalence of long COVID was relatively similar (50–60%) at 30–90 days, >90 days and >180 days after a positive test.[13-15] The prevalence of long COVID in hospitalised patients also varied across time. However, it is unclear whether the prevalence increased or decreased, owing to inconsistent results across the systematic reviews and the different definition used in the study by Domingo (2021).[14] There was no literature reporting whether the prevalence of long COVID differed over time among male and female patients or by region.

Table 3 Prevalence of long COVID in adults

Date from acute COVID-19 infection	Overall prevalence mean (95%CI)	Subgroups mean (95%CI)			
		Hospitalised	Non-hospitalised	Male	Female
Overall[11, 22]	43% (39–46%) to 56% (45–66%)	54% (44–63%)	34% (CI 25–46%)	37% (24–51%)	49% (35–53%)
30 days[22]	37% (26–49%)	-	-	-	-
60 days[22]	25% (15–38%)	-	-	-	-
90 days[22]	32% (15–57%)	-	-	-	-
120 days[22]	49% (40–59%)	58% (47–68%)	-	-	-
30–90 days[14, 15]	59–61%* (NA)	44% (34–54%)	-	-	-
>90 days[14, 15]	53–62%* (NA)	14% (8–26%)	-	-	-
≥180 days[13]	54% (31–67%)	-	-	-	-

Abbreviations:
CI = confidence interval, NA = not available.
Notes:
*Prevalence range reflects the results from 2 meta-analyses: 30–90 days was equivalent to 4–12 weeks, >90 days was >12 weeks, 180 days was ≥6 months.

Symptoms and signs of long COVID in adults

Eleven systematic reviews were used to determine the symptoms associated with long COVID.[11, 12, 14, 16, 17, 22-27] Owing to the availability of systematic reviews evaluating symptoms, 3 representative systematic reviews were selected per symptom (Table 4). Reviews were selected based on recency and size of the review. Symptoms reported in only a single meta-analysis were excluded from the narrative (owing to their relative rarity) and are listed in Table A9.

Increased oxygen requirements, and chest imaging and pulmonary diffusion abnormalities were the most common clinical signs associated with long COVID (Table 4). Lung fibrosis and tachycardia were less frequently encountered in individuals with long COVID.

The most common long COVID symptoms relevant to surgery and anaesthesia are effort intolerance, generalised pain and discomfort, and mobility dysfunction/decline (Table 5). The prevalence of these

symptoms varied substantially based on the lowest and highest pooled estimates from the included reviews. The prevalence of symptoms varied across time but a clear trend could not be ascertained.

Table 4 Clinical signs of long COVID in adults

Clinical sign	Median prevalence	Interquartile range
Increased oxygen requirement[13]	65%	39.3–76.1
Overall chest imaging abnormalities[13]	62%	45.8–76.5
Pulmonary diffusion abnormalities[13]	30%	22.1–38.5
Ground glass opacification[13]	23%	19.7–43.0
Restrictive patterns on spirometry[13]	10%	6.1–24.1
Lung fibrosis[13]	7%	2.5–17.7
	Prevalence	**95% CI**
Elevated D-dimer[31]	30%	N/A
Elevated C-reactive protein[31]	10%	N/A
Persisting lymphopaenia[31]	7%	N/A
Tachycardia[22]	6%	3–11%

Notes:
Median prevalence reflects the results from 1 meta-analysis, which included patients with ongoing symptoms 1–6 months following the initial SARS-CoV-2 infection.
Prevalence reflects the results from a single cross-sectional study.

Table 5 Most common symptoms relevant to surgery associated with long COVID in adults

	Cumulative pooled prevalence		Prevalence per timepoint				
Clinical manifestation	**Lowest pooled estimate (95% CI)**	**Highest pooled estimate (95% CI)**	**1 to 3 months* pooled estimate (95% CI)**	**6 to <6 months pooled estimate (95% CI)**	**6 to <9 months pooled estimate (95% CI)**	**>180 days pooled estimate (95% CI)**	**12 months pooled estimate (95% CI)**
Effort intolerance	19% (7–35%)[23]	45% (25–67%)[23]	-	19% (7–35%)[23]	45% (25–67%)[23]	-	-
Pain/discomfort	13% (7–24%)[24]	42% (28–55%)[35]	-	-	-	-	-
Mobility dysfunction/decline	15% (8–31%)[24]	37% (28–47%)[12]	-	-	-	-	-
Fatigue	23% (17–30%)[22]	36% (27–46%)[23]	23% (17–30%)[22]	32% (22–44%)[23]	36% (27–46%)[23]	-	-
Sleep disorders	12% (7–17%)[26]	29% (15–45%)[23]	-	24% (8–44%)[23]	29% (15–45%)[23]	-	12% (7–17%)[26]
Dyspnoea	18% (13–24%)[26]	25% (17–34%)[23]	-	25% (17– 34%)[23]	25% (20– 30%) [23]	-	-
Joint pain/arthralgia	8% (3–21%)[25]	23% (15–31%)[23]	-	14% (4–27%)[23]	23% (15–31%)[23]	8% (3–21%)[25]	26% (8–44%)[26]
Cognitive disorder	14% (3–31%)[23]	19% (7–31%)[26]	-	14% (3–31%)[23]	15% (6–27%)[23]	-	19% (7–31%)[26]
Cough	5% (4–7%)[26]	15% (10–21%)[23]	-	15% (10–21%)[23]	12% (6–20%)[23]	-	5% (4–7%)[26]
Palpitations	5% (3–7%)[26]	14% (8–31%)[23]	-	14% (5–24%)[23]	14% (8–31%)[23]	-	5% (3–7%)[26]

Abbreviations:
CI = confidence interval
Notes:
* documented as 30–120 days in the literature

Two observational studies reported the difference in symptoms between vaccinated and unvaccinated individuals experiencing post-COVID symptoms (Table 6 and Table A10).[29, 32] Kuodi et al (2021) reported that individuals who received 2 vaccine doses prior to a positive SARS-CoV-2 test were less likely to report fatigue (relative risk [RR] 0.36; p = 0.003), headache (RR 0.46; p = 0.010), weakness in limbs (RR 0.43; p = 0.033), persistent muscle pain (RR 0.32; p = 0.028), hair loss (RR 0.17; p = 0.005), dizziness (RR 0.26; p = 0.018) and shortness of breath (RR 0.23; p = 0.026) compared to individuals who were unvaccinated at the time of initial SARS-CoV-2 infection.[32] Fernández-de-Las-Peñas et al (2022) reported that exertional dyspnoea was the only symptom that statistically differed between individuals vaccinated and unvaccinated against SARS-CoV-2 at the time of initial infection (93 vaccinated individuals experienced the symptom (85.2%) compared with 16 unvaccinated (17.4%); p < 0.001).[29]

Table 6 Proportion of individuals experiencing long COVID symptoms in individuals vaccinated (1 or 2 doses) at time of initial infection

Clinical manifestation	Proportion of individuals experiencing symptom who received 1 vaccine dose[32]	Proportion of individuals experiencing symptom who received 2 vaccine doses[32]	Risk of experiencing symptoms in individuals who received 2 vaccine doses[32] Risk ratio (95% CI)
Effort intolerance	-	-	-
Pain/discomfort	-	-	-
Mobility dysfunction/decline	6%	3%	NR
Fatigue	27%	11%	0.36 (0.16–0.71)
Sleep disorders	12%	5%	0.53 (0.18–1.61)
Dyspnoea	9%	5%	0.23 (0.07–0.84)
Joint pain/arthralgia	6%	2%	0.32 (0.11–0.88)
Cognitive disorder	13%	4%	NR
Cough	8%	7%	0.72 (0.28–1.83)
Palpitations	8%	4%	NR

Abbreviation:
NR = not reported
Notes:
Not all symptoms underwent adjusted analyses to calculate risk ratio in Kuodi et al (2021).[32]

Risk factors associated with developing long COVID

Nine studies and one clinical guideline were used to inform the risk factors associated with developing long COVID (Table 7).[17-20, 26, 28, 32, 33, 36]

Table 7 Risk factors (and protective factors) of long COVID in adults

Risk factor	Odds of developing long COVID odds ratio (95% CI)	Increased risk for specific signs/symptoms
Female sex compared to male sex	1.52 (1.27–1.82)[28] 1.72 (1.53–1.94)[19]	Dyspnoea, respiratory symptoms, fatigue
Acute disease severity (severe or critical) compared to non-severe or non-critical acute COVID-19	1.66 (1.08–2.57)[28] 2.31 (1.55–3.45)[19]	Dyspnoea, joint pain, palpitations TLC <80%, FEV1 <80%, FVC <80%, DLCO <80%
Acute disease severity (admitted to ICU compared with outpatient)	3.10 (1.18–8.11)[19]	-

BMI (≥25 kg/m^2 compared with <25 kg/m^2)	1.67 (1.00–2.78)[19]	-
Comorbidities ≥1	1.75 (1.36–2.24)[19]	-
Chronic pulmonary disease	1.47 (1.08–1.99)[19]	-
Asthma	1.32 (1.07–1.62)[1]	-
Smoking	1.35 (1.28–1.41)[1]	-
Vaping	1.26 (1.18–1.34)[1]	-
Poor pre-pandemic health	1.46 (1.17–1.83)[1]	-
Poor general health	1.62 (1.25–2.09)[1]	-
Protective factor	**Odds of developing long COVID odds ratio (95% CI)**	**Decreased risk for specific signs/symptoms**
Double vaccinated compared with unvaccinated	0.51 (N/A)–0.59 (0.50–0.69)[20]	-
Omicron strain compared to Delta with vaccine >6 months prior	0.36 (0.20–0.32)[33]	-
Omicron strain compared to Delta with vaccine 3–6 months prior	0.24 (0.19–0.32)[33]	-
Omicron strain compared to Delta with vaccine <3 months prior	0.50 (0.43–0.59)[33]	-

Abbreviations:
BMI = body mass index, CI = confidence interval, DLCO = diffusing capacity for carbon monoxide, FEV1 = force expiratory volume in 1 second, FVC = forced vital capacity, N/A = not available, TLC = total lung capacity.

Female sex

Three reviews, 2 of which included meta-analyses, informed this risk factor.[18, 19, 28] Two meta-analyses noted an increased odds of reporting long COVID in female compared with male patients (OR [odds ratio] 1.20 and 1.54, respectively).[19, 28] One narrative systematic review noted no difference in long COVID between males and females from 4 weeks to 6 months.[18] However, female patients were more likely to report specific symptoms such as fatigue and dyspnoea.[18]

Acute disease severity

Four reviews, 3 of which included a meta-analysis, evaluated the impact of initial COVID-19 severity on the development of long COVID.[18, 19, 28, 37] Individuals who had severe/critical COVID-19 had a greater risk of developing long COVID compared to those with non-severe/non-critical COVID-19 (OR 1.66 and 2.31, respectively).[19, 28] Furthermore, individuals admitted to ICU had an increased risk of long COVID compared to outpatients (OR 3.10).[19]

Long, Li (2021) determined the impact of initial COVID-19 severity on the prevalence of specific long COVID symptoms at 1–4 months post-discharge or 2–6 months post-admission.[37] Individuals with severe acute COVID-19 were more likely to develop musculoskeletal (OR 1.60; 95% CI 1.12–2.29), cardiopulmonary (OR 1.36; 95% CI 1.13–1.64) and psychosocial symptoms (OR 1.23; 95% CI 1.02–1.48). When compared to individuals with non-severe COVID-19, those with severe COVID-19 had increased odds of developing joint pain (OR 1.84; 95% CI 1.11–3.04), dyspnoea (OR 1.52; 95% CI 1.12–2.06), palpitations (OR 1.57; 95% CI 1.03–1.97), persistent abnormal pulmonary function (OR 2.17; 95% CI 1.73–2.72) and reduced lung volume measures including total lung capacity <80% (OR 3.05; 95% CI 1.88–4.96), forced expiratory volume in 1 second <80% (OR 2.72; 95% CI 1.3–5.63), forced vital capacity <80% (OR 2.52; 95% CI 1.28–4.98) and diffusing capacity for carbon monoxide <80% (OR 1.82; 95% CI 1.32–2.50).

Age

One narrative systematic review informed this risk factor.[18] Individuals age 40–60 years had increased risk of developing long COVID at 4–12 weeks. From 12 weeks to 6 months, individuals age 50–66 were more likely to have persistent symptoms compared to those in the youngest age group (0–17 years).

Body mass index

One meta-analysis reported that increased BMI (>25 kg/m^2) was associated with increased odds of developing long COVID compared with lower BMI (OR 1.67; 95% CI 1.00–2.78).[19]

Comorbidities

Two systematic reviews (one narrative and one with a meta-analysis) reported that individuals with at least one comorbidity had an increased risk of developing long COVID (OR 1.75; 95% CI 1.36–2.24).[18, 19] Additionally, hospitalised populations with chronic pulmonary disease had an increased risk of long COVID (OR 1.47; 95% CI 1.08–1.99).[19]

Vaccination status

Two systematic reviews, one of which performed a meta-analysis, reported individuals who were vaccinated before acquiring SARS-CoV-2 had a lower relative risk of developing long COVID (RR 0.71 95% CI 0.58–0.87).[20, 21] Two included studies found that 2 doses were more effective in reducing the risk of long COVID than a single dose. One included study also concluded that BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines were more successful for lessening the risk of long-COVID compared to Ad26.COV2.S (Janssen) vaccine.[20] Further data are awaited on the risk of long COVID following receipt of Omicron variant-specific vaccines.

COVID-19 strain

One cohort study compared the prevalence of long COVID between different SARS-CoV-2 strains. Following vaccination, individuals infected with the Omicron variant were less likely to report long COVID symptoms compared to those infected with the Delta variant at all timepoints and age groups (Table 8).[33]

Table 8 Risk of long COVID by age group, based on COVID-19 strain

Age group	Vaccine >6 months prior; Omicron compared with Delta OR (95% CI)	Vaccine 3–6 months prior; Omicron compared with Delta OR (95% CI)	Vaccine <3 months prior; Omicron compared with Delta OR (95% CI)
All age groups	0.36 (0.20–0.32)	0.24 (0.19–0.32)	0.50 (0.43–0.59)
18–59 years	0.23 (0.16–0.32)	0.33 (0.24–0.44)	0.41 (0.32–0.53)
≥60 years	0.28 (0.20–0.39)	0.46 (0.20–1.03)	0.54 (0.43–0.68)

Abbreviations:
CI = confidence interval, OR = odds ratio

Pathophysiology of long COVID in adults

Two systematic reviews informed the hypothesised pathophysiology of long COVID.[38, 39] The findings are reported by physiological system.

Central and peripheral nervous system

Neurological signs and symptoms are believed to be caused by a variety of central, peripheral and psychological factors.[39] Both systematic reviews report that the persisting neurological sequalae associated with long COVID may reflect SARS-CoV-2-induced neuroinflammation.[38, 39] SARS-CoV-2 is hypothesised to directly or indirectly activate resident immune cells of the central nervous system. The corresponding neuroinflammatory response may result in neuronal damage and dysfunction, particularly to the trigeminal nerve. The hypercoagulative state and mitochondrial failure arising from the peripheral immune response to SARS-CoV-2 may result in local micro-thrombosis within the central nervous system, furthering neural dysfunction. Collectively, these processes may underlie persisting neurological symptoms such as cognitive dysfunction, headache and loss of taste or smell.

Three mechanisms have been proposed to explain persistent fatigue; all relate to metabolic disruptions induced by inflammation. These include ongoing brain hypometabolism, mitochondrial dysfunction and dysregulated lymphatic drainage.[38, 39]

Cardiovascular system and coagulation disorders

Cardiovascular and coagulation disorders manifest physically as chest pain, palpitations, chest tightness and tachycardia, appearing biochemically as elevated serum troponin levels. Persisting symptoms may result from unresolved myocardial injury following the initial SARS-CoV-2 infection. The heart is a key site of SARS-CoV-2 infection owing to high levels of angiotensin-converting enzyme 2 receptor levels. This may result in a local immune response damaging cardiomyocytes, leading to cardiac injury and myocarditis and resultant coagulopathy and micro-thrombosis. This localised immune response appears to be sustained in individuals with long COVID, which likely contributes to the ongoing cardiovascular symptoms.[38]

Respiratory system

Respiratory system disorders manifest as dyspnoea, persistent cough, effort intolerance and increased oxygen requirements, chest imaging abnormalities, pulmonary diffusion abnormalities and lung fibrosis. Acute COVID-19 illness may damage the lungs and respiratory tract due to SARS-CoV-2 replicating in endothelial cells. The infection and corresponding immune response results in endothelial cell dysfunction and damage.[39] However, most patients have no signs of permanent or persistent lung damage.[39] Individuals exposed to supplementary oxygen are at risk of oxidative stress, potentially contributing to an inflammatory state producing lung fibrosis, a clinical sign of long COVID.[38] Lung vascular disorders may play a role in persistent symptoms, with micro-vessel damage potentially leading to pulmonary hypotension.[38] Furthermore, dyspnoea without pulmonary lesions may be related to inappropriate ventilation regulation resulting from a disordered or damaged autonomic nervous system.[38]

Immune, musculoskeletal, hepatobiliary and renal system

Mast cell activation and ongoing immune system deregulation with subsequent chronic low-grade inflammation could contribute to autoimmunity, leading to organ dysfunction and possibly long COVID symptomatology.[38] It has been suggested that thrombo-inflammatory mechanisms relating to tissue injuries and autoimmune processes may be a potential cause of bone, joint and muscle pain.[38] It has also been hypothesised that a cytokine storm during the acute phase of severe SARS-CoV-2 infection could lead to hepatobiliary damage, potentially leading to persistent symptoms.[38]

4 Prevalence, symptoms and risk factors associated with long COVID in children

4.1 Summary

- Three systematic reviews and 5 cohort studies addressed this question. The included studies varied in their definitions of long COVID, timepoints and outcomes measured, and method of data collection. This variability likely contributed to the observed heterogeneity of the results.
- In children who previously tested positive for SARS-CoV-2, the pooled prevalence of long COVID was 25.2%. In individuals without a history of SARS-CoV-2 infection, symptoms typical of those associated with long COVID occurred in 2% to 53% of children.
- Factors associated with increased risk of developing long COVID include female sex, previous SARS-CoV-2 exposure, older age, pre-existing conditions (allergies, mobility issues, pain issues, neurological comorbidities), greater number of acute SARS-CoV-2 symptoms and being hospitalised for COVID-19 for ≥48 hours.
- In children, the most common symptoms associated with long COVID include fatigue, dyspnoea, headache, myalgia/arthralgia, abdominal pain, fever, cough, mood disorders, diarrhoea and sleep disorders. Yet, it was unclear whether these symptoms occurred more frequently in children with long COVID compared to children without a history of COVID-19.

4.2 Methodology

As for the information pertaining to adults (Section 3), a mixed methods approach was utilised to address the aims of this review, consisting of a rapid review and input from a working group of clinicians.

To identify relevant literature, systematic searches of MEDLINE (via PubMed) were performed on 14 April 2022 (Table A5 and A6) using a combination of medical subject headings and key words relating to the PICO criteria (Table 9). A targeted keyword search of medRxiv and bioRxiv was also conducted (Table A7). Grey literature searches of government agencies and health department websites, as well as pearling of reference lists, were completed in October–November 2022 to identify further relevant literature.

The population of interest was children and young people (≤18 years) with long COVID. At the time of searching, there was no standardised definition of paediatric long COVID. As such, this review included articles with varying definitions of long COVID. Minimum criteria are based on the NICE definition of long COVID, which defines the condition as ongoing symptomatic COVID-19 (4–12 weeks) and post-COVID-19 syndrome (≥12 weeks).[40]

When selecting eligible studies, a hierarchical approach was used. In the first instance, studies were limited to systematic reviews and meta-analyses. Where evidence gaps remained, lower levels of evidence were utilised (e.g. large cohort studies). Data of interest were those relevant to surgery and anaesthesia in paediatric populations with long COVID. Studies exclusively focusing on mental health symptoms (e.g. anxiety and depression) or specific symptoms (e.g. fatigue only) were excluded from this review.

Identified citations were imported into Rayyan (Qatar Computing Research Institute, Al-Rayyan, Qatar) and underwent title and abstract screening by 2 researchers. Two researchers screened the full text of articles for inclusion; one reviewer extracted data into a standardised template.

Table 9 PICO criteria for research questions 1–4 (paediatrics)

Population	Paediatric patients (≤18 years) with long COVID, defined as signs and symptoms that continue or develop after acute COVID-19 at a minimum of 30 days (as per the minimum follow-up period in the included studies)
Intervention	NA
Comparator	NA
Outcome	Prevalence of long COVID in children Symptoms of long COVID in children Risk factors associated with developing long COVID in children Impact of long COVID on surgery in the paediatric population
Study design	Comparative and single-arm studies (systematic reviews, meta-analyses, RCTs, cohort, cross-sectional, case control)
Exclusion criteria	Letters, editorials, conference abstracts, literature reviews

Abbreviations:
NA = not applicable, RCTs = randomised controlled trials

4.3 Results

Three systematic reviews,[41-43] 2 of which performed meta-analyses,[41, 43] and 5 cohort studies[44-48] were included in this section (Table A11). All were published in 2022.

Included studies varied with respect to the definition of long COVID. Three studies had similar definitions based around new or persisting symptoms present at or beyond 4 weeks from acute COVID-19 infection.[41-43] Two studies defined long COVID as symptoms persisting for 3 months or longer.[47, 48] A further study used the definition of persistent or new symptoms at 3 months that last at least 2 months.[44] One study provided no definition.[46]

The method for diagnosing COVID-19 (or SARS-CoV-2 infection) was similar across studies; all used one or a combination of nucleic acid testing (in particular RT-PCR), antigen testing, serology, clinical diagnosis or lateral flow test.[41-48]

Total numbers in the systematic reviews ranged from 21–22 studies and 23,141–81,896 participants. The paediatric population consisted of patients age ≤18 years, with equal representation of males and females. The 3 systematic reviews[41-43] and 2 of the cohort studies[44, 46] included both hospitalised and non-hospitalised populations. One study recruited only hospitalised individuals, but these were not all hospitalised as a result of COVID-19.[47] Hospitalisation status was not reported in 2 studies.[45, 48]

Limited information regarding further demographic factors and comorbidities was provided in the systematic reviews and 3 of the cohort studies.[41-45] Two other cohort studies reported comorbidities[46, 47] and one reported demographics (index of multiple deprivation).[48]

Prevalence of long COVID in paediatric population

The overall prevalence of long COVID in children with a history of SARS-CoV-2 infection was reported in 2 systematic reviews with meta-analyses (42 studies combined) (Table 10).[41, 42] The pooled prevalence in children and adolescents was 25.2% (95% CI 18.2–33.0%), and it was 29% (95%CI 17.8–41.9%) in children hospitalised for acute COVID-19 symptoms.[41] In another review, the median prevalence was 13% (range 0–66.5%) yet, among children without prior SARS-CoV-2 infection, 2–53% reported symptoms typical of long COVID in the follow-up period.[42]

The variability and range within the reported data may reflect differences in the definition of long COVID, exposure definitions, outcome measures used, and heterogeneity of studies included within the

systematic review and meta-analysis. The large variability of post-COVID symptoms reported in paediatric individuals without acute COVID-19 reflects the broad definition and relatively non-specific symptoms associated with long COVID and highlights the importance of a control group when interpreting the data. Due to the variability of symptoms reported, it is probable that a child or young person without prior SARS-CoV-2 infection, could report symptoms similar to post-COVID-19 symptoms over the course of a year.

Table 10 Prevalence of long COVID in paediatric population

Author (year)	Individuals who tested positive to SARS-CoV-2 median (range) or mean (95% CI)	Individuals who tested positive to SARS-CoV-2 and hospitalised mean (95% CI)	Individuals without acute SARS-CoV-2 who reported symptoms typical of long COVID (range)
Hirt (2022)[42]	13% (0–66.5%)	NR	2–53%
Lopez-Leon (2022)[41]	25.2% (95% CI 18.2–33.0%)	29.2% (95% CI 17.8–41.9%)	NR

Abbreviations:
CI = confidence interval, NR = not reported

Symptoms of long COVID in paediatric patients

Two systematic reviews with meta-analyses,[41, 43] and a population-based cohort study[44] were available to determine the symptoms associated with long COVID in a paediatric population. Where symptoms were reported in more than one review a range is provided. The complete list of paediatric symptoms is shown in Table A12.

The most common symptoms relevant to surgery are fatigue, dyspnoea, headache, myalgia/arthralgia, abdominal pain and fever (Table 11). Prevalence of these symptoms spanned a wide range based on the lowest and highest pooled estimates from the included reviews. (This is likely attributable to heterogeneity in the included studies and differing definitions of long COVID.)

The relative prevalence of long COVID symptoms between cases and controls was compared in two meta-analyses and one population cohort study. The meta-analyses identified few differences in the prevalence of symptoms typical of long COVID in children and adolescents who tested positive for SARS-CoV-2 and those who did not throughout the follow up period.[41, 43] In the population study, children and adolescents who tested positive for SARS-CoV-2 had a higher incidence of fatigue, dyspnoea, headache, abdominal pain and fever compared to those who tested negative over the study period.[44] The relative risk and incidence risk ratio of symptoms for children with and without prior COVID-19 are presented in Table 11.

Table 11 Common symptoms of long COVID in paediatric population

	Non-comparative evidence (case)	Comparative evidence (case vs controls)		
	Meta-regression	Meta-analyses		Population cohort study
Symptoms	Pooled estimate of prevalence (95% CI) [41, 43]	Risk difference (95% CI)[43]	Odds ratio (95% CI)[41]	IRR (95% CI)[44]
Fatigue	9.7% (4.5–16.5%) to 47.0% (32.0–62.0%)	7.0% (-1.0–14.0%)	2.79 (0.66–11.75)	2.28 (1.71–3.06)*

Dyspnoea	43.0% (18.0–68.0%)	4.0% (-0.09–16.0%)	2.69 (2.30–3.14)*	2.88 (2.73–3.02)*
Headache	7.8% (4.0–12.7%) to 35.0% (19.0–51.0%)	5.0% (1.0–8.0%)	1.95 (0.69–5.52)	1.58 (1.35–1.84)*
Myalgia/arthralgia	3.7% (2.2–5.7%) to 25% (11.0%–40.0%)	1.0% (-1.0–4.0%)	1.09 (0.91–1.31)	NR
Abdominal pain	2.9% (2.0–3.9%) to 25.0% (9.0%–42.0%)	1.0% (0.0%–2.0%)	NR	1.45 (1.27–1.64)*
Fever	1.8% (0.5%–3.9%) to 18.0% (5.0%–32.0%)	0.0% (0.0%–1.0%)	2.23 (1.22–4.07)*	1.56 (1.30–2.02)*

Abbreviations:
CI = confidence interval, NA = not available
Notes:
*p value < 0.05

Risk factors for developing long COVID in paediatric populations

Four cohort studies were used to inform the risk factors associated with developing long COVID (Table 12).[45-48] There was no information regarding the impact of vaccination on the risk of developing long COVID in a paediatric population.

Table 12 Risk factors (and protective factors) associated with long COVID in paediatric population

Risk factor	Odds of developing long COVID OR (95% CI)	Increased risk for specific signs/symptoms
Age		
<2 years (compared to age 2–11)[45]	1.87 (0.66–5.32)	-
12–17 years (compared to age 2–11)[45]	2.67 (1.56–4.57)	-
14–18 years (compared to <1 year)[46]	2.67 (1.43–4.99)	-
6–11 years (compared to <2 years)[47]	2.57 (1.29–5.36)	-
12–18 (compared with <2 years)[47]	2.52 (1.34–5.01)	-
14–15 years (compared to age 11–13)[48]	1.88 (1.65–2.16)	-
16–17 years (compared to age 11–13)[48]	2.16 (1.92–2.45)	-
Previous SARS-CoV-2 exposure		
Evidence of/tested positive to SARS-CoV-2 (compared to no exposure) [45, 48]	1.49 (1.35–1.64) to 2.48 (1.00–6.13)	-
Sex		
Female (compared to males) [45, 48]	1.79 (1.07–2.99) to 2.22 (2.00–2.48)	Cough, fatigue, headache, myalgia, dyspnoea, loss of smell
Pre-existing conditions		
General pre-existing conditions[45]	2.95 (1.59–5.45)	-
History of allergic diseases at >5 months[47]	1.67 (1.04–2.67)	-
History of allergic disease at 12 months[47]	2.66 (1.04–6.47)	-

Problems with mobility before SARS-CoV-2[48]	4.19 (3.32–5.30)	-
Problems with pain before SARS-CoV-2[48]	5.51 (4.77–6.36)	-
Pre-existing neurological comorbidities (symptoms at 6 months)[47]	4.38 (1.36–15.67)	-
Pre-existing neurological comorbidities (symptoms at 12 months)[47]	8.96 (2.55–34.82)	-
Acute COVID-19 symptoms		
5+ acute SARS-CoV-2 symptoms (compared to no symptoms)[48]	1.86 (1.62–2.15)	-
4–6 acute SARS-CoV-2 symptoms (compared to 1–3 symptoms)[46]	2.35 (1.28–4.31)	-
≥7 acute SARS-CoV-2 symptoms (compared to 1–3 symptoms)[46]	4.59 (2.50–8.44)	-
Hospitalisation status		
Hospitalised for acute illness ≥48 hours (compared to no hospitalisation)	2.67 (1.63–4.38)	-
Protective factor	**Odds of developing long COVID OR (95% CI)**	**Decreased risk for specific signs/symptoms**
Asian/Asian-British ethnicity (compared to Caucasian)	0.76 (0.62–0.93)	-
1–4 symptoms during COVID-19 infection (compared to 0 symptoms)	0.44 (0.34–0.57)	-

Abbreviations:
CI = confidence interval, OR = odds ratio

Age

Four studies described the effect of age on risk of long COVID in paediatric populations.[45-48] Relative to younger children, older children had increased odds of reporting long COVID symptoms.

Female sex

Four studies described the effect of sex on the risk of long COVID in paediatric populations.[45-48] Of these, 2 studies reported no significant effect,[46, 47] whereas 2 found that females had increased odds of reporting long COVID symptoms compared to males (OR 1.79 95% CI 1.07–2.99 to 2.22 95% CI 2.00–2.48).[45, 48] Females were more likely to report specific symptoms such as cough, fatigue, headache, myalgia, dyspnoea and loss of smell.[43]

Comorbidities

Four studies described the effect of pre-existing conditions on risk of long COVID in paediatric populations.[45-48] General pre-existing conditions increased the odds of long COVID symptoms (OR 2.95 95% CI 1.59–5.45). [45] Three studies were more specific, listing history of allergic diseases at >5 months (OR 1.67; 95% CI 1.04–2.67)[47] and 12 months (OR 2.66; 95% CI 1.04–6.47)[47], pre-existing neurological comorbidities at 6 months (OR 4.38, 95% CI: 1.36–15.67) and 12 months (OR 8.96, 95% CI: 2.55–34.82)[48], mobility problems (OR 4.19; 95% CI 3.32–5.30) and problems with pain (OR 5.51 (95% CI 4.77–6.36)[48] as being associated with increased odds of long COVID. One study found no effect of general pre-existing chronic conditions.[46]

Acute disease severity

Two studies reported the effect of acute SARS-CoV-2 symptoms on long COVID risk.[46, 48] Both showed that a greater number of acute SARS-CoV-2 symptoms increased the odds of long COVID. Increased odds of long COVID were reported in paediatric patients with ≥5 symptoms when compared to those with no symptoms at the time of testing (OR 1.86; 95% CI 1.62–2.15)[48] and in paediatric patients who reported 4–6 symptoms (OR 2.35; 95% CI 1.28–4.31) or ≥7 symptoms (OR 4.59; 95% CI 2.50–8.44) compared to 1–3 symptoms.[46]

One study compared the effect of ≥48 hours of hospitalisation for acute COVID-19 illness compared to no hospitalisation and found an increased risk of long COVID with hospitalisation (OR 2.67; 95% CI 1.63–4.38).[46]

Previous SARS-CoV-2 infection

Two studies reported the effect of previous SARS-CoV-2 infection on the risk of long COVID in paediatric populations.[45, 48] Both reported that children who had evidence of SARS-CoV-2 infection or tested positive were more likely to report persistent symptoms typical of long COVID compared to children without prior SARS-CoV-2 infection (OR 1.49 95% CI 1.35–1.64 to 2.48 95% CI 1.00–6.13).

5 Postoperative outcomes in patients with prior SARS-CoV-2 infection

5.1 Summary

- Two prospective and 7 retrospective comparative studies were included. The studies evaluated postoperative outcomes in patients with prior SARS-CoV-2 infection. The studies were heterogeneous and differed in the outcomes and timepoints assessed as well as baseline patient characteristics.
- Generally, postoperative mortality and complications in patients with prior SARS-CoV-2 infection decrease with increasing time between the date of the positive test and surgery.
- At 7 weeks or longer after testing positive for SARS-CoV-2, patients who underwent surgery had similar odds/risk of postoperative mortality or developing pulmonary, thrombotic, septic or any other complications as did patients without prior SARS-CoV-2 infection.
- Patients with ongoing COVID-19 symptoms at the time of surgery (whether 7 weeks or longer after testing positive for SARS-CoV-2) had increased risk of postoperative mortality, pulmonary complications and VTE relative to patients who were asymptomatic or whose symptoms had resolved before surgery.
- Severity of the initial infection was associated with postoperative outcomes. There was no difference in postoperative complications among patients with mild COVID-19 whose surgery occurred 0–4, 4–8, 8–12 or >12 weeks after testing positive for SARS-CoV-2. Patients with moderate and severe COVID-19 had increased odds of postoperative complications. The odds remained elevated when surgery occurred ≥8 and ≥12 weeks after testing positive, respectively.
- There was no difference in postoperative complications between vaccinated patients who underwent surgery within 0–4, 4–8 and ≥8 weeks after testing positive for SARS-CoV-2 compared to patients who acquired COVID-19 30 days after surgery.
- The grade or urgency of surgery did not impact postoperative mortality or pulmonary complications in patients who tested positive to SARS-CoV-2 ≤7 weeks before surgery.

5.2 Methods

The research questions aimed to determine whether postoperative mortality and complications increase in patients with prior history of SARS-CoV-2 infection compared to patients without prior infection. Targeted searches of PubMed and google scholar were conducted on 17–18 September 2022 using the following phrases: ‘timing of surgery’, ‘SARS-CoV-2 infection’, ‘post COVID’ and ‘surgery’. In addition, the reference lists of identified studies were pearled to identify other literature of relevance. Study selection and data extraction were performed by a single reviewer.

To be eligible for inclusion, studies were screened against the PICO criteria outlined in Table 13. The population of interest was patients undergoing surgery who had previously tested positive to SARS-CoV-2 (case group). The comparator population was patients undergoing surgery who had not previously tested positive to SARS-CoV-2 or patients who tested positive ≥30 days after surgery (control group). Only studies that included a case and control group were eligible for inclusion. Outcomes of interest related to the safety of the operation, including postoperative mortality and complications. Complications were grouped according to the following themes: respiratory and pulmonary complications (respiratory failure, acute respiratory distress syndrome [ARDS], need for mechanical ventilation), cardiovascular and thrombotic complications (deep vein thrombosis [DVT], pulmonary

embolism, myocardial infarction [MI], arrhythmia, ischaemic stroke), renal complications (renal failure, urinary tract infection) sepsis and mortality (30- and 90-day).

Table 13 PICO Criteria for research question 5

Population	Patients undergoing surgery who have previously tested positive for SARS-CoV-2
Comparator population	Patients undergoing surgery who have not previously tested positive for SARS-CoV-2 or patients who tested positive for SARS-CoV-2 ≥30 days after surgery
Outcome	Postoperative mortality and complications (e.g. pulmonary, respiratory, cardiovascular, thrombotic, renal, hepatic)
Study design	Comparative studies with a control group (comparator population),
Exclusion criteria	Case reports, single-arm studies, letters, reviews

5.3 Characteristics of included studies

Ten publications encompassing 9 unique studies were included. Two publications were derived from the prospective COVIDSurg and GlobalSurg Collaborative study that included 1,674 hospitals across 116 countries.[49, 50] The remaining 7 studies were retrospective analyses of hospital databases in the US or prospective analyses of French tertiary centres. Four studies were propensity-matched; 5 did not match the control and case groups. Six studies were performed in 2020–2021 before the widespread availability of COVID-19 vaccines. Three studies were performed in 2020–2023 and included vaccinated patients (9–86% of included patients). Three studies stratified results by vaccination status. The studies did not specify the COVID-19 variant to which patients tested positive; however, the study dates of 5 trials indicate the outcomes likely reflect earlier variants of COVID-19 (e.g. pre-Omicron). Four studies covered timepoints encompassing the Alpha, Delta and Omicron variants.

Study eligibility criteria were generally broad, including adult patients who underwent any surgical procedure during the specified timeframe. Two studies were exclusively of patients undergoing elective major surgery. The remaining studies did not specify the type of operation or included a mix of major and minor procedures. General surgery and orthopaedics-related procedures were the most common, accounting for approximately 40% of evaluated procedures. Neurosurgery, cardiothoracic, head and neck, obstetrics and gynaecology, plastic and reconstructive, and urological procedures were less common (<10% per speciality). Most procedures were major elective operations requiring general anaesthesia.

Positive COVID-19 cases were confirmed using RT-PCR. The COVIDSurg Collaborative study also inferred SARS-CoV-2 infection from changes on computed tomography (CT) scans, antibody tests and presentation of symptoms consistent with COVID-19 because access to RT-PCR and rapid antigen tests (RATs) was limited during the study period. All studies stratified patients based on the date of their first positive test relative to the date of surgery; however, there was limited consistency among stratification groups and each study differed slightly (e.g. 0–2 weeks and 0–4 weeks before surgery). Control groups also varied, including patients who tested negative to SARS-CoV-2 or had no symptoms prior to surgery and patients who tested positive (via RT-PCR) to SARS-CoV-2 more than 30 days after surgery.

Patient demographics varied between studies, with the largest variations observed in the proportions of female patients (5–61%), patients with comorbidities (4–79%), and degree of surgical risk according to ASA score (American Society of Anesthesiologists physical status classification system) (15–82%). Larger propensity-matched studies tended to have more representative datasets with limited differences between groups. Studies that did not conduct propensity-matching contained small statistical differences in age, presence of comorbidities, surgery type and proportions of vaccinated patients. Only three studies reported the proportions of patients that were symptomatic at the time of surgery.

Reported outcomes included postoperative mortality or complications within 30 or 90 days post-surgery. Several studies combined pulmonary- or thrombosis-related complications into a pooled outcome rather than reporting individual complications separately. Most studies performed multivariate analyses of the dataset and accounted for confounding variables such as age, sex, race, BMI, smoking status, ASA score and urgency of surgery. The reference group for comparisons in the multivariate analysis was patients without a history of SARS-CoV-2 or COVID-19, patients who developed COVID-19 after surgery or patients who tested positive for SARS-CoV-2 more than 8 weeks prior to surgery.

5.4 Postoperative outcomes

Adverse postoperative outcomes decline with increasing time since infection in patients with perioperative SARS-CoV-2 infection, yet uncertainty remains as to how long surgery should be postponed following a positive SARS-CoV-2 test.[51] Older recommendations are based predominantly on the COVIDSurg and GlobalSurg Collaborative trial.[49] More recent studies evaluating postoperative mortality and complications in patients with prior SARS-CoV-2 have since been published. Table 14 provides an overview of contemporary research summarising the optimal timing of surgery after SARS-CoV-2 infection. Specifically, it highlights the time at which patients with prior SARS-CoV-2 infection exhibit similar postoperative mortality and complication outcomes to patients without prior SARS-CoV-2 infection.

Table 14 Time interval before postoperative outcomes for SARS-CoV-2-positive patients are equivalent to outcomes for patients without prior SARS-CoV-2 infection

	Mortality	Any complication	Pulmonary / respiratory complication	Cardiovascular / thrombotic complication	Sepsis
COVIDSurg Collaborative & GlobalSurg Collaborative (2021)[49]	≥7 weeks	NA *	≥7 weeks	NR	NR
COVIDSurg Collaborative & GlobalSurg Collaborative (2022)[50]	≥7 weeks	NA	NR	≥7 weeks	NR
Lal (2021)[52]	NR	NR	NR	NR	Did not return to baseline in study period (>30 days)
Deng (2022)[53]	NR	8 weeks	4–8 weeks [a]	NR	4–8 weeks [a]
Kougias (2022)[54]	>9 weeks	NR	NR	NR	NR
Le (2022)[55]	NR	4–8 weeks [a, b]	NR	NR	NR
Prasad (2022)[56]	Did not return to baseline in study period (≥5 weeks)		Did not return to baseline in study period (≥5 weeks)	≥5 weeks	≥5 weeks
Garnier (2023)[57]	3 weeks [c]	NR	3 weeks [c]	NR	NR
SenthilKumar (2023)[58]	NA	NR	NR	4–8 weeks [d]	NR
Verhagen (N.D)[e59]	8–12 weeks	8–12 weeks	NR	NR	4–8 weeks

Abbreviations:

NA = not available, NR = not reported

Notes:

[a] = Outcomes in patients undergoing major elective surgery

[b] = Pooled complications included arrhythmia, deep vein thrombosis, pulmonary embolism, pneumonia, respiratory failure, renal failure, sepsis and urinary tract infection

[c] = There was no difference in respiratory complications or mortality at any time point assessed; 3 weeks was the earliest timepoint reported

[d] = Major adverse cardiac events

[e] = article identified on medRxiv; yet to be published in a peer-reviewed journal

Mortality

The impact of prior SARS-CoV-2 infection on postoperative mortality was assessed in 5 studies (6 publications).[49, 50, 54, 56, 57, 59] In general, patients with prior SARS-CoV-2 infection had higher postoperative mortality than did patients without prior SARS-CoV-2 infection. Postoperative mortality was highest in patients diagnosed with SARS-CoV-2 at 0–2[49] and 0–4 weeks[56, 59] before surgery. Postoperative mortality in patients with prior SARS-CoV-2 decreased with increasing time between the date of diagnosis and surgery. There was no difference in relative postoperative mortality when surgery was performed ≥7 weeks after SARS-CoV-2 infection in the COVIDSurg Collaborative trial,[49] 8–12 weeks in a large study of patients undergoing elective surgery,[59] and ≥9 weeks in a smaller trial of patients undergoing elective major surgery.[54] The study by Prasad et al, found that postoperative mortality remained elevated in patients with prior SARS-CoV-2 infection at the maximum timepoint assessed (≥5 weeks). [56]

A recent study enrolled vaccinated patients (86% fully vaccinated) who underwent surgery from March to May 2022 (during the Omicron wave).[57] There was no difference in postoperative mortality between patients with preoperative COVID-19 3 or 6 weeks before surgery and patients without prior history of COVID-19.

Any complications

The impact of prior SARS-CoV-2 infection on any postoperative complication was reported in 2 studies.[53, 59] Postoperative complications were greater in patients diagnosed with SARS-CoV-2 at 0–4 and 4–8 weeks before surgery relative to patients without prior SARS-CoV-2 infection. There was no difference in postoperative complications when surgery was performed ≥8 weeks or 8–12 weeks after SARS-CoV-2 infection.[53 59]

Respiratory and pulmonary complications

Pooled complications

The impact of prior SARS-CoV-2 infection on pooled postoperative pulmonary complications was reported in 2 studies.[49, 56] In general, patients with prior SARS-CoV-2 infection had greater pulmonary complications than did patients without prior SARS-CoV-2 infection. Pulmonary complications were highest in patients diagnosed with SARS-CoV-2 at 0–4 and 0–6 weeks before surgery. Surgery performed at ≥5 or ≥7 weeks after SARS-CoV-2 diagnosis was still associated with higher postoperative pulmonary complications relative to patients without prior SARS-CoV-2 diagnosis.[49, 56]

A recent study enrolled vaccinated patients (86% fully vaccinated) who underwent surgery from March 2022 to May 2022 (during the Omicron wave).[57] Patients with preoperative COVID-19 3 or 6 weeks before surgery had no increase in respiratory complications compared to patients without history of COVID-19.

Individual complications

The odds of specific pulmonary complications (pneumonia, respiratory failure, ARDS, need for postoperative mechanical ventilation) were reported across 3 studies.[52, 53, 59] In patients with prior SARS-CoV-2 infection, the odds of developing respiratory failure or pneumonia remained high when surgery occurred at 0–4 and 0–8 weeks of diagnosis, relative to patients without prior SARS-CoV-2 infection.[53, 59] There was no difference in either outcome when surgery occurred ≥8 weeks after SARS-CoV-2 infection.[53, 59] Surgery performed >30 days after SARS-CoV-2 diagnosis was associated with higher odds of ARDS relative to patients without prior diagnosis of SARS-CoV-2, whereas the need for postoperative mechanical ventilation was similar in patients with or without prior SARS-CoV-2 infection.[52]

Cardiovascular and thrombotic complications

Pooled complications

The impact of prior SARS-CoV-2 infection on pooled postoperative cardiovascular or thrombotic complications was reported in 3 studies.[50, 56, 58] In general, patients with prior SARS-CoV-2 infection had greater cardiovascular and thrombotic complications than did patients without prior SARS-CoV-2 infection. Cardiovascular and thrombotic complications were highest in patients diagnosed with SARS-CoV-2 at 0–4 and 1–6 weeks before surgery relative to patients without prior SARS-CoV-2. [50, 56, 58] There were no differences in postoperative thrombotic complications when surgery was performed at ≥7 weeks after SARS-CoV-2 infection (COVIDSurg Collaborative trial[50]) or ≥5 weeks (Prasad et al, 2022[56]).There were no differences in cardiovascular complications when surgery was performed 4–8 weeks after SARS-CoV-2 infection.[58]

Individual complications

The odds of specific postoperative thrombotic complications, including pulmonary embolism, DVT, ischaemic stroke, MI and arrhythmia, were reported across 4 studies.[52, 53, 58, 59] Odds of pulmonary embolism were higher in patients diagnosed with SARS-CoV-2 at 0–4 weeks before surgery relative to patients without prior SARS-CoV-2; there was no difference when surgery was performed 4–8 weeks post-diagnosis.[53] There were increased odds of ischaemic stroke when surgery occurred 11–30 days after SARS-CoV-2 diagnosis, but not at earlier or later timepoints.[52] Three studies found no difference in arrhythmia or MI at any timepoint.[52, 53, 59] One study reported increased odds of DVT when surgery occurred 0–4 weeks after SARS-CoV-2 diagnosis, but not at later timepoints.[59] Two studies found no difference in DVT occurrence.[52, 53]

SenthilKumar et al (2023), reported significant differences in the occurrence of atrial fibrillation, carditis, pulmonary embolism, DVT, superficial vein thrombosis, transient cerebral ischaemic attack and cardiac arrest between patients who did not have COVID-19 before surgery and those who had COVID-19 0–4, 4–8 and >8 weeks before surgery.[58] The study reported no further statistics or relevant timepoints associated with the increased complications.

Sepsis

The impact of prior SARS-CoV-2 infection on postoperative sepsis was reported in 4 studies.[52, 53, 56, 59] In general, patients with prior SARS-CoV-2 infection had a higher risk of sepsis than did patients without prior SARS-CoV-2 infection. Risk of sepsis was greatest in patients diagnosed with SARS-CoV-2 at ≤10 days or 0–4 weeks before surgery relative to patients without prior SARS-CoV-2 infection.[52, 53, 56, 59] Two studies found no difference in rates of postoperative sepsis when surgery occurred at 4–8 weeks after diagnosis,[53, 59] whereas 2 trials found a higher risk for sepsis persisted when surgery was performed

>30 days and ≥5 weeks (maximum timepoint) after SARS-CoV-2 infection relative to patients without prior diagnosis of SARS-CoV-2. [52] [56]

Other complications

There was no difference in the odds of postoperative urinary tract infection in patients diagnosed with SARS-CoV-2 at 0–4, 4–8 and ≥8 weeks prior to surgery relative to patients who underwent surgery before the COVID-19 pandemic.[53, 59] Odds of renal failure increased in patients diagnosed with SARS-CoV-2 at 0–4 weeks before surgery but not at later timepoints, relative to patients who underwent surgery before the COVID-19 pandemic.[53, 59]

Factors influencing postoperative mortality and complications

Several studies performed multivariate analyses accounting for operative and COVID-19-related confounding factors that may influence postoperative outcomes.

Symptomatic at time of surgery

Three studies investigated whether the presence of COVID-19 symptoms at the time of surgery influenced postoperative mortality or pulmonary and thrombotic complications.[49, 50, 57] Patients with ongoing symptoms at the time of surgery had significantly higher mortality and pulmonary and thrombotic complications compared to asymptomatic patients or those whose symptoms had resolved prior to surgery.[49, 50, 57] The higher rates of postoperative mortality and pulmonary and thrombotic complications persisted in symptomatic patients irrespective of the time interval between SARS-CoV-2 diagnosis and surgery (0–2, 3–4, 5–6 and ≥7 weeks before surgery). Patients whose symptoms had resolved prior to surgery had greater postoperative mortality and pulmonary complications than did asymptomatic patients.

A smaller study of patients undergoing major elective surgery within 8 weeks of SARS-CoV-2 diagnosis noted that 90-day mortality was unchanged by the presence of respiratory or any other symptoms, or fever.[54]

Vaccinated at time of initial infection

Three studies evaluated postoperative complications in patients fully vaccinated at the time of SARS-CoV-2 infection (1 dose of Ad.26.COV2.S or 2 doses of BNT162b2 or mRNA-1273) compared with those who were not.[55, 58, 59] There was no difference in postoperative mortality and complications between vaccinated patients undergoing surgery within 0–4, 4–8 and ≥8 weeks compared to patients who acquired COVID-19 ≥30 days after surgery (control group).[55] Two studies found that preoperative vaccination reduced postoperative mortality and complications in patients both with and without a history of COVID-19.[58, 59]

Patients not fully vaccinated at the time of SARS-CoV-2 infection had higher rates of postoperative complications when surgery occurred within 0–4 weeks of a positive test relative to patients who acquired COVID-19 at ≥30 days after surgery. There was no difference in postoperative complications for patients not fully vaccinated when surgery occurred at later timepoints (4–8 weeks and >8 weeks).[55]

Severity of initial SARS-CoV-2 infection

Three studies evaluated the association of postoperative complications with mild, moderate and severe forms of COVID-19. In general, postoperative outcomes were worse for patients who had moderate and severe COVID-19. Patients with mild COVID-19 had no increase in postoperative complications regardless of the time between infection and surgery.[57-59] Patients with moderate COVID-19 had increased odds of postoperative complications when undergoing surgery 0–4 and 4–8 weeks after testing positive for SARS-CoV-2; there were no differences when surgery occurred at later timepoints

(>8 or 12 weeks).[58, 59] Patients with severe COVID-19 had increased odds of postoperative complications irrespective of the time interval between SARS-CoV-2 diagnosis and surgery. These odds remained elevated >8 and >12 weeks following diagnosis.[58, 59]

Grade of surgery

Patients who underwent major surgery within 0–2, 3–4 and 5–6 weeks of a positive SARS-CoV-2 test had higher risks of postoperative mortality and pulmonary and thrombotic complications (DVT, pulmonary embolism) compared to patients without prior SARS-CoV-2. By ≥7 weeks after testing positive, patients undergoing major surgery had similar rates of postoperative mortality and complications relative to patients without SARS-CoV-2 infection.[49, 50]

Likewise, patients undergoing minor surgery within 0–2, 3–4 and 5–6 weeks of a positive test had higher risks of postoperative mortality and pulmonary complications, which reduced to similar rates relative to patients without prior SARS-CoV-2 by ≥7 weeks. There was no difference in thrombotic complications (DVT, pulmonary embolism) for patients undergoing minor surgery with or without prior SARS-CoV-2 infection.[49, 50]

Urgency of surgery

Three studies evaluated postoperative mortality and complications in patients who underwent elective, urgent or emergency surgery.[49, 50 53]

Patients who underwent elective surgery within 0–2, 3–4 and 5–6 weeks of testing positive for SARS-CoV-2 had higher risks of postoperative mortality and pulmonary and thrombotic complications (DVT, pulmonary embolism) compared to patients without prior SARS-CoV-2 infection.[49, 50] Patients undergoing elective surgery ≥7 weeks after testing positive had similar rates of postoperative mortality and complications as did patients without SARS-CoV-2 infection.

Patients who underwent urgent elective major surgery within 0–4 weeks of testing positive for SARS-CoV-2 had higher risks of postoperative pneumonia, respiratory failure and sepsis relative to patients who had surgery before the COVID-19 pandemic.[53] Patients who tested positive at 4–8 weeks before surgery had higher risk of postoperative pneumonia than did patients who underwent surgery before the pandemic; those who tested positive at ≥8 weeks had no increased risk.

Patients who underwent emergency surgery within 0–2, 3–4 and 5–6 weeks of testing positive for SARS-CoV-2 had higher risks of postoperative mortality and pulmonary complications compared to patients without prior SARS-CoV-2 infection.[49, 50] There were no differences when surgery was performed ≥7 weeks after testing positive. The odds ratio for thrombotic complications did not differ between emergency surgery patients without SARS-CoV-2 and those who tested positive at 1–6 and ≥7 weeks before surgery.[49, 50]

Type of anaesthesia

Patients not fully vaccinated at the time of SARS-CoV-2 infection had higher postoperative complications when surgery occurred at 0–4 weeks after a positive test and general anaesthesia was used compared to patients who acquired COVID-19 30 days after surgery.[55] There was no difference in postoperative complications at other timepoints, or when patients were fully vaccinated or no general anaesthesia was used.

6 Surgical and perioperative considerations when operating on adult and paediatric patients post-COVID

There is limited evidence regarding the surgical implications of long COVID and how the disease impacts surgical risk and recovery; however, operating staff must be aware of ongoing COVID-19 symptoms and accompanying management options.[60] It has previously been recommended that patients with persistent symptoms are likely to remain at greater risk of morbidity and mortality following surgery, even after a 7-week postponement following initial SARS-CoV-2 infection.[61] Further delaying surgery beyond 7 weeks should be considered, with the proviso that the risks of surgery are balanced against the risks and potential consequences of delay.[61]

First-line preoperative management for long COVID recommends that all patients with a history of COVID-19 infection have a formal clinical review prior to surgery, especially those who have not returned to their pre-COVID baseline.[62] NICE recommends that questions are asked during the subjective assessment regarding history of acute COVID-19 (suspected or confirmed), nature and severity of previous and current symptoms, timing and duration of symptoms since the start of acute COVID-19, history of other health conditions, and exacerbation of pre-existing conditions.[1] It has also been recommended that all patients over age 65 or who required hospitalisation during acute SARS-CoV-2 infection undergo a frailty assessment.[63] The Australian and New Zealand College of Anaesthetists recommends that the preoperative assessment includes evaluation of the cardiorespiratory system, as well as other potentially affected systems such as the renal, hepatic, haematological, immunological, musculoskeletal, neurological and psychological systems.[62] The Royal Australian College of General Practitioners recommends that the clinician considers and excludes possible alternative causes of the ongoing symptoms reported and investigates new or worsening symptoms that may be caused by delayed sequelae, including VTE, cardiac implications or pneumonia.[64]

As reported in Section 3, there are a number of highly prevalent symptoms that occur in individuals with long COVID (effort intolerance, pain/discomfort, mobility dysfunction/decline, fatigue, sleep disorders, dyspnoea, joint pain/arthralgia, cognitive disorders, cough and palpitations). Preoperative assessment tools such as those listed in Table 1 (repeated below for convenience) can aid the decision-making process to determine the effect of these symptoms on the risk of perioperative and postoperative complications in surgery.

Table 1 Suggested preoperative assessment tools

Subjective assessment	
All patients	Formal clinical review History of acute COVID-19 Nature and severity of previous and current symptoms, including fatigue/effort intolerance Timing and duration of symptoms since start of acute COVID-19 History of other health conditions Exacerbations of pre-existing conditions
Patients presenting with cognitive symptoms/disorder	History of cognitive symptoms
Patients presenting with respiratory symptoms (cough and/or dyspnoea)	History of dyspnoea (at rest and exertion), cough, discomfort, pleuritic pain, wheezing
Objective assessment	
All patients over age 65 or who required hospitalisation during acute COVID-19 infection	Frailty assessment Sarcopenia assessment
All patients with persisting COVID-19 symptoms	Immune system tests
Patients presenting with effort intolerance/fatigue	Cardiopulmonary exercise testing 6-minute walk test Incremental shuttle walk Stair-climb test Lung function tests Complete blood count with differential chemistries: • renal and hepatic function tests • thyroid stimulating hormone • C-reactive protein • creatine kinase
Patients presenting with cardiac symptoms	Physical examination Postural blood pressure Electrocardiogram Thyroid-stimulating hormone level Transthoracic echocardiogram
Patients presenting with respiratory symptoms	Modified Borg dyspnoea scale SpO2 Presyncope or syncope [a] Postural blood pressure Chest CT Pulmonary function testing Echocardiogram CT pulmonary angiogram [b]
Patients presenting with fatigue	Complete blood count with differential chemistries: • renal and hepatic function tests • thyroid stimulating hormone • C-reactive protein • erythrocyte sedimentation rate • creatine kinase
Patients presenting with cognitive disorders/memory deficit/concentration difficulties	Physical examination determining: • baseline deficits • palsies • asymmetries • cognitive testing

Patients presenting with sleep disorders	Pittsburgh sleep quality index
Musculoskeletal symptoms	
Patients presenting with mobility dysfunction/decline	Cardiopulmonary exercise testing 6-minute walk test Incremental shuttle walk Stair-climb test Muscle strength testing
Patients presenting with pain, discomfort, joint pain, arthralgia	Visual analogue pain scale
Patients presenting with haematologic symptoms	Preoperative D-dimer measurement Venous ultrasound for thrombosis

Notes:
a = patients with orthostasis
b = if unexplained cardiopulmonary symptoms and/or low peripheral oxygen saturation despite normal chest imaging

Respiratory and cardiopulmonary considerations

As previously discussed (Section 5), pulmonary complications (e.g. pneumonia, respiratory failure, ARDS and need for postoperative mechanical ventilation) are greatest in patients diagnosed with SARS-CoV-2 at 0–6 weeks prior to surgery. There is a lack of published literature encompassing broad peri- or postoperative pulmonary risks of surgery for individuals with persistent symptoms of SARS-CoV-2, but individual risk factors can be considered. The operating team should complete specific tests and outcome measures to determine whether delaying surgery would be beneficial for any individual presenting with persisting respiratory and pulmonary symptoms.

Multidisciplinary preoperative optimisation is particularly important for individuals displaying respiratory symptoms.[65] It is recommended that subjective examination is undertaken regarding ongoing dyspnoea (at rest and exertion), cough, chest discomfort, pleuritic pain and wheezing.[66] The modified Borg dyspnoea scale can be used to assess dyspnoea symptoms.[66] Preoperative assessment should also heed SpO2 measurements; for patients with orthostasis, presyncope or syncope postural blood pressure (up to 10 minutes after standing) pulse rate should be assessed.[66] Some patients may require a complete work-up, including chest CT scan, pulmonary function testing or echocardiography.[65] Mikkelsen and Abramoff (2022) recommend that patients with unexplained cardiopulmonary symptoms and/or low SpO2 despite normal chest imaging, should be investigated for VTE (e.g. use of CT pulmonary angiography).[66] Patients using inhaled bronchodilators and corticosteroids prior to surgery should continue usage afterwards.[65]

Effort intolerance is the most prevalent long COVID symptom among adults. This can be likened to exercise intolerance—the reduced ability of the cardiovascular and musculoskeletal systems to perform physical activity. Poor exercise tolerance is associated with increased risk of serious perioperative complications, independent of age and all other patient characteristics.[67, 68] The likelihood of serious complication is inversely related to the number of blocks walked or flights of stairs able to be climbed by an individual.[67] For those with self-reported effort intolerance, it may be beneficial to complete cardiopulmonary exercise testing or field tests such as the 6-minute walk test, incremental shuttle walk or stair-climb test to determine patient risk of perioperative or postoperative complications.

General deconditioning/ongoing immune response considerations

Mobility decline, asthenia, weakness, pain (myalgia, arthralgia, general), weight loss, anorexia and anosmia are all symptoms of long COVID and may contribute to a patient's general deconditioning. Because reduced preoperative cardiorespiratory fitness, muscle strength and performance of physical

activities are risk factors for postoperative complications,[68] it may be beneficial to complete preoperative screening to determine risk of functional decline. This allows surgeons, physicians and physiotherapists to determine surgical risk and compile a patient management plan for optimal surgical outcomes and postoperative rehabilitation, if required. Multimodal prehabilitation and rehabilitation may be beneficial to reduce perioperative risk and the risk of morbidity and postoperative complications.[69]

For any patient showing symptoms of pain or discomfort, a preoperative pain assessment can be beneficial to determine baseline levels of pain. This can be used as a postoperative guide to determine if pain is being adequately managed or is significantly higher than previously recorded. Increased pain can indicate postoperative complications such as thrombosis, sepsis or surgical site infection requiring further investigation.

Immune dysfunction in patients following acute SARS-CoV-2 infection can lead to adverse outcomes due to sustained elevated inflammatory responses.[70] Unresolved inflammation can contribute to long COVID and may mediate lung damage, reducing the efficiency of gas exchange leading to breathing difficulties and decreased blood oxygen levels.[71-73] If cytokine levels remain elevated, septic shock and organ failure can occur, with individuals over age 60 and those with comorbidities at particular risk.[71] In the surgical setting, immune status tests may be recommended for individuals with persistent symptoms. If the operation proceeds, the patient should be monitored for signs and symptoms of sepsis and organ failure.

Haematologic considerations

Due to the acute haematological effects of COVID-19, individuals who have previously had COVID-19 may be in a hypercoagulable state.[64] Some individuals may be on anticoagulation therapy when scheduled for elective surgery. This therapy should cease prior to surgery (after consideration of the risks and benefits) and resume postoperatively.[65] Preoperative D-dimer measurement for thrombosis (with or without venous ultrasound) has been recommended for patients not on anticoagulation therapy.[65]

It is recommended that patients are evaluated for possible cardiopulmonary, autoimmune and endocrine conditions that may exacerbate symptoms of fatigue.[74] A complete blood count with differential chemistries including renal and hepatic function tests, thyroid stimulating hormone, C-reactive protein, erythrocyte sedimentation rate and creatinine kinase may be beneficial to determine underlying causes of fatigue.[74] Postoperative fatigue should be monitored and evaluated against baseline levels; post-COVID fatigue may impact postoperative rehabilitation for some individuals. The Royal Australian College of General Practitioners recommends that patients experiencing post-COVID fatigue should pace their activity and be selective in prioritising daily activities.[64] Postoperative rehabilitation programs and return to exercise should be monitored by an exercise physiologist or physiotherapist.

Cardiac considerations

Perioperative cardiovascular challenges should be anticipated when operating on individuals with long COVID, especially for those showing persistent cardiac symptoms. Long COVID chest pain and palpitations may have significant underlying causes of relevance to the surgeon and anaesthesiologist.[65] Kopanczyk et al (2022) reported that palpitations and chest pain should be investigated with a focused history and physical examination for heart failure, coronary artery disease and arrhythmia, employing electrocardiogram, thyroid-stimulating hormone level tests and transthoracic echocardiogram.[65] If a significant cardiac abnormality is discovered intraoperatively, the patient may require invasive monitoring and preparation of vasopressors, inotropes and antiarrhythmic medications, depending on the underlying pathology.[65]

Neurocognitive considerations

There was no specific information regarding the impact of COVID-19 on neurocognitive function in respect to surgery or surgical outcomes. However, sleep disorders and disturbances correlate with postoperative pain, delirium and cognitive disorder and have the potential to negatively impact postoperative prognosis and physiological function.[75] It may be beneficial for patients to complete a subjective sleep quality assessment such as the Pittsburgh Sleep Quality Index questionnaire.

Cognitive disorders are also relevant to perioperative and postoperative care. Initial evaluations should focus on medical history and physical examinations to determine baseline deficits, palsies and asymmetries.[65] Due to an increased risk of postoperative delirium and cognitive dysfunction, benzodiazepine use is generally discouraged in individuals older than 65 years and in patients who are experiencing cognitive disorders or dysfunction,[65] although carefully titrated doses might be considered for intraoperative use.[76] The Royal Australian College of General Practitioners recommends that for those with severe cognitive disorder it may be beneficial to arrange cognitive testing, occupational therapy support and referral to a speech pathologist for any communication impairments.[64]

Other considerations

Baseline signs and symptoms should be measured for all individuals with persisting SARS-CoV-2 symptoms to monitor post-surgery changes that may indicate a postoperative complication.

7 Discussion

To date, much of the literature regarding surgery during the COVID-19 pandemic has focused on individuals with acute COVID-19. It has now become evident that long COVID pathophysiology and symptomology needs attention in the field of surgery. This rapid review indicates that long COVID may persist up to 12 months and beyond from acute COVID-19 and may have implications in surgical practice for both adult and paediatric populations. Symptoms of long COVID need to be adequately assessed preoperatively to determine the impact on peri- and postoperative outcomes.

The overall prevalence of long COVID in adults ranges from 43% to 56%, with factors such as female sex, severe or critical acute COVID-19 disease, hospitalisation during acute COVID-19, BMI ≥25 kg/m^2, ≥1 comorbidity, chronic pulmonary disease, unvaccinated status or receiving only a single dose of COVID-19 vaccine, and infection with the Delta strain of SARS-CoV-2 all increasing the risk of residual symptoms and consequently long COVID. Overall prevalence of long COVID in the paediatric population ranges from 13% to 25%. Data regarding risk factors were minimal but showed similarities with the adult population, including female sex, older age, previous SARS-CoV-2 exposure, comorbidities, greater acute SARS-CoV-2 symptoms and hospitalisation ≥48 hours for COVID-19.

Overall, the literature identified 64 symptoms for the adult population and 44 symptoms for the paediatric population associated with long COVID. In the adult population, the 10 most prevalent symptoms relevant to surgery include effort intolerance, generalised pain/discomfort, mobility dysfunction/decline, fatigue, sleep disorders, dyspnoea, joint pain/arthralgia, cognitive disorder, cough and palpitations. In the paediatric population, the most common symptoms include fatigue, dyspnoea, headache, myalgia/arthralgia, abdominal pain, fever, mood disorders, diarrhoea and sleep disorders. The severity of these symptoms is undocumented in the literature, so it is difficult to state the implications for pre-, peri- and postoperative management. No information was found on the specific impact that long COVID pathophysiology and symptoms have on surgical management.

Advice regarding delaying surgery for individuals with persisting COVID-19 symptoms has changed since the beginning of the pandemic. For patients whose initial SARS-CoV-2 infection was moderate to severe, there may be a greater risk of morbidity and mortality with surgery, even after a 7-week postponement. Further delaying surgery may be considered, while weighing the risk of delay against the risk of proceeding.[61] For patients who had mild COVID-19 symptoms during their initial infection, the operative risk is lower.

It is impossible to draw firm conclusions from the current literature available, especially with lingering uncertainty regarding how long persisting symptoms may last. Tools to accurately determine the risk profile of patients must be defined, as operating on individuals with long COVID will be inevitable as the pandemic continues.

Regarding the evidence base that informed this rapid review, significant heterogeneity exists in the definition of long COVID and the timepoints analysed. Data comparing long COVID symptoms to control cases were also limited, leading to uncertainty regarding the prevalence of each of symptom and the subsequent overall prevalence of long COVID. Further research is needed to determine the true global impact of long COVID and its surgical implications.

8 Conclusion

The epidemiology of COVID-19 continues to evolve, as it is influenced by currently circulating strains of SARS-CoV-2, underlying population immunity from vaccination and/or infection, and current case numbers in the community, which is more difficult to determine with the decline in individual testing by either RT-PCR and/or rapid antigen tests. Likewise, the effect of long COVID on perioperative processes and postoperative outcomes is constantly evolving. The evidence presented in this review highlights the symptoms and predicted pathophysiology and mechanisms that may affect a patient's surgical risk. These factors should be considered during the preoperative phase and a pragmatic approach taken to the preoperative assessment. This may include specific objective measurements for any organ systems that appear to be affected. For each patient the risks and benefits of delaying surgery should be assessed. As more studies are published and further evidence accumulates, stronger recommendations will be possible regarding the potential risks of long COVID on surgical morbidity and mortality.

9 References

1. NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19, https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742 (2022, accessed 13 October 2022).

2. World Health Organisation. Weekly epidemiological update on COVID-19 - 24 August 2021, https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---24-august-2021 (2021, 30 August 2021).

3. World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020, https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (2020, 30 August 2021).

4. Hu B, Guo H, Zhou P, et al. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021; 19: 141-154. doi: 110.1038/s41579-41020-00459-41577. Epub 42020 Oct 41576. Research Support, Non-U.S. Gov't

Review.

5. National Institute of Health (NIH). Clinical Spectrum of SARS-CoV-2 Infection, https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (2023, accessed 12th June 2023).

6. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021; 38:101019.: 10.1016/j.eclinm.2021.101019. Epub 102021 Jul 101015.

7. Crook H, Raza S, Nowell J, et al. Long covid-mechanisms, risk factors, and management. *BMJ* 2021; 374:n1648.: 10.1136/bmj.n1648. Review.

8. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021; 11. DOI: 10.1038/s41598-021-95565-8.

9. RACS. Delaying Surgery for Patients Recovering from COVID-19, https://www.surgeons.org/-/media/Project/RACS/surgeons-org/files/news/covid19-information-hub/2021-04-23-RACS-Post-covid-delay-to-surgery-report.pdf?rev=db571f977d664e5aa7b8108a531eb274&hash=15E9AC11D5D083A673E3B52DB9B3F4F4 (2021, 30 August 2021).

10. Garritty C, Gartlehner G, Nussbaumer-Streit B, et al. Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. *J Clin Epidemiol* 2021; 130: 13-22. 2020/10/18. DOI: 10.1016/j.jclinepi.2020.10.007.

11. De-la-Rosa-Martinez D, Delaye-Martínez MA, Bello-Chavolla OY, et al. Long-term manifestations and modifiers of prevalence estimates of the post-COVID-19 syndrome: A systematic review and meta-analysis. *medRxiv* 2021: 2021.2010.2017.21265123. DOI: doi:.

12. van Kessel SAM, Olde Hartman TC, Lucassen P, et al. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. *Family Practice* 2022; 39: 159-167. DOI: doi:.

13. Groff D, Sun A, Ssentongo AE, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Netw Open* 2021; 4: e2128568. DOI: doi:.

14. Domingo FR, Waddell LA, Cheung AM, et al. Prevalence of long-term effects in individuals diagnosed with COVID-19: an updated living systematic review. *medRxiv* 2021: 2021.2006.2003.21258317. DOI: doi:.

15. Jennings G, Monaghan A, Xue F, et al. A Systematic Review of Persistent Symptoms and Residual Abnormal Functioning following Acute COVID-19: Ongoing Symptomatic Phase vs. Post-COVID-19 Syndrome. *Journal of Clinical Medicine* 2021; 10: 16. DOI: doi:.

16. Malik J, Zaidi SMJ, Iqbal R, et al. Post-acute COVID-19 syndrome and its prolonged effects: An updated systematic review. *medRxiv* 2021: 2021.2005.2009.21256911. DOI: doi:.

17. Patrucco F, Zeppegno P, Baricich A, et al. Long-lasting consequences of coronavirus disease 19 pneumonia: a systematic review. *Minerva Med* 2022; 113: 158-171. DOI: doi:.

18. Nguyen NN, Hoang VT, Dao TL, et al. Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review. *Eur J Clin Microbiol Infect Dis* 2022; 41: 515-545. DOI: doi:.

19. Pillay J, Rahman S, Guitard S, et al. Risk factors and preventive interventions for post Covid-19 condition: systematic reviews. *medRxiv* 2022: 2022.2003.2025.22272949. DOI: doi:.

20. Notarte KI, Catahay JA, Velasco JV, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. *EClinicalMedicine* 2022; 53: 101624. 2022/09/03. DOI: 10.1016/j.eclinm.2022.101624.

21. Gao P, Liu J and Liu M. Effect of COVID-19 Vaccines on Reducing the Risk of Long COVID in the Real World: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health* 2022; 19: 12422.

22. Chen C, Haupert SR, Zimmermann L, et al. Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review. *J Infect Dis* 2022 2022/04/17. DOI: 10.1093/infdis/jiac136.

23. Alkodaymi MS, Omrani OA, Fawzy NA, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clin Microbiol Infect* 2022. DOI: doi:.

24. Middleton S, Chalitsios C, McKeever TM, et al. Patient-reported respiratory outcome measures in the recovery of adults hospitalised with COVID-19: A systematic review and meta-analysis. *medRxiv* 2022: 2022.2003.2016.22272509. DOI: doi:.

25. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021; 92: 55-70. DOI: doi:.

26. Han Q, Zheng B, Daines L, et al. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. *Pathogens* 2022; 11: 19. DOI: doi:.

27. Natarajan A, Shetty A, Delanerolle G, et al. A systematic review and meta-analysis of Long COVID symptoms. *medRxiv* 2022: 2022.2003.2008.22272091. DOI: doi:.

28. Maglietta G, Diodati F, Puntoni M, et al. Prognostic Factors for Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis. *J Clin Med* 2022; 11. DOI: doi:.

29. Fernández-de-Las-Peñas C, Ortega-Santiago R, Fuensalida-Novo S, et al. Differences in Long-COVID Symptoms between Vaccinated and Non-Vaccinated (BNT162b2 Vaccine) Hospitalized COVID-19 Survivors Infected with the Delta Variant. *Vaccines (Basel)* 2022; 10 2022/09/24. DOI: 10.3390/vaccines10091481.

30. Augustin M, Schommers P, Stecher M, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. *The Lancet Regional Health Europe* 2021; 6: 100122. DOI: doi:.

31. Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2021; 76: 396-398. DOI: 10.1136/thoraxjnl-2020-215818.

32. Kuodi P, Gorelik Y, Zayyad H, et al. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021. *medRxiv* 2022: 2022.2001.2005.22268800. DOI: doi:.

33. Antonelli M, Pujol JC, Spector TD, et al. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet* 2022; 399: 2263-2264. 2022/06/20. DOI: 10.1016/s0140-6736(22)00941-2.

34. Ayoubkhani D, Bosworth ML, King S, et al. Risk of Long Covid in people infected with SARS-CoV-2 after two doses of a COVID-19 vaccine: community-based, matched cohort study. *medRxiv* 2022: 2022.2002.2023.22271388. DOI: doi:.

35. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *Journal of Medical Virology* 2022; 94: 253-262. DOI: doi:.

36. Ayoubkhani D, Bermingham C, Pouwels KB, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. *Bmj* 2022; 377: e069676. 2022/05/19. DOI: 10.1136/bmj-2021-069676.

37. Long Q, Li J, Hu X, et al. Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis. *Frontiers in Medicine* 2021; 8: 702635. DOI: doi:.

38. Castanares-Zapatero D, Chalon P, Kohn L, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. *Ann Med* 2022; 54: 1473-1487. 2022/05/21. DOI: 10.1080/07853890.2022.2076901.

39. Crook H, Raza S, Nowell J, et al. Long covid—mechanisms, risk factors, and management. *BMJ* 2021; 374: n1648. DOI: 10.1136/bmj.n1648.

40. National Institue for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19, https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742 (2022, accessed 26 Nov 2022).

41. Lopez-Leon S, Wegman-Ostrosky T, del Valle CA, et al. Long COVID in Children and Adolescents: A Systematic Review and Meta-analyses. *medRxiv* 2022: 2022.2003.2010.22272237. DOI: 10.1101/2022.03.10.22272237.

42. Hirt J, Janiaud P, Gloy V, et al. Validity of reported post-acute health outcomes in children with SARS-CoV-2 infection: a systematic review. *medRxiv* 2022: 2022.2003.2018.22272582. DOI: 10.1101/2022.03.18.22272582.

43. Behnood SA, Shafran R, Bennett SD, et al. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies. *J Infect* 2022; 84: 158-170. 2021/11/24. DOI: 10.1016/j.jinf.2021.11.011.

44. Roessler M, Tesch F, Batram M, et al. Post-COVID-19-associated morbidity in children, adolescents, and adults: A matched cohort study including more than 157,000 individuals with COVID-19 in Germany. *PLOS Medicine* 2022; 19: e1004122. DOI: 10.1371/journal.pmed.1004122.

45. Miller F, Nguyen V, Navaratnam AM, et al. Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales. *medRxiv* 2021: 2021.2005.2028.21257602. DOI: 10.1101/2021.05.28.21257602.

46. Funk AL, Kuppermann N, Florin TA, et al. Post–COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. *JAMA Network Open* 2022; 5: e2223253-e2223253. DOI: 10.1001/jamanetworkopen.2022.23253.

47. Osmanov IM, Spiridonova E, Bobkova P, et al. Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study. *Eur Respir J* 2022; 59 20220203. DOI: 10.1183/13993003.01341-2021.

48. Nugawela MD, Stephenson T, Shafran R, et al. Developing a model for predicting impairing physical symptoms in children 3 months after a SARS-CoV-2 PCR-test: The CLoCk Study. *medRxiv* 2022: 2022.2004.2001.22273117. DOI: 10.1101/2022.04.01.22273117.

49. COVIDSurg Collaborative and GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. *Anaesthesia* 2021; 76: 748-758. 20210309. DOI: 10.1111/anae.15458.

50. COVIDSurg Collaborative and GlobalSurg Collaborative. SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. *Anaesthesia* 2022; 77: 28-39. 20210824. DOI: 10.1111/anae.15563.

51. Abate SM, Mantefardo B and Basu B. Postoperative mortality among surgical patients with COVID-19: a systematic review and meta-analysis. *Patient Saf Surg* 2020; 14: 37. 20201012. DOI: 10.1186/s13037-020-00262-6.

52. Lal BK, Prasad NK, Englum BR, et al. Periprocedural complications in patients with SARS-CoV-2 infection compared to those without infection: A nationwide propensity-matched analysis. *Am J Surg* 2021; 222: 431-437. 20201228. DOI: 10.1016/j.amjsurg.2020.12.024.

53. Deng JZ, Chan JS, Potter AL, et al. The Risk of Postoperative Complications After Major Elective Surgery in Active or Resolved COVID-19 in the United States. *Ann Surg* 2022; 275: 242-246. DOI: 10.1097/sla.0000000000005308.

54. Kougias P, Sharath SE, Zamani N, et al. Timing of a Major Operative Intervention After a Positive COVID-19 Test Affects Postoperative Mortality: Results From a Nationwide, Procedure-matched Analysis. *Ann Surg* 2022; 276: 554-561. 20220715. DOI: 10.1097/sla.0000000000005552.

55. Le ST, Kipnis P, Cohn B, et al. COVID-19 Vaccination and the Timing of Surgery Following COVID-19 Infection. *Ann Surg* 2022; 276: e265-e272. 20220715. DOI: 10.1097/sla.0000000000005597.

56. Prasad NK, Mayorga-Carlin M, Sahoo S, et al. Mid-term Surgery Outcomes in Patients with COVID-19: Results from a Nationwide Analysis. *Ann Surg* 2022 20220628. DOI: 10.1097/sla.0000000000005515.

57. Garnier M, Constantin JM, Cinotti R, et al. Association of preoperative COVID-19 and postoperative respiratory morbidity during the Omicron epidemic wave: the DROMIS-22 multicentre prospective observational cohort study. *EClinicalMedicine* 2023; 58: 101881. 20230301. DOI: 10.1016/j.eclinm.2023.101881.

58. SenthilKumar G, Verhagen NB, Sheriff SA, et al. Preoperative SARS-CoV-2 infection increases risk of early postoperative cardiovascular complications following noncardiac surgery. *Am J Physiol Heart Circ Physiol* 2023; 324: H721-h731. 20230317. DOI: 10.1152/ajpheart.00097.2023.

59. Verhagen NB, SenthilKumar G, Jaraczewski T, et al. Severity of Prior COVID-19 Infection is Associated with Postoperative Outcomes Following Major Inpatient Surgery, https://www.medrxiv.org/content/10.1101/2023.04.12.23288412v1.full.pdf (N.D, 14 April 2023).

60. NSW Health. Timing of surgery after COVID-19 in adults, https://www.health.nsw.gov.au/Infectious/covid-19/communities-of-practice/Pages/timing-surgery-covid19-adults.aspx#long (2022, accessed 12 October 2022).

61. El-Boghdadly K, Cook TM, Goodacre T, et al. Timing of elective surgery and risk assessment after SARS-CoV-2 infection: an update: A multidisciplinary consensus statement on behalf of the Association of Anaesthetists, Centre for Perioperative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists, Royal College of Surgeons of England. *Anaesthesia* 2022; 22: 22. DOI: doi:.

62. ANZCA. Guideline on surgical patient safety for SARS-CoV-2 infection and vaccination, https://www.anzca.edu.au/getattachment/af1fb728-5e87-413a-b006-c54cecf282b1/PG68(A)-Guideline-surgical-patient-safety-SARS-CoV-2 (2022, accessed 11 October 2022).

63. Bui N, Coetzer M, Schenning KJ, et al. Preparing previously COVID-19-positive patients for elective surgery: a framework for preoperative evaluation. *Perioperative Medicine* 2021; 10: 1. DOI: doi:.

64. RACGP. Caring for patients with post-COVID-19 conditions, https://www.racgp.org.au/getattachment/8c5b3936-5551-4b94-81d4-614e2b69da51/Caring-for-patients-with-post-COVID-19-conditions.aspx (accessed 12 October 2022).

65. Kopanczyk R, Kumar N and Papadimos T. Post-Acute COVID-19 Syndrome for Anesthesiologists: A Narrative Review and a Pragmatic Approach to Clinical Care. *J Cardiothorac Vasc Anesth* 2022; 36: 2727-2737. 2021/10/25. DOI: 10.1053/j.jvca.2021.09.051.

66. Mikkelsen M and Abramoff B. COVID-19: Evaluation and management of adults with persistent symptoms following acute illness ("Long COVID"), https://www.uptodate.com/contents/covid-19-evaluation-and-management-of-adults-with-persistent-symptoms-following-acute-illness-long-covid (2022, accessed 12 October 2022).

67. Reilly DF, McNeely MJ, Doerner D, et al. Self-reported Exercise Tolerance and the Risk of Serious Perioperative Complications. *Archives of Internal Medicine* 1999; 159: 2185-2192. DOI: 10.1001/archinte.159.18.2185.

68. Moran J, Wilson F, Guinan E, et al. The preoperative use of field tests of exercise tolerance to predict postoperative outcome in intra-abdominal surgery: a systematic review. *J Clin Anesth* 2016; 35: 446-455. 2016/11/23. DOI: 10.1016/j.jclinane.2016.09.019.

69. Li J. Rehabilitation management of patients with COVID-19: lessons learned from the first experience in China. *Eur J Phys Rehabil Med* 2020; 56: 335-338. 20200424. DOI: 10.23736/s1973-9087.20.06292-9.

70. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nature Immunology* 2022; 23: 210-216. DOI: 10.1038/s41590-021-01113-x.

71. Tay MZ, Poh CM, Rénia L, et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; 20: 363-374. 20200428. DOI: 10.1038/s41577-020-0311-8.

72. Tavakolpour S, Rakhshandehroo T, Wei EX, et al. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. *Immunol Lett* 2020; 225: 31-32. 20200620. DOI: 10.1016/j.imlet.2020.06.013.

73. Kong M, Zhang H, Cao X, et al. Higher level of neutrophil-to-lymphocyte is associated with severe COVID-19. *Epidemiol Infect* 2020; 148: e139. 20200709. DOI: 10.1017/s0950268820001557.

74. Herrera JE, Niehaus WN, Whiteson J, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. *Pm r* 2021; 13: 1027-1043. 2021/08/05. DOI: 10.1002/pmrj.12684.

75. Lin D, Huang X, Sun Y, et al. Perioperative Sleep Disorder: A Review. *Front Med (Lausanne)* 2021; 8: 640416. 2021/06/25. DOI: 10.3389/fmed.2021.640416.

76. Wang E, Belley-Côté EP, Young J, et al. Effect of perioperative benzodiazepine use on intraoperative awareness and postoperative delirium: a systematic review and meta-analysis of randomised controlled trials and observational studies. *Br J Anaesth* 2023 20230106. DOI: 10.1016/j.bja.2022.12.001.

10 Appendices

10.1 Search strategy

Table A1 Search strategy for systematic reviews via MEDLINE (PubMed April 2022)

No.	Search term	Results
1	"Severe acute respiratory syndrome"[MH]	5,679
2	COVID[MH]	154,126
3	COVID-19[tiab]	214,192
4	Sars-CoV-2[tiab]	80,449
5	Coronavirus[tiab]	96,988
6	"COVID symptom*"[tiab]	198
7	"COVID syndrom*"[tiab]	238
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	253,554
9	Chronic[tiab]	1,304,467
10	"Late sequelae"[tiab]	1,825
11	"Long"[tiab]	1,682,209
12	"Long-COVID"[ALL]	1,110
13	"Long term effect"[tiab]	9,257
14	"Long post"[tiab]	269
15	"Long-haul"[tiab]	983
16	"Long-tail"[tiab]	802
17	"Long-term sequalae"[tiab]	62
18	"Ongoing symptoms"[tiab]	538
19	Persist*[tiab]	529,517
20	"Persistent symptoms"[tiab]	4,082
21	Post-COVID[tiab]	3,437
22	"Post-acute"[tw]	4,265
23	"Post-acute sequelae"[tiab]	180
24	Aftereffect[tiab]	2,357
25	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	3,258,134
26	#8 AND #25	29,293
27	((((((((((((((((((((((((((((((((Embase*[tiab]) OR Cinahl*[tiab]) OR systematic overview*[tiab]) OR methodological overview*[tiab]) OR methodologic overview*[tiab]) OR methodological review*[tiab]) OR methodologic review*[tiab]) OR quantitative review*[tiab]) OR quantitative overview*[tiab]) OR quantitative synthes*[tiab]) OR pooled analy*[tiab]) OR Cochrane[tiab]) OR Medline[tiab]) OR Pubmed[tiab]) OR Medlars[tiab]) OR handsearch*[tiab]) OR meta-regression*[tiab]) OR metaregression*[tiab]) OR data synthes*[tiab]) OR data extraction[tiab]) OR data abstraction*[tiab]) OR mantel haenszel[tiab]) OR peto[tiab]) OR der-simonian[tiab]) OR dersimonian[tiab]) OR fixed effect*[tiab]) OR "Cochrane Database Syst Rev"[Journal]) OR "health technology assessment winchester, england"[Journal]) OR "Evid Rep Technol Assess (Full Rep)"[Journal]) OR "Int J Technol Assess Health Care"[Journal]) OR "GMS Health Technol Assess"[Journal]) OR "Health Technol Assess (Rockv)"[Journal]) OR "Health Technol Assess Rep"[Journal])) OR ((((indirect treatment[tiab]) OR mixed-treatment[tiab])) AND comparison*[tiab])) OR (((((((((((((((((((systematic[sb]) OR meta-	553,720

	analysis[pt]) OR meta-analysis as topic[mh]) OR meta-analysis[mh]) OR meta analy*[tw]) OR integrative review*m[tiab]) OR integrative overview*[tiab]) OR research integration*[tiab]) OR research overview*[tiab]) OR collaborative review*[tiab]) OR collaborative overview*[tiab]) OR systematic review*[tiab]) OR technology assessment*[tiab]) OR technology overview*[tiab]) OR "Technology Assessment, Biomedical"[mh]) OR HTA[tiab]) OR HTAs[tiab]) OR comparative efficacy[tiab]) OR comparative effectiveness[tiab]) OR outcomes research[tiab]) OR indirect comparison*[tiab])	
28	#8 AND #25 AND #27	1,463

Table A2 Search strategy for surgical adverse events via MEDLINE (PubMed April 2022)

No.	Search term	Results
1	*Coronavirus Infections/	4,223
2	(COVID-19 or COVID19).mp.	235,626
3	((pneumonia or COVID* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*) and (hubei or wuhan or beijing or shanghai)).ti,kf.	1,718
4	Wuhan virus*.ti,kf.	10
5	(19nCoV or 2019-nCoV or 2019nCoV).ti,kf.	1,080
6	(nCoV* or n-CoV*).ti,kf.	1,608
7	("CoV 2" or CoV2).ti,kf.	60,442
8	(OC43 or NL63 or 229E or HKU1 or HCoV* or Sars-coronavirus*).ti,kf.	1,715
9	(2019-novel CoV or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or ((novel or new or nouveau) adj2 (CoV or nCoV or COVID or coronavirus* or corona virus or Pandemi*2)) or (coronavirus* and pneumonia)).ti,kf.	6,141
10	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	7,194
11	severe acute respiratory syndrome coronavirus 2.ti,kf.	4,675
12	(SARSCoV* or SARS-CoV* or SARS2 or SARS-2).ti,kf.	61,459
13	(novel coronavirus* or novel corona virus* or novel CoV).ti,kf.	3,442
14	((coronavirus* or corona virus*) adj2 "2019").ti,kf.	13,502
15	((coronavirus* or corona virus*) adj2 "19").ti,kf.	2,423
16	(coronavirus 2 or corona virus 2).ti,kf.	5,042
17	COVID*.ti,kf.	191,770
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	249,120
19	(201911* or 202*).dp. or 20191101:20301231.(ep). or 20191101:20301231.(dt).	3,813,191
20	18 and 19	243,666
21	*Coronavirus Infections/su [surgery]	53
22	exp *Specialties, Surgical/	167,379
23	exp *Surgical Procedures, Operative/	2,186,002
24	(intraoperat* or intra-operat* or operation? or operative* or preoperat* or pre-operat* or peroperat* or per-operat* or perioperat* or peri-operat* or postoperat* or post-operat* or presurg* or pre-surg* or perisurg* or peri-surg* or postsurg* or post-surg* or reoperat* or re-operat* or surgeries or surgery or surgeon? or surgical*).ti,kf.	1,104,075
25	21 or 22 or 23 or 24	2,882,547
26	*Failure to Rescue, Health Care/ or *Hospitalization/ or exp *Intensive Care Units/ or exp *Mortality/ or *Patient Admission/	165,018
27	exp *Specialties, Surgical/ae, co, mo [adverse effects, complications, mortality]	1,212
28	exp *Surgical Procedures, Operative/ae, co, mo [adverse effects, complications, mortality]	273,171

29	(admission? or admitted or admitting or adverse* or complication? or complicat* or death* or fatal or fatalit* or hospitalis* or hospitaliz* or icu? or ((coronary or intensive* or respiratory) adj2 (care or unit?)) or mortalit*).ti,kf.	876,197
30	(ae or co or mo).fs.	4,234,643
31	26 or 27 or 28 or 29 or 30	4,753,612
32	*Brain Ischemia/ or exp *Intracranial Hemorrhages/ or exp *Stroke/ or *Stroke Rehabilitation/	203,096
33	(stroke* or poststroke? or post-stroke? or CVA or CVAs).ti,kf.	141,454
34	((cerebrovascular* or cerebro-vascular* or cerebral vascular*) adj2 (apoplex* or accident* or infarct*)).ti,kf.	2,424
35	((brain or cerebral or intracerebral or intra-cerebral or arachnoid or subarachnoid or sub-arachnoid or intracranial* or intra-cranial* or cranial*) adj2 (infarct* or isch?emi* or h?emorrhag*)).ti,kf.	66,151
36	((postacute or post-acute or chronic) adj5 (stroke* or poststroke? or post-stroke?)).ti,kf.	2,912
37	(((postacute or post-acute or chronic) adj5 (hemipare* or paretic or paresis or phase? or stage? or state? or condition? or paraly* or spastic*)) and (stroke* or poststroke? or post-stroke?)).ti,kf.	420
38	exp *Heart Diseases/	1,046,588
39	((cardiac* or heart? or myocardia* or myo-cardia*) adj2 (attack? or event? or failure? or infarct* or ruptur*)).ti,kf.	211,995
40	*Lung/pa, pp	25,602
41	exp *Lung Injury/	36,353
42	((lung? adj2 (damag* or injur*)) or pulmonary function*).ti,kf.	28,120
43	*Respiratory Distress Syndrome, Adult/	17,846
44	(((acute or syndrome?) adj (respiratory distress or respiratory failure)) or ARDS or ARDSS).ti,kf.	16,309
45	*Venous Thrombosis/ or *Upper Extremity Deep Vein Thrombosis/	22,901
46	((deep adj (vein or venous) adj (thrombos?s or thrombus)) or deep thrombophlebitis or deep thrombo-phlebitis or DVT or DVTs).ti,kf.	13,184
47	exp *Pulmonary Embolism/	31,265
48	((lung? or pulmonary) adj (embol* or infarct* or micro-embol* or microembol* or thrombo-embol* or thromboembol*)).ti,kf.	25,555
49	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	5,638,224
50	exp *Intraoperative Complications/	26,971
51	exp *Postoperative Complications/	313,777
52	50 or 51	333,032
53	exp animals/	25,352,078
54	exp animal experimentation/ or exp animal experiment/	10,126
55	exp models animal/	627,084
56	nonhuman/	0
57	exp vertebrate/ or exp vertebrates/	24,638,924
58	53 or 54 or 55 or 56 or 57	25,354,052
59	exp humans/	20,360,962
60	exp human experimentation/ or exp human experiment/	12,664
61	59 or 60	20,361,619
62	58 not 61	4,993,060
63	(20 and 52) or (20 and 25 and 49)	3,579
64	63 not 62	3,573

65	limit 64 to english language	3,497
66	*Long Term Adverse Effects/	538
67	((duration? or follow-up* or followup* or long-term* or longterm* or persistent* or post-recover* or postrecover*) adj2 (complication? or consequence? or (adverse* adj effect?) or implication? or outcome? or sequelae or symptom?)).ti,kf.	31,885
68	*Recovery of Function/	14,344
69	((recover* or return*) adj2 (baseline? or base-line? or disease? or function* or health* or patient* or usual)).ti,kf.	10,740
70	(Previous* or timing or prior).ti,kf.	87,011
71	(Previous* or timing or prior).ti,kf. adj2 ((*Coronavirus Infections/ or (COVID-19 or COVID19).mp. or ((pneumonia or COVID* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*) and (hubei or wuhan or beijing or shanghai)).ti,kf. or Wuhan virus*.ti,kf. or (19nCoV or 2019-nCoV or 2019nCoV).ti,kf. or (nCoV* or n-CoV*).ti,kf. or ("CoV 2" or CoV2).ti,kf. or (OC43 or NL63 or 229E or HKU1 or HCoV* or Sars-coronavirus*).ti,kf. or (2019-novel CoV or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or ((novel or new or nouveau) adj2 (CoV or nCoV or COVID or coronavirus* or corona virus or Pandemi*2)) or (coronavirus* and pneumonia)).ti,kf. or (COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.) or severe acute respiratory syndrome coronavirus 2.ti,kf. or (SARSCoV* or SARS-CoV* or SARS2 or SARS-2).ti,kf. or (novel coronavirus* or novel corona virus* or novel CoV).ti,kf. or ((coronavirus* or corona virus*) adj2 "2019").ti,kf. or ((coronavirus* or corona virus*) adj2 "19").ti,kf. or (coronavirus 2 or corona virus 2).ti,kf. or COVID*.ti,kf.) and ((201911* or 202*).dp. or 20191101:20301231.(ep). or 20191101:20301231.(dt).))	511
72	66 or 67 or 68 or 69 or 71	14,1570
73	20 and 72	1,916
75	limit 74 to english language	1,880
76	limit 75 to dt=20201004-20301231	1,565

Table A3 Search strategy for MedRxiv and BioRxiv search (April 2022)

No.	Search term	Results
1	"Long-COVID" AND "Systematic review"	407
2	"post-acute COVID" and abstract or title "surgery" (match all words)	215
3	""Long-COVID" AND "surgery""	77

Table A4 Search strategy for systematic review (paediatric long COVID) via MEDLINE (PubMed April 2022)

No.	Search Term	Results
1	Adolescen*[tiab]	340,202
2	Child*[tw]	2,617,678
3	Paediat*[tw]	79,483
4	Pediatric*[tiab]	351,963
4	Pediatrics[MH]	62,314
5	Adolescent medicine[MH]	1,557
6	“Young people”[tiab]	33,677
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	2,868,100
8	“Severe acute respiratory syndrome”[MH]	5,679

9	COVID[MH]	154,126
10	COVID-19[tiab]	214,192
11	Sars-CoV-2[tiab]	80,449
12	Coronavirus[tiab]	96,988
13	“COVID symptom*”[tiab]	198
14	“COVID syndrom*”[tiab]	238
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	257,595
16	Chronic[tiab]	1,304,467
17	“Late sequelae”[tiab]	1,825
18	“Long”[tiab]	1,682,209
19	“Long-COVID”[ALL]	1,110
20	“Long term effect”[tiab]	9,257
21	“Long post”[tiab]	269
22	“Long-haul”[tiab]	983
23	“Long-tail”[tiab]	802
24	“Long-term sequalae”[tiab]	62
25	“Ongoing symptoms”[tiab]	583
26	Persist*[tiab]	529,517
27	“Persistent symptoms”[tiab]	4,082
28	Post-COVID[tiab]	3,437
29	“Post-acute”[tw]	4,265
30	“Post-acute sequelae”[tiab]	180
31	Aftereffect[tiab]	2,456
32	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	3,258,134
33	((((((((((((((((((((((((((((((((((((Embase*[tiab]) OR Cinahl*[tiab]) OR systematic overview*[tiab]) OR methodological overview*[tiab]) OR methodologic overview*[tiab]) OR methodological review*[tiab]) OR methodologic review*[tiab]) OR quantitative review*[tiab]) OR quantitative overview*[tiab]) OR quantitative synthes*[tiab]) OR pooled analy*[tiab]) OR Cochrane[tiab]) OR Medline[tiab]) OR Pubmed[tiab]) OR Medlars[tiab]) OR handsearch*[tiab]) OR meta-regression*[tiab]) OR metaregression*[tiab]) OR data synthes*[tiab]) OR data extraction[tiab]) OR data abstraction*[tiab]) OR mantel haenszel[tiab]) OR peto[tiab]) OR der-simonian[tiab]) OR dersimonian[tiab]) OR fixed effect*[tiab]) OR "Cochrane Database Syst Rev"[Journal]) OR "health technology assessment winchester, england"[Journal]) OR "Evid Rep Technol Assess (Full Rep)"[Journal]) OR "Int J Technol Assess Health Care"[Journal]) OR "GMS Health Technol Assess"[Journal]) OR "Health Technol Assess (Rockv)"[Journal]) OR "Health Technol Assess Rep"[Journal])) OR ((((indirect treatment[tiab]) OR mixed-treatment[tiab])) AND comparison*[tiab])) OR ((((((((((((((((((((systematic[sb]) OR meta-analysis[pt]) OR meta-analysis as topic[mh]) OR meta-analysis[mh]) OR meta analy*[tw]) OR integrative review*[tiab]) OR integrative overview*[tiab]) OR research integration*[tiab]) OR research overview*[tiab]) OR collaborative review*[tiab]) OR collaborative overview*[tiab]) OR systematic review*[tiab]) OR technology assessment*[tiab]) OR technology overview*[tiab]) OR "Technology Assessment, Biomedical"[mh]) OR HTA[tiab]) OR HTAs[tiab]) OR comparative efficacy[tiab]) OR comparative effectiveness[tiab]) OR outcomes research[tiab]) OR indirect comparison*[tiab])	555,651
34	#7 AND #15 AND #32	2,792
35	("adolescen*"[Title/Abstract] OR "child*"[Text Word] OR "paediat*"[Text Word] OR "pediatric*"[Title/Abstract] OR "pediatrics"[MeSH Terms] OR "adolescent medicine"[MeSH Terms] OR "Young people"[Title/Abstract]) AND ("severe acute respiratory syndrome"[MeSH	

	Terms] OR ("Sars-CoV-2"[MeSH Terms] OR "COVID-19"[MeSH Terms]) OR "COVID-19"[Title/Abstract] OR "Sars-CoV-2"[Title/Abstract] OR "Coronavirus"[Title/Abstract] OR "covid symptom*"[Title/Abstract] OR "covid syndrom*"[Title/Abstract]) AND ("Chronic"[Title/Abstract] OR "Late sequelae"[Title/Abstract] OR "Long"[Title/Abstract] OR "Long-COVID"[All Fields] OR "Long term effect"[Title/Abstract] OR "Long post"[Title/Abstract] OR "Long-haul"[Title/Abstract] OR "Long-tail"[Title/Abstract] OR "Long-term sequalae"[Title/Abstract] OR "Ongoing symptoms"[Title/Abstract] OR "persist*"[Title/Abstract] OR "Persistent symptoms"[Title/Abstract] OR "Post-COVID"[Title/Abstract] OR "Post-acute"[Text Word] OR "Post-acute sequelae"[Title/Abstract] OR "Aftereffect"[Title/Abstract])	
36	#34 AND #35	159
37	#36 AND SR and MA Filter	78
38	#36 AND Date Filter after 6/9/21	49

Table A5 Search strategy for observational studies (paediatric long COVID) via MEDLINE (PubMed April 2022)

No.	Search term	Results
1	Adolescen*[tiab]	340,202
2	Child*[tw]	2,617,678
3	Paediat*[tw]	79,483
4	Pediatric*[tiab]	352,963
5	Pediatrics[MH]	62,314
6	Adolescent medicine[MH]	1,557
7	"Young people"[tiab]	33,677
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	2,868,100
9	Severe acute respiratory syndrome[MH]	5,679
10	COVID[MH]	154,126
11	COVID-19[tiab]	214,192
12	Sars-CoV-2[tiab]	80,449
13	Coronavirus[tiab]	96,988
14	"COVID symptom*"[tiab]	198
15	"COVID syndrom*"[tiab]	238
16	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	257,595
17	Chronic[tiab]	1,304,467
18	"Late sequelae"[tiab]	1,825
19	"Long"[tiab]	1,682,209
20	"Long-COVID"[ALL]	1,110
21	"Long term effect"[tiab]	9,257
22	"Long post"[tiab]	269
23	"Long-haul"[tiab]	983
24	"Long-tail"[tiab]	802
25	"Long-term sequalae"[tiab]	62
26	"Ongoing symptoms"[tiab]	538
27	Persist*[tiab]	529,517
28	"Persistent symptoms"[tiab]	4,082
29	Post-COVID[tiab]	3,437

30	"Post-acute"[tw]	4,265
31	"Post-acute sequelae"[tiab]	180
32	Aftereffect[tiab]	2,356
33	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	3,258,134
34	#8 AND #16 AND #33	2,792
35	Meta-Analysis[pt] OR Meta-Analysis[Mesh:no exp] OR review, systematic[Mesh:no exp] OR "Meta-Analysis as Topic"[Mesh:no exp] OR "Technology Assessment, Biomedical"[Mesh] OR "Network Meta-Analysis"[Mesh:no exp] OR ((systematic*[tw] AND (review*[tw] OR overview*[tw])) OR (methodologic*[tw] AND (review*[tw] OR overview*[tw]))) OR ((quantitative[tw] AND (review*[tw] OR overview*[tw] OR synthes*[tw])) OR (research[tw] AND (integrati*[tw] OR overview*[tw]))) OR ((integrative[tw] AND (review*[tw] OR overview*[tw])) OR (collaborative[tw] AND (review*[tw] OR overview*[tw])) OR (pool*[tw] AND analy*[tw])) OR ("data synthes*"[tw] OR "data extraction*"[tw] OR "data abstraction*"[tw]) OR (handsearch*[tw] OR "hand search*"[tw]) OR ("mantel haenszel"[tw] OR peto[tw] OR "der simonian"[tw] OR dersimonian[tw] OR "fixed effect*"[tw] OR "latin square*"[tw]) OR ("met analy*"[tw] OR metanaly*[tw] OR "technology assessment*"[tw] OR HTA[tw] OR HTAs[tw] OR "technology overview*"[tw] OR "technology appraisal*"[tw]) OR ("meta regression*"[tw] OR metaregression*[tw]) OR (meta-analy*[tw] OR metaanaly*[tw] OR "systematic review*"[tw] OR "biomedical technology assessment*"[tw] OR "medical technology assessmen*"[tw]) OR (medline[tiab] OR cochrane[tiab] OR pubmed[tiab] OR medlars[tiab] OR embase[tiab] OR cinahl[tiab]) OR (cochrane OR (health AND "technology assessment") OR "evidence report") OR (comparative[tw] AND (efficacy[tw] OR effectiveness[tw])) OR ("outcomes research"[tw] OR "relative effectiveness"[tw]) OR ((indirect[tw] OR "indirect treatment"[tw] OR mixed-treatment[tw] OR bayesian[tw]) AND comparison*[tw]) OR (multi*[tw] AND treatment[tw] AND comparison*[tw]) OR (mixed[tw] AND treatment[tw] AND (meta-analy*[tw] OR metaanaly*[tw])) OR "umbrella review*"[tw] OR (multi*[tw] AND paramet*[tw] AND evidence[tw] AND synthesis[tw]) OR (multiparamet*[tw] AND evidence[tw] AND synthesis[tw]) OR (multi-paramet*[tw] AND evidence[tw] AND synthesis[tw])	1,283,286
36	#34 AND #35	241
37	"Clinical Trial, Phase IV"[pt] OR "Clinical Trials, Phase IV as Topic"[Mesh:no exp] OR "Consumer Product Safety"[Mesh:no exp] OR "Equipment Failure"[Mesh] OR "Equipment Safety"[Mesh:no exp] OR "Intraoperative Complications"[Mesh] OR "Length of Stay"[Mesh:no exp] OR "Medical Device Recalls"[Mesh:no exp] OR "Patient Satisfaction"[Mesh] OR "Postoperative Complications"[Mesh] OR "Product Recalls and Withdrawals"[Mesh:no exp] OR "Product Surveillance, Postmarketing"[Mesh:no exp] OR Recurrence[Mesh:no exp] OR Reoperation[Mesh:no exp] OR Safety[Mesh] OR "Safety-Based Medical Device Withdrawals"[Mesh:no exp] OR "Adverse Effects"[sh] OR ((adverse[tiab] OR undesirable[tiab] OR harm*[tiab] OR toxic[tiab] OR injurious[tiab] OR serious[tiab] OR fatal[tiab]) AND (effect*[tiab] OR reaction*[tiab] OR event*[tiab] OR outcome*[tiab] OR incident*[tiab])) OR (death[ti] OR deaths[ti] OR fatal[ti] OR fatality[ti] OR fatalities[ti]) OR (hazard*[tiab] OR defect*[tiab] OR misuse*[tiab] OR failure*[tiab] OR malfunction*[tiab] OR error*[tiab]) OR (length*[tiab] AND stay*[tiab]) OR (patient*[tiab] AND (preference*[tiab] OR satisfaction[tiab] OR satisf*[tiab])) OR ((intraoperati*[ti] OR intra-operati*[ti] OR postoperati*[ti] OR post-operati*[ti]) AND (complicati*[tiab] OR hematoma*[tiab] OR haematoma*[tiab] OR infect*[tiab] OR injur*[tiab] OR migration*[tiab] OR pain*[tiab] OR reject*[tiab] OR seroma*[tiab])) OR (recrudescence*[tiab] OR recurrence*[tiab] OR relapse*[tiab]) OR (reoperati*[ti] OR re-operati*[ti] OR ((repeat[ti] OR revision[ti]) AND (operation*[tiab] OR surger*[tiab] OR surgical*[tiab]))) OR (safe*[tiab] OR adverse*[tiab] OR undesirable[tiab] OR harm*[tiab] OR injurious[tiab] OR risk[tiab] OR risks[tiab] OR reaction*[tiab] OR complication*[tiab]) OR ("side effect*"[tw] OR safety[tw] OR unsafe[tw]) OR (warning*[tiab] OR recall*[tiab] OR withdrawn*[tiab] OR withdrawal*[tiab])	9,711,266
38	#34 AND #37	1,576
39	"Epidemiologic Studies"[Mesh] OR "Observational Studies as Topic"[Mesh:no exp] OR "Clinical Studies as Topic"[Mesh:no exp] OR ("Observational Study"[pt] OR "Comparative Study"[pt] OR "Clinical Study"[pt]) OR (observational[tw] AND (study[tw] OR studies[tw] OR design[tw] OR	9,959,706

	analysis[tw] OR analyses[tw])) OR (cohort*[tw] OR compared[tw]) OR (comparative[tw] AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR (prospective[tw] AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR (("follow up"[tw] OR followup[tw]) AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR ((longitudinal[tw] OR longterm[tw] OR (long[tw] AND term[tw])) AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw] OR data[tw])) OR (retrospective[tw] AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw] OR data[tw] OR review[tw])) OR ((case[tw] AND control[tw]) OR (case[tw] AND comparison[tw]) OR (case[tw] AND controlled[tw])) OR (case-referent[tw] AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR (population[tw] AND (study[tw] OR studies[tw] OR analysis[tw] OR analyses[tw])) OR (descriptive[tw] AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR ((multidimensional[tw] OR (multi[tw] AND dimensional[tw]) OR multivariate[tw] OR multi-variate[tw]) AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR (cross[tw] AND sectional[tw] AND (study[tw] OR studies[tw] OR design[tw] OR research[tw] OR analysis[tw] OR analyses[tw] OR survey[tw] OR findings[tw])) OR ((natural[tw] AND experiment[tw]) OR (natural[tw] AND experiments[tw])) OR (quasi[tw] AND (experiment[tw] OR experiments[tw] OR experimental[tw])) OR (("non experiment*"[tw] OR nonexperiment[tw] OR "non experimental"[tw] OR nonexperimental[tw]) AND (study[tw] OR studies[tw] OR design[tw] OR analysis[tw] OR analyses[tw])) OR (prevalence[tw] AND (study[tw] OR studies[tw] OR analysis[tw] OR analyses[tw]))	
40	#34 AND #39	1,716
41	#34 AND #37 AND #39	1,007

Table A6 Paediatric search strategy for MedRxiv and BioRxiv search (April 2022)

No.	Query	Results
1	[“long-COVID" OR "Post-COVID") AND children	215

10.2 Characteristics and results of studies assessing long COVID in adults

Table A7 Characteristics of included studies for adult long COVID

Author year	Study design	Country	Sample Size	Diagnostic criteria	Duration of follow-up; mean ± SD, median (IQR) or [range]	Sex (% female)	Outcomes reported	Long COVID definition
Systematic review with/without meta-analysis								
Alkodaymi (2022)[23]	Systematic review and meta-analysis	Austria: 1 Belgium: 2 Canada: 1 China: 11 Czech Republic: 1 Egypt: 1 Finland: 1 France: 5 Germany: 3 India: 2 Iran: 2 Iraq: 1 Israel: 2 Italy: 8 Mexico: 1 Norway: 3 South Korea: 1 Spain: 9 Sweden: 1 Switzerland: 1 UK: 1 USA: 4	258, 228 <100: 16 100–500: 34 501–1000: 6 >1,000: 6	Laboratory-confirmed COVID-19	90–365 days	NR	Prevalence of post-acute COVID-19 syndrome symptoms	Post-COVID-19 subacute phase of ongoing symptoms lasting 4–12 weeks after onset of illness, and chronic phase or long COVID-19 defined as symptoms and abnormalities that last >12 weeks after onset of illness and not explained by alternative diagnosis
Chen (2022)[22]	Systematic review and meta-analysis	China: 5 India: 3 Bangladesh: 1 Iran: 1	886,388 COVID-19-positive patients	NR for individual included studies. PCR test, antibody test or	28 days–12 months	Range 32.9%–82.1%	Prevalence of post-COVID condition and symptoms at least 28 days after index date.	(1) Any symptoms or (2) ≥1 new or persisting symptom during follow-up time.

		Russia: 1 UK: 3 Germany: 2 Switzerland: 2 Italy: 3 Spain: 2 France: 1 USA: 10 Brazil: 1 Mexico: 1 UK, Sweden,	<100: 0 100–500: 14 501–1,000: 14 >1,000: 22	diagnosis as per inclusion criteria			Risk factors for post-COVID condition	Follow-up time defined as 28–30 days (stratified to 30 days, 60 days, 90 days, and 120 days after index date
De-la-Rosa-Martinez (2021)[11]	Systematic review and meta-analysis	Austria: 1 China: 2 Egypt: 1 France: 2 Greece: 1 Ireland: 2 Italy: 6 Korea: 1 Spain: 4 Switzerland: 1 UK: 3 USA: 4 multicentre (Germany, Italy): 1	8,175 <100: 8 100–500: 20 501–1,000: 0 >1,000: 1	RT-PCR or RAT	21–180 days	Range 27%–75%	Pooled prevalence of long-term PASC manifestations. Modifiers of PASC prevalence.	Persistent manifestation 21 days from onset of COVID-19 symptoms
Domingo (2021)[14]	Systematic Review	Bangladesh: 1 Belgium: 1 Brazil: 2 Canada: 1 China: 7 Faroe Islands: 1 France: 2 Germany: 1	16,336 <100: 11 100–500: 46 501–1,000: 4 >1,000: 2	Laboratory-confirmed COVID-19. Clinically diagnosed. Both laboratory-confirmed and clinically diagnosed.	20 days–8 months from acute infection	Range 20%–100%	Frequency of post-COVID sequelae. Prevalence of post-COVID symptoms.	Post-COVID condition defined as symptoms that usually appear 3 months from onset of COVID-19 symptoms and last for ≥2 months in individuals with history of probable or

		Greece: 2 Iran: 1 Ireland: 3 Israel: 1 Italy: 9 Jordan: 1 Mexico: 1 multiple: 2 Norway: 4 Romania: 1 Russia: 1 Saudi Arabia: 2 Spain: 4 Sweden: 1 Turkey: 1 UK: 5 USA: 5 unclear: 1						confirmed SARS-CoV-2 infection
Fernandez-de-la-Penas (2021)[25]	Systematic review and meta-analysis	China: 4 Egypt: 1 Faroe Islands: 1 France: 4 Ireland: 1 Italy: 3 Mexico: 1 Multi-country: 1 Netherlands: 1 Norway: 1 Pakistan: 1 Russia: 1 Spain: 1 Switzerland: 1 UK: 4 USA: 8	24,255 <100: 3 100–500: 22 501–1,000: 3 >1,000: 6	RT-PCR assay of nasopharyngeal swab samples	21 days–252 days (36 weeks)	Hospitalised population: 42.7% Non-hospitalised: 70.2%	Prevalence of post-COVID-19 symptoms Timeframe of post-COVID-19 symptoms in months following SARS-CoV-2. Is there a difference in post-COVID-19 between hospitalised and non-hospitalised patients	Defined as illness in people who have recovered from exhibiting COVID-19 symptoms far longer than would be expected

Gao (2022)[21]	Systematic review and meta-analysis	France: 1 India: 1 Israel: 1 Italy: 2 Morocco: 1 Netherlands: 1 Saudi Arabia: 1 Spain: 1 Switzerland: 1 UK: 2 UK, Italy, Spain: 1 USA: 5	989,342 <100: 0 100–500: 4 501–1000: 2 >1,000: 12	NR	NR	NR	Impact of COVID-19 vaccination on risk of developing long COVID and specific symptoms	Symptoms in individual with history of probable or confirmed SARS-CoV-2 infection, usually 3 months from onset of COVID-19, and lasting for ≥2 months which cannot be explained by alternative diagnosis Included studies of all long COVID definition
Groff (2021)[13]	Systematic review	Austria: 2 Bangladesh: 1 Belgium: 1 Canada: 2 China: 7 France: 3 Germany: 6 India: 1 Iran: 1 Ireland: 1 Italy: 6 Netherlands: 2 Norway: 2 Spain: 5 Switzerland: 2 Turkey: 1 UK: 7 US: 8	25,0351 <100: 8 100–500: 20 501–1,000: 0 >1,000: 1	NR	1–8 months	44%	Frequency of PASC. Rates of clinical manifestations of PASC	Presence of ≥1 abnormality diagnosed by laboratory investigation, radiologic pathology, or clinical signs and symptoms present at least 1 month after COVID-19 diagnosis or after discharge from hospital
Han (2022)[26]	Systematic review and meta-analysis	China: 7 Italy: 5 Spain: 4	8591 <100: 5 100–500: 8	'Confirmed SARS-CoV-2 infection'	12 months	23%–61%	Prevalence of post-COVID symptoms	NR

		Germany: 2	501–1,000: 1 >1,000: 3					
Jennings (2021)[15]	Systematic review	USA: 3 Argentina: 1 Belgium: 1 Canada: 2 China: 7 France: 2 Germany: 1 Iran: 1 Ireland: 1 Italy: 4 Japan: 1 UK: 7 Mexico: 1 Nigeria: 1 Norway: 2 Pakistan: 1 Spain: 3	8,293 <100: 10 100–500: 26 501–1,000: 2 >1,000: 1	Participants who tested positive for SARS-CoV-2 infection or were suspected of SARS-CoV-2 infection (no specific testing listed)	4 weeks–31 weeks	Range 31%–72%	Prevalence of symptoms in OSC and PCS phases	Symptoms persisting beyond 4-week acute COVID-19 period. Ongoing symptomatic COVID-19 (persistent signs and/or symptoms from 4–12 weeks) and post-COVID-19 syndrome (persistent signs and/or symptoms from 12 weeks post-infection)
Maglietta (2022)[28]	Systematic review and meta-analysis	Brazil: 1 China: 8 France: 2 Italy: 2 Russia: 1 Spain: 5 Netherlands: 1	13,340 <100: 4 100–500: 8 501–1000: 3 >1000: 5	NR	3 months–12 months	47.6%	Risk factors for developing long COVID in individuals hospitalised for COVID-19	Signs and symptoms that develop during or after infection consistent with COVID-19, continue for >12 weeks and not explained by alternative diagnosis
Malik (2021)[16]	Systematic review	Australia: 1 Bangladesh: 1 China: 2 Denmark: 1 Egypt: 1 France: 2 Ireland: 1 Mexico: 1	54,730 <100: 1 100–500: 16 501–1,000: 1 >1,000: 3	Not reported in all studies. RT-PCR. Laboratory confirmed. Diagnosed as per WHO interim guidance	14 days–186 days	Range 33.9%–71.5%	Prevalence of post-acute clinical manifestations	Post-acute COVID-19 syndrome defined as symptomatology 2 weeks after recovery from COVID-19

		Nigeria: 1 Saudi Arabia: 1 Spain: 1 UK: 4 US: 3						
Middleton (2022)[24]	Systematic review and meta-analysis	Italy: 11 China: 10 UK: 5 France: 4 Spain: 3 Switzerland: 3 Canada: 2 Netherlands: 2 Norway: 2 Belgium: 2 USA: 1 Denmark: 1 Russia: 1 Brazil: 1 Japan: 1	13,668 <100: 24 100–500: 18 501–1,000: 3 >1,000: 4	Clinically confirmed COVID-19. Laboratory-confirmed COVID-19. Clinically and laboratory-confirmed COVID-19. RT-PCR confirmed. Nucleic acid testing for confirmation.	60 days–348 days	10%–63%	Respiratory/general functioning PROMs. Quality of life. Return to work. Healthcare utilisation following acute COVID-19 infection	Patients hospitalised with COVID-19 >8 weeks after hospitalisation
Natarajan (2022)[27]	Systematic review and meta-analysis	Bangladesh: 1 China: 2 UK: 8 Iran: 1 Brazil: 2 Faroe Islands: 1 Pakistan: 1 France: 4 Italy, Spain, and Norway: 1 Israel: 1 USA: 7 Taiwan: 1 Ireland: 2 Germany: 3	220,759 <100: 14 100–500: 26 501–1000: 3 >1,000: 6	Confirmed positive test for SARS-CoV-2	1 month–9 months	12.5%–90%	Prevalence of symptoms pertaining to neuropsychiatry, neurology and pain	symptoms that continue or develop after acute SARS-CoV-2 diagnosis post-4 weeks

		Scotland: 1 Nigeria: 1 India: 1 Australia: 1 Spain: 1 Netherlands and Belgium: 1 Norway: 1 Poland: 1 Greece: 1						
Notarte (2022)[20]	Systematic review	USA: 5 UK: 5 India: 1 Japan: 1 Italy: 1 multination (UK, Israel, Russia, India, South): 1 Israel: 1 Switzerland: 1 France: 1	17,256,654 <100: 0 100–500: 0 501–1000: 1 >1,000: 5	RT-PCR	NR due to variable nature of each included study	44%–63%	Impact of COVID-19 vaccines on risk of developing long COVID	Development and/or persistence of symptoms after acute phase of SARS-CoV-2 infection (typically >3 months)
Nguyen (2022)[18]	Systematic Review	Italy: 7 France: 4 Norway: 3 Spain: 2 Germany: 2 Faroe Islands: 1 Denmark: 1 Switzerland: 1 UK: 1 China: 6 US: 5 Iran: 2 Turkey: 1	17,678 <100: 8 100–500: 20 501–1,000: 3 >1,000: 7	RT-PCR	4 weeks–12 months	10%–77%	Prevalence of long-term persistence of somatic clinical symptoms in discharged COVID-19 patients.	Post-acute COVID (4–12 weeks after onset of symptoms) and long COVID (>12 weeks post-onset) Post-COVID-19 syndrome defined by persistence of symptoms ≥12 weeks after onset

Patrucco (2022)[17]	Systematic review	NR	3,665 <100: 0 100–500: 4 501–1,000: 2 >1,000: 1	NR	46 days–6 months	NR	Persistent adverse effects of SARS-CoV-2 infection in months following hospitalisation for COVID-19	Long-term sequelae defined as persistent symptoms and evidence of organ damage ≥2 months after hospital discharge
Pillay (2022)[19]	Systematic review	China: 5 Italy: 2 Norway: 2 Russia: 2 Switzerland: 2 UK, USA, Sweden, Turkey: 1	24,697 <100: 0 100–500: 6 501–1000: 6 >1,000: 5	Laboratory-confirmed (using RT-PCR or antigen test) via records	3–12 months	Median: 51%	Pre-existing and clinical risk factors and development of post-COVID-19 condition	Post-COVID-19 condition defined as symptoms persisting ≥12 weeks after positive COVID-19 test or symptom onset
Van Kessel (2022)[12]	Systematic review	Netherlands: 4 Italy: 1 Ireland: 1 US: 1 UK: 1	3,000 <100: 3 100–500: 5 501–1,000: 0 >1,000: 1	Positive test for COVID-19 not a prerequisite for diagnosis	2 weeks–13 weeks	NR	Nature and frequency of persistent symptoms in patients after acute COVID-19 infection	Post-acute COVID-19 described as symptoms extending beyond 3 weeks from initial symptoms. Long COVID described as symptoms extending beyond 12 weeks from initial symptoms
Cohort studies								
Antonelli (2022)[33]	Case control	UK	97,364	RT-PCR or lateral flow antigen test	>6 months	NR	Odds of long COVID based on COVID-19 variant	New or ongoing symptoms ≥4 weeks after start of acute COVID-19
Augustin (2021)[30]	Prospective cohort study	Germany	353	Previously confirmed SARS-CoV-2 in PCR in swab or sputum	6.8 months (median 207 days (IQR 187-234)	Control group: 51.3%	SARS-CoV-2 serology Symptoms and predictor for Post Covid Syndrome	NR

						Post-COVID-19 syndrome: 68.3%		
Fernandez-de-las-Penas (2022)[29]	Cohort study	Spain	201	RT-PCR assay of nasopharyngeal and oral swab samples	Mean 6.3 (SD 1.0) months after hospital discharge	54.40%	Post-COVID symptoms and psychological symptoms according to vaccine status	Development or persistence of symptoms after acute phase
Kuodi (2022)[32]	Cross-sectional	Israel	3,572	RT-PCR	8 months (unvaccinated group) 4 months (received 2 doses)	Uninfected participants: 39% All infected participants: 49.1%	Proportion overall and in specific age groups, of participants reporting selected health outcomes according to vaccination and infection status.	Condition that occurs in individuals with history of probable or confirmed SARS-CoV-2 infection, usually 3 months from onset of COVID-19 with symptoms that last for ≥2 months and cannot be explained by alternative diagnosis
Mandal (2021)[31]	Cross-sectional	UK	384	Nasopharyngeal swab confirmed	Median 54 days post-hospital discharge	38%	Blood biomarkers of long COVID	NR
Guidelines								
The National Institute of Health and Care Excellence (2022)[1]	Clinical guideline	UK	N/A	N/A	N/A	N/A	N/A	Ongoing symptomatic COVID-19 – signs and symptoms of COVID-19 from 4–12 weeks Post-COVID-19 syndrome – Signs and symptoms that develop during or after infection consistent with COVID-19, continues for >12 weeks and not

	explained by alternative diagnosis. Usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while possibility of alternative underlying disease also being assessed

Abbreviations:
COVID-19 = coronavirus disease 2019, IQR = interquartile range, N/A = not applicable, NR = not reported, PASC = post-acute sequelae of COVID-19, PCR = polymerase chain reaction, RAT = rapid antigen test, RT-PCR = reverse transcription polymerase chain reaction, SD = standard deviation, WHO = World Health Organization

Table A8 Range of symptoms prevalence reported in the systematic reviews

Symptoms	Lowest estimated prevalence (%)	Highest estimated prevalence (%)
Diminished general health[11]	-	60%
Poor quality of life[16]	-	59%
Persisting symptoms[17]	-	52%
Effort intolerance[23]	19%	45%
Pain/discomfort[14, 16, 24]	13%	42%
Anxiety/depression[16, 27]	23%	38%
Fatigue/weakness[13, 26]	29%	38%
Mobility dysfunction/decline[12, 16, 24]	15%	37%
Fatigue[22, 23]	23%	36%
Perceived lack of recovery: patient stating 'not feeling fully recovered'[17]	-	34%
Hindered in daily function[12]	-	33%
Asthenia[11, 17]	24%	32%
Sleep disorders[23, 26]	12%	29%
Physical decline/fatigue[17]	-	28%
Attention disorder[11]	-	27%
Arthromyalgia[26]	-	26%
Modified Medical Research Council Dyspnoea Scale (mMRC)≥1[17]	-	26%
Dyspnea[14, 23]	18%	25%
Night sweats[17]	-	24%
Sweating[17]	-	24%
Anosmia/dysgeusia[11, 12, 17]	3%	23%
Anxiety[23, 26]	21%	23%
Depression[23, 26]	14%	23%
Joint pain/arthralgia[23, 25]	8%	23%
Memory deficit[11, 22]	14%	23%
Difficulty concentrating[22, 23, 26]	6%	22%
Fever-like symptoms[12]	-	22%
Hair loss[17, 23, 26]	7%	22%
Post activity polypnea[17]	-	21%
Reduced tolerance to exercise[13, 17]	15%	21%
Voice changes[11]	-	20%
Cognitive disorder[23, 26]	14%	19%
Body ache[11]	-	17%
Tinnitus[11]	-	17%
Cough[23, 26]	5%	15%
Loss of smell/anosmia[23, 26]	6%	15%

Mental health/PTSD[16, 27]	12%	15%
Chest distress[17]	-	14%
Headache[23, 26]	7%	14%
Palpitations[23, 26]	5%	14%
Functional deficit[11]	-	13%
Hearing loss[27]	-	13%
Loss of taste[23, 26]	4%	13%
Weakness[11]	-	13%
Chest pain[22, 23, 25]	3%	12%
Myalgia/muscle pain[23, 25, 26]	8%	12%
Flu-like symptoms[13]	-	10%
Continence problems[11]	-	10%
Diarrhoea[22, 23]	3%	10%
Abdominal pain[11, 22, 27]	1%	9%
Confusion[11]	-	9%
Weight loss[11, 27]	5%	9%
Dysphagia[11]	-	8%
Nausea[23]	4%	8%
Dysgeusia[11]	-	7%
Poor appetite[11, 22]	4%	7%
Dizziness/vertigo[17, 22, 26]	4%	6%
Tachycardia[22]	-	6%
Skin rash[26, 27]	3%	5%
Chills[17]	-	5%
Residual mortality[17]	-	5%
Diarrhoea and vomiting[17]	-	5%
Backache/waist pain[26]	-	4%
Severe dyspnea[17]	-	4%
Fever persistence[11, 22]	2%	4%
Limb oedema[17]	-	3%
Migraine[11]	-	3%
Sore throat[22, 26]	2%	3%
Sputum production[17, 26]	2%	3%
New-onset diabetes[11]	-	2%
Renal failure[11]	-	1%
Vomiting[27]	-	1%
Low-grade fever[17]	-	<1%

Table A9 Prevalence of long COVID symptoms (adults) stratified by vaccination status

			Unadjusted analysis						Adjusted analysis	
Symptoms	**Uninfected**	**Unvaccinated**	**Received one dose**			**Received two doses**			**Received two doses**	**p value**
	Sample size	*Sample size*	*Sample size*	*RR (95% CI)*	*p value*	*Sample size*	*RR (95% CI)*	*p value*	*RR (95% CI)*	*p value*
Fatigue	430	82	93	1.06 (0.82–1.36)	0.67	33	0.43 (0.30–0.63)	<0.001	0.36 (0.19–0.71)	0.003
Headache	387	95	110	1.08 (0.81–1.44)	0.59	77	0.64 (0.45–0.91)	0.01	0.46 (0.26–0.83)	0.01
Weakness in arms and legs	199	103	127	1.04 (0.74–1.47)	0.82	82	0.42 (0.26–0.69)	0.001	0.43 (0.20–0.94)	0.03
Persistent muscle pain	147	86	106	1.17 (0.77–1.76)	0.47	80	0.51 (0.29–0.89)	0.02	0.32 (0.11–0.88)	0.03
Loss of concentration	88	55	59	1.24 (0.81–1.90)	0.32	48	0.43 (0.23–0.79)	0.007	0.59 (0.17–2.10)	0.41
Hair loss	81	36	43	1.11 (0.74–1.69)	0.61	9	0.27 (0.13–0.55)	<0.001	0.17 (0.06–0.60)	0.005
Sleeping problems	184	29	42	1.35 (0.86–2.11)	0.19	14	0.52 (0.28–0.97)	0.04	0.53 (0.18–1.61)	0.26
Dizziness	152	32	30	0.87 (0.54–1.40)	0.58	12	0.40 (0.21–0.77)	0.01	0.26 (0.09–1.79)	0.02
Persistent cough	134	24	26	1.01 (0.59–1.71)	0.97	20	0.90 (0.51–1.59)	0.71	0.72 (0.28–1.83)	0.48
Shortness of breath	77	25	29	1.08 (0.65–1.81)	0.76	14	0.60 (0.32–1.14)	0.20	0.23 (0.07–0.84)	0.03

Abbreviations:
CI = confidence interval, RR = risk ratio

10.3 Characteristics and results of studies assessing long COVID in paediatric patients

Table A10 Characteristics of included studies for paediatric long COVID

Author year	Study design	Country	Sample Size	Diagnostic criteria	Duration of follow-up; Mean ± SD, median (IQR) or [range]	Sex (% female)	Outcomes reported	Long COVID definition
Systematic reviews with/without meta-analysis								
Behnood (2022)[43]	Systematic review and meta-analysis	Australia: 1 England: 1 England and Wales: 1 Faroe Islands: 1 Germany: 2 Italy: 3 Latvia: 1 Russia: 2 Spain: 1 Sweden: 2 Switzerland: 1 Netherlands: 1 UK: 3 USA: 2	23,141 <100: 11 100–500: 2 501–1000: 3 >1000: 6	RT-PCR RT-PCR/serology Serology Unclear RT-PCR/lateral flow Clinical diagnosis RT-PCR/serology/CD/suspected RT-PCR/LFT/CD/Suspected RT-PCR/CD/confirmed contact RT-PCR/confirmed contact	>1–8.5 months	41–61%	Prevalence of persistent symptoms following SARS-CoV-2 infection compared with uninfected controls. Identify potential risk factors.	'ongoing symptomatic COVID-19' defined as signs and symptoms that persist 4–12 weeks from onset of infection and 'post-COVID-19 syndrome' defined as signs and symptoms persisting beyond 12 weeks from date of onset
Hirt (2022)[42]	Systematic review	Europe: 12 Asia: 6 North America: 2 Oceania: 1	81,896 <100: 12 100–500: 4 501–1000: 2 >1000: 3	RT-PCR RT-PCR, antigen or serology RT-PCR or serology Serology NR	>2–7 months (median 5.3; IQR 3–6) in 12 studies starting follow-up at infection or onset and >2–11.5 months (median 5; IQR 3.5–8) in 9	NR	Prevalence of children with post-COVID syndrome.	≥1 month since recovery from acute illness and/or hospital discharge

					studies starting follow-up at recovery			
Lopez-Leon (2022)[41]	Systematic review and meta-analysis	Australia: 1 Brazil: 1 Denmark: 2 France: 1 Germany: 3 Iran: 1 Italy: 1 Latvia: 2 Russia: 2 Sweden: 1 Switzerland: 1 Turkey: 1 UK: 4	80,071 <100: 4 100–500: 8 501–1000: 2 >1000: 7	RT-PCR, RT-PCR/antigen or serology Serology Unclear Nasal swab RT-PCR/IgG IgG NR	1–13 months	Range 39–58%	Prevalence of long COVID in children. Full spectrum of symptoms.	NICE definition: signs and symptoms that continue or develop after acute COVID-19, including ongoing symptomatic COVID-19 (4–12 weeks) and post-COVID-19 syndrome (≥12 weeks)
Cohort study								
Funk (2022)[46]	Prospective cohort study	Argentina Canada Costa Rica Italy Paraguay Singapore Spain US	8,642	Nucleic acid test performed on swab sample obtained from nares, nasopharynx, or oral cavity	90–120 days	47.2	Risk factors for persistent symptoms	NR
Miller (2021)[45]	Prospective cohort study	England and Wales	4,678	Positive swab test Serology Positive swab and serology VirusWatch swabbing programme	NR	40.6–48.7	Risk factors for persistent symptoms	Persistent symptoms lasting >4 weeks
Nugawela (2022)[48]	Prospective cohort study	England	7,096	PCR-positive	3 months	62.88	Risk factors for long term COVID-19 outcomes in children	3 months post-PCR test

Osmanov (2022)[47]	Prospective cohort study	Russia	518	PCR-positive	268 (range 233–284)	52.1	Incidence and risk factors for long-term COVID-19 outcomes in children post-hospital discharge	'persistent symptoms' defined as symptoms present at time of follow-up period
Roessler (2022)[44]	Matched cohort study	Germany	11,950	PCR confirmed diagnosis	Mean: 236 days (SD 44 days, range 121–339)	48.1	Health sequelae at least 3 months after SARS-CoV-2 infection	'Post-COVID-19 condition'– broad spectrum of otherwise unexplained health conditions present 3 months after onset of symptoms or date of SARS-CoV-2 infection and lasting ≥2 months

Abbreviations:
COVID-19 = coronavirus disease 2019, IgG = immunoglobulin G, IQR = interquartile range, NR = not reported, PCR = polymerase chain reaction, RAT = rapid antigen test, RT-PCR = reverse transcription PCR, SD = standard deviation, WHO = World Health Organization.

Table A11 Range of prevalent symptoms reported in paediatric systematic reviews

Symptoms	Pooled estimate of prevalence (95% CI)	Risk difference (95% CI)	IRR (95% CI; p value)
Fatigue[41, 43, 44]	9.7% (4.5–16.5%) to 47.0% (32.0–62.0%)	7.0% (-1.0–14.0%) (NS)	2.28 (1.71–3.06; <0.01)[44]
Dyspnoea[43]	43.0% (18.0–68.0%)	4.0% (-0.09–16.0%) (NS)	-
Headache[41, 43, 44]	7.8% (4.0–12.7%) to 35.0% (19.0–51.0%)	5.0% (1.0–8.0%)	1.58 (1.35–1.84; <0.01)[44]
Myalgia/arthralgia[41, 43]	3.7% (2.2–5.7%) to 25% (11.0%–40.0%)	1.0% (-1.0–4.0%) (NS)	-
Abdominal pain[41, 43, 44]	2.9% (2.0–3.9%) to 25.0% (9.0%–42.0%)	1.0% (0.0%–2.0%)	1.45 (1.27–1.64; <0.01)[44]
Fever[41, 43, 44]	1.8% (0.5%–3.9%) to 18.0% (5.0%–32.0%)	0.0% (0.0%–1.0%)	1.56 (1.30–2.02; <0.01)[44]
Cough[41, 43, 44]	3.8% (2.6%–5.2%) to 17% (7.0%–27.0%)	1.0% (-0.0%–1.0%) (NS)	1.74 (1.48–2.04; <0.01)[44]
Mood disorders[41]	16.5% (7.4%–28.2%)	-	-
Diarrhoea[41, 43]	1.7% (0.6%–3.2%) to 15.0% (4.0%–26.0%)	1.0% (0.0%–1.0%)	-
Sleep disorders[41, 43]	8.4% (3.4%–15.2%)	2.0% (-1.0%–5.0%) (NS)	-
Respiratory symptoms[41]	7.6% (2.1%–15.7%)	-	-
Sputum/nasal congestion[41]	7.53 (3.8%–12.4%)	-	-
Loss of appetite[41]	6.1% (3.9%–8.6%)	-	-
Exercise intolerance[41]	5.7% (0.0%–19.4%)	-	-
Chest pain[41, 44]	4.6% (1.5%–9.1%)	-	1.72 (1.39–2.12; <0.01)[44]
Dizziness[41, 43]	4.4% (1.5%–8.5%)	3.0% (1.0%–7.0%)	-
Ophthalmic disorders[41, 43]	3.0% (1.7%–4.7%)	2.0% (1.0%–3.0%)	-
Sore throat[41, 43]	2.5% (0.3%–6.2%)	2.0% (1.0%–3.0%)	-
Variations in heart rate[41]	2.3% (0.0%–7.4%)	-	-
Vomiting/nausea[41]	2.0% (0.4%–4.7%)	-	-
Palpitations[41]	1.3% (0.0%–3.8%)	-	-
Urinary symptoms[41]	0.6% (0.2%–1.2%)	-	-
Dysphagia[41]	0.5% (0.1%–0.9%)	-	-

10.4 Characteristics and results of studies assessing postoperative outcomes following COVID-19

Table A12 Characteristics of included studies for postoperative outcomes in patients with prior SARS-CoV-2 infection

Author (year)	Location, setting Study design Study period	Eligibility criteria	Study groups Timing of SARS-CoV-2 test in relation to surgery	Patient and operative demographics	Outcomes of interest
COVIDSurg Collaborative & GlobalSSurg Collaborative (2021)[49]	International (116 countries), multicentre (1674 hospitals) Prospective cohort study October–November 2020	Adult patients undergoing elective or emergency surgery SARS-CoV-2 infection confirmed by RT-PCR, RAT, CT scan, antibody test, symptoms consistent with COVID in absence of RT-PCR or CT Index date: NR	No SARS-CoV-2 (n = 137,104) 0–2 weeks before surgery (n = 1,138) 3–4 weeks before surgery (n = 461) 5–6 weeks before surgery (n = 326) ≥7 weeks before surgery (n = 1,202)	All groups 18–49 years: 55.3% Female: 57.0% ASA 1–2: 82.5% COVID-19 symptoms at time of surgery: 13.6% Major surgery: 65.4% Elective surgery: 76.1% General anaesthesia: NR%	Primary: Mortality within 30 days following surgery Secondary: Pulmonary complication within 30 days following surgery (included ARDS, pneumonia, unexpected ventilation)
Lal (2021)[52]	USA, multicentre (170 VA hospitals) Propensity-matched, retrospective cohort study 1 March 2020–15 August 2020	Patients who underwent a surgical procedure SARS-CoV-2 infection confirmed by RT-PCR	No SARS-CoV-2 (n = 1,256) ≤ 10 days before surgery (n = 70) 11–30 days before surgery (n = 96) > 30 days before surgery (n = 266)	All groups Age: 64.8–65.1 years* Female: 7% ASA 1–2: 15.3% COVID-19 symptoms at time of surgery: NR Major surgery: NR Elective surgery: 46.0%	Primary: Mortality, readmission, reoperation within 30 days following surgery Secondary: Postoperative pneumonia, need for ventilation, ARDS, sepsis, MI, ischaemic stroke, acute PE

				General anaesthesia: 59.6%	
COVIDSurg Collaborative & GlobalSurg Collaborative (2022)[50]	International (115 countries), multicentre (1630 hospitals) Prospective cohort study October–November 2020	Adult patients undergoing elective or emergency surgery SARS-CoV-2 infection confirmed by RT-PCR, RAT, CT scan, antibody test, symptoms consistent with COVID in absence of RT-PCR or CT Index date: NR	No SARS-CoV-2 (n = 123,591) 7 days before surgery–30 days after surgery (n = 2,317) 1–6 weeks before surgery (n = 953) ≥7 weeks before surgery (n = 1,148)	All groups 18–49 years: 45.0% Female: 53.7% ASA 1–2: 73.4% COVID-19 symptoms at time of surgery: 13.7% Major surgery: 62.0% Elective surgery: 69.9% General anaesthesia: 72.1%	Primary: Venous thromboembolism (DVT or PE) within 30 days following surgery Secondary: Pneumonia and mortality within 30 days following surgery
Deng (2022)[53]	USA, Covid-19 Research Database (hospital and health plan database) Retrospective cohort study 1 March 2020–30 May 2021 (case) 1 May 2019–1 January 2020 (control)	Patients with confirmed COVID-19 diagnosis (ICD-10-CM code U07.1) who underwent surgery Index date: first positive RT-PCR test Exclude: patients who had received the COVID-19 vaccine, operations performed for emergency reasons	≥30 days after surgery (n = 2,621) 0–4 weeks before surgery (n = 780) 4–8 weeks before surgery (n = 445) ≥8 weeks before surgery (n = 1,633)	All groups Age: 55–56 years* Female: 65.1% Comorbidities*: >51.2–59.0% COVID-19 symptoms at time of surgery: NR Major: 100% Elective: 100%** General anaesthesia: NR	Primary: Postoperative pneumonia and respiratory failure Secondary: Postoperative DVT, PE, arrhythmia, sepsis
Kougias (2022)[54]	USA, Covid-19 Research Database (VA's Corporate Data	Patients who underwent a high-risk surgical procedure (>1% 30-day mortality)	No SARS-CoV-2 (n = 200) 1–2 weeks before surgery	All groups Age: 71.3 years	Primary: Mortality within 90 days following surgery

	Warehouse's COVID-19 Shared Data Resource) Propensity-matched, retrospective cohort study 1 January 2020–11 May 2021	SARS-CoV-2 infection confirmed by laboratory test (no further information provided) Index date: first positive test	(n =19) 3–4 weeks before surgery (n = 9) 5–6 weeks before surgery (n = 6) 7–8 weeks before surgery (n = 7) 9–10 weeks before surgery (n = 2) 11–12 weeks before surgery (n = 2) 13–14 weeks before surgery (n = 0)	Female: 5.5% Comorbidities*: >79.2% COVID-19 symptoms at time of surgery: NR Major: 100% Elective: 92.2% General anaesthesia: NR Vaccinated: 1%	Secondary: None
Le (2022)[55]	USA, Hospital and clinic database (21 KPNC medical centres) Retrospective cohort study 1 January 2018–28 February 2022	Patients who underwent surgery SARS-CoV-2 infection confirmed by RT-PCR Index date: first positive RT-PCR test Excluded: Labour and delivery, ophthalmological, interventional pain management, cardiac, maxillofacial, podiatry, gynaecologic oncology robotics, transgender procedures	No SARS-CoV-2 (n = 198,597) ≥30 days after surgery (n = 19,420) 0–4 weeks before surgery (n = 765) 4–8 weeks before surgery (n = 961) ≥8 weeks before surgery (n = 9,170)	All groups Age: 51.1–57.1 years* Female: 55.7% Comorbidities: 21.5–25.7*** COVID-19 symptoms at time of surgery: NR Major: NR Elective: 71.6% General anaesthesia: 74.0%	Primary: Complications within 30 days following surgery (arrythmia, DVT, PE, pneumonia, respiratory failure, renal failure, sepsis, UTI) Secondary: Readmission, emergency department treat and release visit

				Vaccinated: 36.8%	
Prasad (2022)[56]	USA, Hospital and clinic database (1,244 VA health centres) Propensity-matched, retrospective cohort study March 2020–March 2021	Patients who underwent surgery Method of confirming SARS-CoV-2 infection NR Index date: first positive test	No SARS-CoV-2 (n = 14,101) SARS-CoV-2 positive (n = 4,778) 0–4 weeks before surgery (n = 765) ≥5 weeks before surgery (n = 961)	All groups Age: 66 years Female: 9.5% Comorbidities: 20.9% COVID-19 symptoms at time of surgery: NR Major: NR Elective: 72.0% General anaesthesia: 52.1% Vaccinated: NR	Primary: All-cause mortality Secondary: Pulmonary complications (pneumonia, acute respiratory failure, ARDS) Thrombotic complications (venous or arterial thromboembolism, MI, ischaemic stroke) Sepsis
Garner (2023)[57]	France, tertiary care centres Prospective cohort study March–May 2022	Patients who underwent surgery SARS-CoV-2 infection confirmed by RT-PCR and/or rapid antigen test Index date: first positive test	No SARS-CoV-2 (n = 4,223) SARS-CoV-2 positive (n = 705) <1 week (n=96) 1–2 weeks (n=33) 2–3 weeks (n=51) 3–4 weeks (n=51) 4–6 weeks (n=168) 6–8 weeks (n=305)	All groups 18–49 years: 39% Female: 51.3% Comorbidities: >0.9%–30.1% First vaccination only: 6.3% Complete vaccination scheme: 86.1% COVID-19 symptoms at time of surgery: 5.4% Major: 21.0% Elective: 83.9%	Primary: Composite respiratory morbidity (occurrence of pneumonia, acute respiratory failure, unplanned or prolonged use of postoperative mechanical ventilation, new symptomatic pulmonary embolism within 30 days) Secondary: Mortality, length of stay, readmission within 30 days, non-respiratory infection

				General anaesthesia: 84.4%	
SenthilKumar (2023)[58]	USA US National COVID Cohort Collaborative (N3C) Data enclave Retrospective cohort study January 2020–November 2022	Elective, non-cardiac surgery SARS-CoV-2 infection confirmed by RT-PCR and/or rapid antigen test or ICD10-CM code U07.1 Index date: first positive test	No SARS-CoV-2 (n = 423,943) SARS-CoV-2 positive (n = 33,861) 0–4 weeks (n = 7,018) 4–8 weeks (n = 3,499) >8 weeks (n = 22,179)	Age: median 59–62 years Female: 59% Comorbidities: >3.4–37% Vaccinated: 9.3–13% COVID-19 symptoms at time of surgery: NR Major: NR Elective: 100%	Primary: MACE (cerebrovascular complication, dysrhythmias, inflammatory heart disease, ischemic heart disease, heart failure, cardiac arrest, cardiac shock, and thrombotic complication within 30 days Secondary: Mortality
Verhagen (N.D)[59]	USA US National COVID Cohort Collaborative (N3C) Data enclave Retrospective cohort study January 2020–February 2023	Elective, major, inpatient surgery SARS-CoV-2 infection confirmed by RT-PCR and/or rapid antigen test or ICD10-CM code U07.1 Index date: first positive test	No SARS-CoV-2 (n = 349,676) SARS-CoV-2 positive (n = 37,354) 0–4 weeks (n = 7,425) 4–8 weeks (n = 3,936) 8–12 weeks (n = 2,604) >12 weeks (n = 23,389)	Age: median 61–63 years Female: 54–56% Comorbidities: >1.6–39% Vaccinated: 14% COVID-19 symptoms at time of surgery: NR Major: 100% Elective: 100%	Primary: Composite adverse postoperative event (mortality, unplanned readmission, acute myocardial infarction, cardiac arrhythmia, deep vein thrombosis, pneumonia, pulmonary embolism, renal failure, respiratory failure, sepsis, and urinary tract infection) within 30 days

Abbreviations:
ARDS = acute respiratory distress syndrome, ASA = American Society of Anesthesiologists physical status classification system, DVT = deep vein thrombosis, MACE = major adverse cardiac event, MI = myocardial infarction, n = sample size, NR = not reported, PE = pulmonary embolism, RT-PCR = reverse transcription polymerase chain reaction, UTI = urinary tract infection.