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National COVID-19 Health and Research Advisory Committee*

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Evidence for the non-respiratory effects of COVID-19

Focus

The Chief Medical Officer (CMO) asked the National COVID-19 Health and Research Advisory Committee (NCHRAC) to consider the available evidence on the non-respiratory effects of COVID-19. Noting its own concurrent work examining the long-term effects of COVID-19 that has produced a separate advice paper on this topic, NCHRAC understood this question to relate to the **acute phase of COVID-19 illness**.

For the purposes of this document, NCHRAC define the 'acute phase of COVID-19 illness' as[a]:

- Mild cases: 10 days from onset of symptoms or 72 hours after resolution of the acute illness, whichever is the later.
- More severe cases who are hospitalised: 10 days from hospital discharge, or complete symptom resolution for 72 hours, whichever is the later.

This advice provided by NCHRAC could be used to:

1. identify evidence that can be used by relevant agencies to develop advice, guidance or similar for clinicians on how best to manage individuals who have not been diagnosed with COVID-19 but present with features consistent with this diagnosis, thereby facilitating optimal speed and efficiency in diagnostic testing, isolation and treatment
2. assist clinicians and health planners anticipate appropriate individual clinical management, and the planning of system-wide healthcare services
3. identify population groups in which there may be differences in the way COVID-19 presents or develops
4. identify potential evidence gaps in the published literature, the methodological challenges encountered by epidemiological studies to date, and the most valuable opportunities to improve the evidence in this field.

This advice is point in time and may need further review as more evidence is available, particularly on the associations between non-respiratory manifestations, comorbidities and the severity of COVID-19 disease, and within the Australian context.

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* NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

[a] Based on the criteria specified for the release of persons recovered from COVID-19 in the *Communicable Diseases Network Australia (CDNA) and Public Health Laboratory Network (PHLN) joint statement: Revised Australian criteria for the release of persons recovered from COVID-19*

This advice paper was developed by a working group of NCHRAC (see membership at **Attachment 1**).

Method

A search for evidence aimed to:

1. identify and describe the spectrum of non-respiratory tract COVID-19 signs and symptoms that have been documented at the time of presentation
2. quantify the proportion of all COVID-19 patients that present with each sign or symptom, alone or in combination, at the time of diagnosis
3. identify any published models that have attempted to predict:
    a. the most likely pattern of signs and symptoms at the time of diagnosis
    b. the likelihood that an undiagnosed individual who presents with one or more respiratory and non-respiratory signs or symptoms has COVID-19
4. identify the incidence or prevalence (as reported) of non-respiratory manifestations of COVID-19, and any associated abnormal imaging and laboratory findings, during the acute phase of illness.

In recognition of the large number of studies that continue to be published on this topic, and the desire to base advice on a body of evidence where possible, the intention was to identify reliable systematic reviews that describe the spectrum of signs, symptoms and/or clinical manifestations of COVID-19. As prospective studies require time to follow patients, and to analyse and report results, it was expected that the evidence included in any systematic reviews identified would largely be observational and retrospective.

This advice paper draws on systematic reviews of published literature, supplemented by inclusion of selected pre-publication manuscripts and published studies identified by discipline specific experts. The method for the evidence search is described in **Attachment 2** (with evidence tables in Supplements 1 to 3).

Overview

There are innumerable anecdotal reports of non-respiratory manifestations of COVID-19. Compiling these into a simple list would have been a straightforward task, but would have produced a document of little value. Knowledge of incidence and severity would be more useful, but the incidence and severity of many COVID-19 clinical manifestations, such as delirium and skin rash, appears to vary greatly with age and comorbidity. Understanding these effects is critical to aid clinicians in diagnosis, and to assist in health service planning. Consequently, the paper attempts to quantify not only the incidence of the various reported manifestations, but how these vary in different populations.

Some COVID-19 effects appear to be a direct consequence of the infection of cells (such as viral myocarditis), others (such as pulmonary thromboembolic disease) appear mediated by endothelial cell damage and associated thrombosis, while others (such as acute kidney impairment) are more likely to be a consequence of severe multisystem dysregulated inflammation, such as occurs in many other types of infection. In many cases, the

pathophysiological mechanism underlying observed clinical manifestations is currently unknown, and most likely is a combination of these factors. Seeking to understand how COVID-19 might differ from other severe viral infections could be important and this advice paper attempts to link what is known of pathophysiology with studies that distinguish between the epidemiology of COVID-19 effects and that of other severe infections.

Early case reports mentioned few non-respiratory effects. Only as various manifestations became more widely appreciated did clinicians and investigators seek and report their occurrence. Consequently, there has been a systematic change over time in the reported incidence of many effects. It is likely that some manifestations of COVID-19 are still not known. Describing, at least briefly, what is known of the pathophysiology of COVID-19 might accelerate identification of these effects, as well as suggesting specific adjuvant therapies.

Reporting incidence figures raises concerns regarding both *precision* and *accuracy*. With respect to *precision*, the level of certainty in the systematic reviews in this topic is low to very low. While the first COVID-19 publications only appeared in early 2020, the evidence review found many hundreds of case series and cohort studies that have been pooled into a large number of systematic reviews of generally poor methodological quality. Many systematic reviews did not have clearly articulated objectives or study eligibility criteria. Most either did not assess the risk of bias in included studies, or did not take this bias into account when pooling or interpreting data. Almost all included only retrospective, observational studies, with many including single case reports. It is likely that many patients are reported in more than one study and review. Some systematic reviews pooled data in a meta-analysis and most had high to very high levels of heterogeneity. Some reviews did not formally pool data in a meta-analysis, but simply calculated averages. Calculating averages does not account for the weight of individual studies. The pooled incidence estimates of individual clinical manifestations quoted vary greatly in many instances, usually without apparent explanation. In addition to pooled data, some descriptive data have been included where meta-analysed data was not available on specific findings of relevance.

Of even greater concern is with respect to *accuracy*, or more specifically the likely context-dependence of the estimates of incidence or prevalence. Almost all of the identified systematic reviews draw upon studies of patients sufficiently unwell to present to hospital. However, most patients with COVID-19 do not require hospitalisation: internationally overall, only 8.4%, but only 0.04% of those aged 10–19 years, rising to 18.4% of patients ≥80 years[1], and in Australia only 13% overall[2]. Patients who are less unwell are probably less likely to display non-respiratory signs and symptoms, although this is an untested assumption that warrants investigation. Further, the limited evidence identified suggests that patients who are less unwell with COVID-19 display different patterns of signs and symptoms: for example skin rashes (see Dermatological section below), but that these are not specific to COVID-19. At the opposite end of the spectrum of disease severity, the most unwell patients rapidly deteriorate to require sedation and mechanical ventilation in an intensive care unit, which is likely to obscure some manifestations of COVID-19, particularly those affecting the central nervous system.

In addition to the quantitative evidence presented below, all of which comes with these caveats, our primary conclusions are:

- COVID-19 appears to have more non-respiratory effects than other severe viral diseases, such as (for example) influenza. However, this is not certain, and might be an artefact of the intense attention paid to COVID-19. Studies specifically comparing COVID-19 to other severe viral infections are required.
- Most COVID-19 patients never present to hospital, but most current evidence is based on hospitalised patients. Overall severity of illness in the population studied is likely to have the greatest effect on the observed incidence of many non-respiratory effects of COVID-19. There is consequently likely to be a mistaken understanding of the effects of COVID-19 on patients not sufficiently unwell to require hospitalisation.
- This lack of knowledge primarily affects younger patients, because these are the patients who are the least likely to require hospitalisation.
- The consequence of this lack of knowledge is likely to be delayed or missed diagnosis, with the resulting higher potential for disease transmission, along with an under-appreciation of individual risk amongst younger patients. Addressing this evidence gap, and communicating the results to both healthcare professionals and the general community at risk of COVID-19, is therefore an urgent priority.

Pathophysiology

NCHRAC conclusion 1: Current evidence suggests that SARS-CoV-2 causes direct viral cytopathic effects (changes to the cell structure) on cells of various organs, and indirect effects due to interaction with vascular endothelium, dysregulated coagulation, and inflammation. The relative importance of each of these mechanisms is not known.

Understanding of the pathogenesis of SARS-CoV-2 infection, especially in the context of non-pulmonary effects (whether they be acute or ongoing) is a field still in its early days. What is clear is that the virus affects a number of tissues and organ systems other than the respiratory tract, especially blood vessels, kidney, heart and brain. What is less clear is the relative contributions of:

- direct cytopathic effects from viral infection of cells in these organs
- effects on the endothelium of their vascular supply and on other factors affecting blood coagulation and
- effects of systemic inflammation.

SARS-CoV-2 entry into cells begins with an interaction between its spike protein and the ACE2 receptor exposed on the outside surface of cells of the respiratory tract. Other host cell surface molecules (serine protease transmembrane protease serine 2, heparan sulfate, and other proteases) are involved in entry. Replication in these respiratory cells is a driver of many of the classic symptoms of COVID-19 (headache, fever, cough and the like). This interaction is more effective than the same interaction between SARS-CoV-1 and ACE2, at least in part explaining differences in the pathogenesis/tropism and transmission of these two viruses.

ACE2 is found on many more cell types than just those lining the respiratory tract, and so there is a theoretical potential for infection of a wide range of tissues and organs. For example, ACE2 is present on gut epithelial cells, potentially explaining gastrointestinal symptoms. Most notable is the presence of ACE2 on vascular endothelial cells (the inner lining of blood vessels), giving the virus access to different tissues and organs. Not all vascular endothelial cells are the same: endothelial cells resident in the blood vessels of different organs have different levels of ACE2 and other entry co-factors on their surface. COVID-19 mediated kidney and heart pathology are likely to be at least partly explained by the vasculitis (blood vessel inflammation) produced as a result. Further, direct infection of endothelial cells may play a role in the intravascular coagulation and thromboembolic disease that has been observed in complicated SARS-CoV-2 infections. Other mechanisms of vascular pathology also appear likely. In one study, prothrombotic antiphospholipid autoantibodies were isolated from the serum of >50% of 172 hospitalised COVID-19 patients[3]. The relative contributions of these and other factors might vary between patients, highlighting the importance of developing clinically practical methods to characterise pathophysiological phenotype in order to better target therapy.

Key signs, symptoms and clinical manifestations of COVID-19 in the acute phase of illness

NCHRAC conclusion 2: The rate of occurrence of various extra-pulmonary manifestations of COVID-19 amongst all patients affected by the disease is not well understood. The most common acute extra-pulmonary manifestations of COVID-19, identified primarily (but not exclusively) in hospital patients, are:

- cardiovascular: acute coronary syndrome, myocarditis, heart failure, arrhythmia, and arterial and venous thrombotic complications
- gastrointestinal: diarrhoea, nausea, vomiting and abdominal pain
- renal: haematuria, acute kidney injury, proteinuria and electrolyte disturbances
- dermatological: pruritus, erythematous rashes, pseudo-chilblain like lesions and urticaria
- neurological: fatigue, anorexia, myalgia, headache, dizziness, confusion, acute cerebrovascular disease (stroke), delirium, and acute inflammatory demyelinating polyneuropathy (Guillian Barre Syndrome)
- ear, nose and throat: changes in taste (dysgeusia) and smell (anosmia)
- ophthalmic: conjunctivitis
- immune: lymphopenia, Multisystem Inflammatory Syndrome in Children (MIS-C).

Cardiovascular

Cardiovascular effects of SARS-CoV-2 infection are common with a reported prevalence of 14.1% [95%CI 10.3 to 20.2%] amongst those with the disease.[4] Cardiovascular complications in COVID-19 can be the result of primary effects of the virus on the heart, or secondary to the acute lung injury caused by the SARS-CoV-2 virus. Current data suggest that the presence of cardiovascular complications is associated with a higher all-cause mortality in comparison to patients with no cardiovascular manifestations.[5]

The main evidence for cardiac injury in COVID-19 is elevation in serum cardiac biomarkers or abnormalities detected by cardiac imaging (reported prevalence amongst those infected ranging between 10.3% [95%CI 6.7 to 14.6%] to 25.3% [95%CI 19.5 to 31.1%]).[4,6] Risk factors associated with cardiovascular morbidity and mortality in COVID-19 are male gender, advanced age, diabetes, hypertension, obesity and patients with pre-existing cardiovascular and cerebrovascular disease.[7]

The cardiovascular complications reported can be broadly divided into 4 categories:

1. acute coronary syndromes with a prevalence of 3.5% [95%CI 2.1 to 5.4%][4]
2. myocarditis and heart failure (highly variable reported prevalence ranging from 1.96% [95%CI 0.9 to 3.4%] to 25.3% [95%CI 19.5 to 31.1%][(4 and 6 respectively)]
3. arrhythmias (reported prevalence of 26.1% [95%CI 5.9 to 46.4%][6] and
4. arterial and venous thrombotic complications (prevalence of 4.4% [95%CI 2.8 to 6.4%] and 26% [95%CI 6 to 66%] respectively.[8,9]

Acute coronary syndromes in COVID-19 can arise due to arterial thrombosis, destabilisation of pre-existing plaques due to immune activation, and microvascular dysfunction.[10] Myocarditis and heart failure result from viral invasion of myocytes and infiltration of the myocardium by interstitial inflammatory cells which could result in a *de novo* cardiomyopathy, exacerbation of pre-existent cardiomyopathy, fulminant myocarditis and/or cardiogenic shock.[10] The stress component of the infection may also trigger Takotsubo's cardiomyopathy (also referred to as stress cardiomyopathy) with a significantly higher incidence of 7.8% compared with pre-pandemic incidences that ranged from 1.5% to 1.8%[11] amongst patients presenting to hospital with acute coronary syndrome. In terms of arrhythmias, the myocardial injury or pro-arrhythmic effects of COVID-19 treatments have been associated with tachycardia (with a reported prevalence of 12% [95%CI 3 to 21%]),[12] bradycardia, out-of-hospital cardiac arrests (two-times increase in incidence of OHCA);[13] and sudden cardiac death. The arterial and venous thrombotic complications are predominantly deep vein thrombosis (prevalence of 14% [95%CI 1 to 75%]),[9] pulmonary emboli (prevalence of 12% [95%CI 2 to 46%])[9] and cerebrovascular events (described in the neurology section, below).

The common cardiovascular symptoms resulting from the manifestations described above would include chest pain, dyspnoea, dizziness, palpitations, hypotension, orthopnoea, reduced exercise tolerance, paroxysmal nocturnal dyspnoea, peripheral oedema and syncope. Of these, the 4 most common symptoms reported are chest pain or tightness (prevalence of 21.8% [95%CI 5.9 to 46.4%]),[6] dyspnoea, dizziness (prevalence of 6.1 to 10%) and palpitations (prevalence of 9.1% [95%CI 6.2 to 12.1%]).[6]

Renal

Few systematic reviews quantify the various renal manifestations of COVID-19, so what is known derives primarily from small observational studies. The majority of data describing renal manifestations of COVID-19 come from hospitalised patients.

The most common reported severe kidney complication of COVID-19 is acute kidney injury (AKI). The reported rate of AKI ranges from a prevalence 4.5% [95%CI 3.0 to 6.0%] to a

pooled incidence of 11.0% [95%CI 7.4 to 15.1%].[14,15] The degree of AKI is associated with disease severity and prognosis in COVID-19 patients:[14] when COVID-19 patient groups were categorised according to overall illness severity as mild/moderate, severe or critical, the prevalence of AKI was 1.3% [95%CI 0.2 to2.4%], 2.8% [95%CI 1.4 to 4.2%], and 36.4% [95%CI 14.6 to 58.3%] respectively. The incidence of AKI was also significantly higher among patients who ultimately did not survive: 52.9% [95%CI 34.5 to 71.4%] (non-survivors) vs 0.7% [95%CI 0.3 to 1.8%] (survivors).[14] There was no evidence patient age (older or younger than 60 years) affected the incidence of AKI,[15] but the incidence in the United States was more than twice as high as in China (19.9% [95%CI 11.4 to 30.0%] vs 8.2% [95%CI 5.0 to 12.0%, p=0.03]),[15] which may have implications for the Australian context.

Proteinuria was reported to be present in most COVID-19 patients (57.2% [95%CI 40.6 to 73.8%]).[14] In a prospective cohort study of COVID-19 patients admitted to hospital, 43.9% of patients (194 of 442 patients) had proteinuria upon admission and haematuria was identified in 26.7% (119 of 442 patients).[16] Additional renal manifestations include electrolyte disturbances (e.g. hyperkalaemia) with a pooled incidence of 12.5% [95%CI 10.1 to 15.0%], acidosis with reported prevalence of 5.0% [95%CI 3.2 to 7.2%] and alkalosis with reported prevalence of 6.9% [95%CI 4.5 to 10.6%].[15] However, the prevalence data for the above renal manifestations are aggregated from one to three small observation studies.[15]

Gastrointestinal

Various gastrointestinal (GI) symptoms have been associated with SARS-CoV-2 infection such as diarrhoea, abdominal pain and nausea and/or vomiting; the reported prevalence rates vary but are generally low. Overall, gastrointestinal symptoms have been reported in 15% of patients with COVID-19 [95%CI 10.0 to 21.0%], with nausea and vomiting, diarrhoea and loss of appetite being most common.[17] The same systematic review also reported that 10% of patients presented with GI symptoms alone [95%CI 4 to 19%] and that patients who presented with GI system involvement had delayed diagnosis (standardised mean difference 2.85 [95%CI 0.22 to 5.48%]).[17] Two systematic reviews reported a pooled prevalence of loss of appetite / anorexia / decreased oral intake in patients of just over 20% (22.3% [95%CI 11.2 to 34.6%];[18] 23% [95%CI 22 to 25%][17]). A meta-analysis of 10,890 patients reported that diarrhoea was present in 7.7% of cases [95%CI 7.2 to 8.2%], nausea and/or vomiting present in 7.8% of cases [95%CI 7.1 to 8.5%] and abdominal pain present in 2.7% of cases [95%CI 2.0 3.4%].[19] Another meta-analysis of 12,797 patients conducted a weighted pooled prevalence which reported an increased prevalence of GI symptoms: diarrhoea 12.4% [95%CI 8.2 to 17.1%], nausea and/or vomiting 9% [95%CI 5.5 to 12.9%] and abdominal pain 6.2% [95%CI 2.6 to 10.3%].[18]

In both reviews the majority of included studies were from hospitalised populations, and they did not report on the timing in which GI symptoms presented in relation to the other symptoms of COVID-19.[18,19] Due to the lack of studies focusing on outpatient populations, it is not possible to ascertain whether the prevalence of GI symptoms has been over or underestimated as a symptom of COVID-19 or whether they are more prevalent in patients who do not require hospitalisation. Notably, as reported by Tariq et al,[18] prevalence data on

GI upset may have been under-reported early in the pandemic as it had not yet been associated as a symptom of COVID-19 and therefore not reported.

The presence of GI symptoms has not been associated with an increased risk of mortality.[18] In a meta-analysis of 12,797 patients it was reported that there was no significant difference in mortality among patients with GI symptoms (0.4% [95%CI 0 to 1.1%]) vs overall mortality (2.1% [95%CI 0.2 to 4.7%; p=0.15]).[18] However, a smaller meta-analysis of 11 studies including 451 patients with severe and 1,731 patients with non-severe COVID-19 found the prevalence of GI symptoms in severe COVID-19 was 17.1% [95%CI 6.9 to 36.7%] compared to 11.8% [95%CI 3.1 to 29.1%] in non-severe COVID-19.[16]

Elevation of hepatic enzymes is frequently associated with systemic infections and has been a well-documented complication in SARS-CoV and MERS-COVID-19,[17,20] in which the reported pooled prevalence of abnormal liver function was 19% [95%CI 9 to 32%]. Liver enzyme abnormalities have also been reported in patients infected with SARS-CoV-2.[20] The most commonly reported enzyme abnormalities are abnormal bilirubin (pooled prevalence of 16.7% [95%CI 15.0 to 18.5%]), aspartate transaminase (15% [95%CI 13.6 to 16.5%]) and alanine transaminase (15% [95%CI 13.6 to 16.4%]).[19] A meta-analysis of 12,756 adult patients found the prevalence of elevated liver enzymes to be 23.1% [95%CI 19.3 to 27.3%].[21] The same study also reported prevalence of 17.8% [95%CI 9.9 to 29.8%] for elevated liver enzymes in children in a meta-analysis of 283 patients.[21]

As with a range of other chronic medical comorbidities, the presence of pre-existing chronic liver disease (CLD) has been associated with more severe COVID-19 infection. In one analysis, the risk ratio of CLD in severe as compared to non-severe COVID-19 patients was 1.7 (95%CI 1.1 to 2.7%).[20] In another meta-analysis, severe/critical illness in COVID-19 was more common in patients with CLD compared to those without CLD (pooled OR 1.48 [95%CI 1.17 to 1.87%]).[22] While no significant difference was noted in the need for ICU admission or mechanical ventilation, overall mortality was significantly higher in patients with CLD (pooled OR 1.8 [95%CI 1.1 to 2.9]).[22]

Dermatological

High quality papers and systematic reviews describing the dermatological symptoms of SARS-CoV-2 infection are scant, with only two systematic reviews noted at the time of writing, both containing a mix of papers with various study designs, small sample sizes and data not pooled.

The reported dermatological presentations of COVID-19 patients are highly variable. Most (59%) of all dermatological presentations appeared after other more common symptoms such as dyspnoea and cough.[23,24] Pruritus is common, with a reported 48% prevalence,[23] however some small case series contradict this finding.[25] Among confirmed cases, the most common dermatological presentations include erythematous rashes, pseudo-chilblain like lesions and urticaria.[23] Erythematous rashes appear with a prevalence of 44.2% with a distribution on patients' trunk, extremities, flexural regions, face, and mucous membranes.[23,26] Pseudo-chilblain like symptoms were reported with a prevalence of 19.7%, developing late in the progression of SARS CoV-2 infection. Urticaria is the other most common symptom with a reported 16.4% prevalence.[23] Other dermatological manifestations

have been recorded in small scale retrospective cohort studies, case series or case reports. Prevalence data is unavailable, or if available unlikely to be representative or accurate. These manifestations include vesicular lesions (13.0%),[23] livedo/necrosis (6.1%),[23] petechiae (1.6%),[23] vesicular eruptions (9.0%),[24] maculopapular eruptions (47.0%),[24] varicella-like exanthema,[25] and necrotic or non-necrotic purpura.[27]

There exists very little information on the correlation between specific dermatological presentations and severity of disease. Similarly, the underlying mechanism responsible for these dermatological symptoms is unclear. Some might be the result of treatment rather than the disease itself. Whilst it is known that ACE2, a cellular portal of entry for SARS-CoV-2, is expressed in skin tissue, no studies have thoroughly investigated this link.[23]

Neurological

There is a growing body of evidence that shows a substantial proportion of patients experience neurological effects associated with COVID-19 infection. In a case series of 214 patients, Mao et al. observed neurological effects in approximately one third (36.4%) of patients. This incidence was higher among patients with severe infection (45.5%).[28] However, the reported incidence of neurological manifestations varies. Favas et al. cited three large retrospective observational studies which reported incidence figures of 4.3%, 15% and 57.4%.[29]

Systematic reviews and meta-analyses of neurological effects are largely limited to retrospective observational studies of hospitalised patients, the majority being small case series or individual case reports published before June 2020. Published data is lacking on the extent to which neurological effects can be extrapolated to, or are experienced among individuals who are not hospitalised and may present to general practice.

A wide range of specific and non-specific neurological effects have been reported. Three effect categories are recognised:

1. effects on the central nervous system (CNS),
2. effects on the peripheral nervous system (PNS) or
3. musculoskeletal effects.

Manifestations in the CNS are the most common overall, followed by the PNS.[29] All three are currently considered to be direct effects of the virus on the nerve cells, para-infectious or post-infectious immune-mediated disease, and neurological complications of the systemic effects of COVID-19.[30]

Further studies to elucidate the onset of neurological effects are needed, however it has been reported that most neurological manifestations have an early onset probably due to direct effects on the nervous system by the virus, unlike SARS-CoV-1 where manifestations appeared only later in established disease.[31,32]

Non-specific neurological effects are quite common in COVID-19, including fatigue (24.8% [95%CI 23.2 to 26.4%]), anorexia (30.0% [95%CI 23.2 to 36.9%]), myalgia (19.3% [95%CI 15.1 to 23.6%]), headache (14.7% [95%CI 10.4 to 18.9%]) dizziness (6.1% [95%CI 5.1 to 7.1%]) and confusion, ranging from 5.2% [95%CI 1.7 to 12.3%] to 11% [95%CI 7 to 15%].[33,34,35] Seizures

(0.9% [95%CI 0.5 to 1.3%]) and ataxia (0.3% [95%CI 0.1 to 0.3%]) are less common.[29] Di Carlo et al.[33] found that the prevalence of CNS symptoms and muscular injury was highest among those with the most severe COVID-19 disease.

Acute cerebrovascular disease has emerged as an unexpected manifestation of COVID-19. The pooled prevalence of acute cerebrovascular disease is reported as 2.3% [95%CI 1.0 to 3.6%] of COVID-19 cases, with acute ischaemic stroke being the most common (2.1% [95%CI 0.9 to 3.3%]), highest in severe COVID-19 patients,[29] in older patients and in the presence of multiple comorbidity.[33] Large vessel strokes account for the majority of ischaemic stroke, including for those with or without risk factors, and have occurred in patients younger than 50 years.[31] A rapid review of COVID-19 related stroke case-series and a case-control analysis reported an association between COVID-19 and stroke in young populations without typical vascular risk factors and at times with mild respiratory symptoms. COVID-19 patients with large vessel stroke were significantly younger than stroke patients who were COVID-19 negative.[36] One retrospective cohort study comprising COVID-19 patients (N=1,916) presenting to two hospitals in New York City and an influenza cohort (N=1,486) reported a substantially higher (nearly eight-fold) incidence of stroke associated with COVID-19 compared with influenza after adjusting for age, sex and race (odds ratio 7.6 [95%CI 2.3 to 25.2%]).[37] Cerebrovascular complications have largely been attributed to inflammation and dysfunction of the coagulation system, marked especially by elevated D-dimer and platelet abnormalities.[31]

Acute altered mental status was the second most common COVID-19 associated neurological presentation after cerebrovascular disease in one of the first known nationwide surveillance studies (UK) of neurological and neuropsychiatric manifestations of COVID-19, accounting for almost one third (31%) of neurological presentations, particularly for younger patients aged <60 years.[38] The pooled prevalence of disturbances in consciousness/altered mental status is reported as 9.6% [95%CI 4.9 to 14.3%].[29]

Some evidence has emerged linking COVID-19 with acute inflammatory demyelinating polyneuropathy (Guillian Barre Syndrome (GBS)). Uncini et al.[39] reviewed international case reports of 42 patients who developed GBS. Most patients (76%) presented to hospital because of neuropathic symptoms; 14.3% were admitted to hospital because of other COVID-19 effects and developed GBS during their admission; and 9.5% had been discharged after seemingly recovering from COVID-19, then readmitted at the onset of neuropathic symptoms. The mean interval between the onset of COVID-19 and GBS for 36 patients was 11.5 days (IQR 7.7–16; range 3–28 days). Diagnosis of COVID-19 was made before the onset of GBS in only 38% of patients, and 50% were diagnosed with COVID-19 during their admission for GBS, highlighting the need for vigilance in testing patients with uncommon neurological conditions for COVID-19 during times of high prevalence. Further clinical experience is needed to determine whether COVID-19-associated GBS characteristically develops during the infection, as appears to have been most common in these cases, or more typically after the resolution of infection, as is more generally the case.[39]

Musculoskeletal effects have been generally diagnosed when serum concentrations of creatine kinase and lactate dehydrogenase have been found to be elevated.[33] Based on

undetectable SARS-CoV in muscle tissue of patients who died of SARS, the pathogenesis of this damage is hypothesised to be an effect of systemic inflammation rather than direct viral damage to muscle cells.[33]

Early recognition of neurologic manifestations not otherwise explained should raise suspicion of SARS-CoV-2 infection.[33] In particular, smell and taste disturbance can be used as a tool to identify COVID-19 in patients who lack any other symptoms.[29]

Extract from Favas et al. [29]:

Table 3: Meta-analysis, summary estimate of pooled prevalence and heterogeneity of each neurological manifestations

	Number of studies (*N*)	Summary estimate (%)	95% CI	I^2
Smell disturbances	17	35.8	(21.4, 50.2)	99.87
Taste disturbances	14	38.5	(24.0, 53.0)	99.65
Headache	54	14.7	(10.4, 18.9)	99.09
Myalgia	38	19.3	(15.1, 23.6)	98.98
Disturbances in consciousness/altered mental status	9	9.6	(4.9, 14.3)	98.26
Dizziness	12	6.1	(3.1, 9.2)	93.44
Acute cerebrovascular disease	8	2.3	(1.0, 3.6)	96.61
Ischaemic stroke	7	2.1	(0.9, 3.3)	96.67
Hemorrhagic stroke	7	0.4	(0.2, 0.6)	62.36
Cerebral venous thrombosis	2	0.3	(0.1, 0.6)	0.00
Syncope	3	1.8	(0.9, 4.6)	98.48
Ataxia	2	0.3	(0.1, 0.7)	0.00
Seizure	5	0.9	(0.5, 1.3)	9.03

Neurological effects in critically ill patients are likely to be underrepresented due to the effects of sedation used to facilitate mechanical ventilation and due to the impracticality of imaging examinations.[33,34]

Ear, throat and nose

Changes in taste (dysgeusia) and smell (anosmia) are commonly reported symptoms of COVID-19. The prevalence of olfactory dysfunction has been reported in nearly half of certain cohorts: 41.0% [95%CI 28.5 to 53.9%][40] and 48.8% [95%CI 22.4 to 71.1%][41], while gustatory dysfunction was observed in 38.2% [95%CI 24.0 to 53.6%][40] and 51.3% [95%CI 27.4 to 72.4%].[41] Olfactory and gustatory dysfunction are commonly present together but can present separately as prodromal symptoms.[41]

Audio-vestibular symptoms have been reported in lower numbers. These include hearing loss (23 cases in four studies), tinnitus (eight patients in four studies), rotary vertigo (seven patients in two studies), and otalgia (359 patients in two studies). Otitis externa and otitis media were only identified in one patient each.[42]

Australian data shows a much lower incidence for loss of taste and smell (<10%).[43] While patients who presented with loss of taste and smell were more likely to test positive to COVID-19, the most common symptoms experienced by patients in Australia were cough, tiredness and fever.[43]

Ophthalmic

Ocular signs and symptoms are not common in patients with COVID-19.[44] The reported prevalence of all ocular manifestations was 11.2% among patients with COVID-19 [95%CI 5.5 to 16.9%; 78/1526 cases].[45] Two systematic reviews that specifically examined ocular symptoms of COVID-19 reported conjunctivitis as the most common manifestation while one review reported the pooled prevalence of conjunctivitis or conjunctival congestion was 5.2%, representing 49 patients, [95%CI 2.9 to 8.0%] and the presence of conjunctivitis as a presenting symptom was only seen in <1% of cases (0.9% [95%CI 0.3 to 1.7%]).[44]

The prevalence of other ocular manifestations is low. One systematic review reported only symptoms associated with conjunctivitis: epiphoria, foreign body sensation, chemosis and itching.[44] The other systematic review reported ocular pain, dry eye, floaters and eyelid dermatitis at low levels: of the 11.2% of patients with ocular manifestations, most (86.4% [38/44]) had conjunctivitis; 34.4% (31/90) had ocular pain; 33.3% (5/15) had dry eye; and 6.7% (1/15) had floaters.[45]

SARS-CoV-2 viral RNA has been detected in ocular samples from COVID-19 patients with conjunctivitis. Using an estimated pooled prevalence, the viral RNA positivity was 32.7% [95%CI 17.5 to 51.3%] in ocular samples from patients with conjunctivitis.[44] While viral RNA was not detected in any of the tear samples from conjunctivitis patients, Inomata et al. reported viral RNA detection in 16.7% (10/60 cases) of conjunctival swabs. This finding is important, as few respiratory viruses infect the conjunctiva.[45] Infected conjunctiva may be a route of potential infection transmission that should be known to health care workers, especially ophthalmologists.[45] Conjunctivitis may present as a prodromal symptom of COVID-19, prior to the development of other symptoms.[45]

Immune system

The immune response to acute COVID-19 involves antibodies and T cells, both of which are presumably responsible for viral clearance. Specific defects in the immune system such as genetic defects in type 1 interferon signalling pathways,[46] or autoantibodies blocking function of type 1 interferons, have been associated with a more severe disease course and worse clinical outcomes.[47] However, from the limited data available, neither drug-induced immunosuppression for autoimmunity nor HIV infection significantly change the clinical manifestations of acute COVID-19 infection at presentation, nor do they substantially affect outcome once intercurrent comorbidities have been taken into account.[48,49,50,51]

COVID-19 infection has direct impacts on the immune system. One of the most common manifestations of COVID-19 in adults is lymphopenia, which is present in the majority (50-80%) of adult patients.[52,53,54] Lymphopenia is less consistently seen in children.[12,55] In adults the degree of lymphopenia correlates with disease severity.[54] In those with severe disease the lymphopenia can be profound. Neutrophilia is less consistently reported, correlating more weakly with outcome.[54] These cellular changes are accompanied by raised acute phase reactants such as C-reactive protein (CRP) which is seen in most patients including children.[53,54,55] In those with severe manifestations of the disease, lymphopenia is accompanied by substantially raised inflammatory and immunological markers in serum, with the most commonly reported being IL-6, IL-1B, TNF, IP-10.[56]

However, the clinical utility of these markers is limited, as typically only research laboratories are capable of their measurement. This pattern of multiple raised cytokines is often associated with a syndrome referred to as a cytokine storm and with multisystem manifestations of septic shock including hypotension, leaking capillaries and progressive respiratory failure.[57] However, more critical assessments of the parameters associated with progressive COVID-19 have questioned this association. This along with the lack of efficacy of the IL-6 receptor antagonist tocilizumab for preventing intubation or death in moderately ill hospitalised patients with COVID-19,[58] has raised the question of the utility of the concept of cytokine storm in understanding the pathophysiology of all severely affected COVID-19 patients.[59] The mechanism underlying the reduction in 28-day mortality among mechanically ventilated COVID-19 patients from 41.1% to 29.3% observed with treatment with the anti-inflammatory corticosteroid dexamethasone (29.3% vs. 41.4%; rate ratio, 0.64; 95%CI 0.51 to 0.81%)[60] is still to be fully understood.

In children, the infection can precipitate MIS-C, an immune-mediated condition described in the paediatric section blow.

Effects in particular population groups

Pregnant women

NCHRAC conclusion 3: Pregnant women are not at a higher risk of death or complex morbidity than non-pregnant women of similar age. Pregnant and recently pregnant women with COVID-19 might manifest fewer symptoms than other patients infected with SARS-CoV-2. The risk of preterm birth is higher for women with COVID-19 compared to those without.

Compared to the general population, a disproportionate number of pregnant women have been tested for COVID-19 on the assumption outcomes might be worse for this group. There have been over 80 systematic reviews of COVID-19 in pregnancy and a further 94 registered in PROSPERO, but most are of poor quality.[61] The most robust systematic review published to date is included here.[61] It seeks to be a 'living review' that will be updated as new evidence emerges. The studies included in this review are mainly drawn from hospital attendees.

A recent report currently in pre-print form analyses longitudinal symptom tracking data from COVID-19 positive pregnant women in the community. The study aims to describe the symptoms and syndromes predictive of disease and severity in pregnant women from the COVID Symptom Study.[62] This study uses a smartphone-based application (app) developed by Zoe Global Limited as a longitudinal symptom-tracking system used by four million people in the UK and 50,000 from Sweden.[63] App users self-report information about overall health and pre-specified symptoms daily. All women aged 18–44 years who specified pregnancy status at baseline were tracked for this study on symptom profiles, outcomes on testing positive for COVID-19 and on hospitalisation; this cohort were called the *discovery cohort*. Molteni et al.[62] also sought to replicate their findings using an independent cross-sectional symptom survey tool on Facebook with nearly 1.9 million women in the US, whom they called the *replication cohort*.

Results from the systematic review by Allotey et al.[61] are described first followed by findings from the community-based study by Molteni et al.[62]

Prevalence

The rate of COVID-19 diagnosis in pregnant or recently pregnant women attending or admitted to hospital for any reason varied depending on if they were universally screened (rates 4–10%) or screened on the basis of symptoms (rates 10–28%).[61] Of studies where universal screening was being conducted, three quarters of the 162 pregnant women who were COVID-19 positive were asymptomatic at the time of diagnosis. This high proportion of asymptomatic cases appeared to be an effect of pregnancy added to that of the young age profile of women of reproductive age.[61]

In the community-based discovery cohort, 8% of the 14,049 pregnant women were tested and only 0.6% were COVID-19 positive with a further 4.5% suspected positives; in the replication cohort (41,796 pregnant) 2.7% were tested, and only 0.4% were positive and 3.0% suspected.[62] Only around 0.1% of the discovery and replication cohorts who tested positive presented to hospital due to COVID-19 symptoms.[62]

Clinical features

The most common symptoms reported by hospital studies of pregnant or recently pregnant women with either suspected or confirmed COVID-19 were fever and cough (both approximately 40%) with raised CRP and lymphopenia being the most common laboratory findings. Compared with COVID-19 non-pregnant women of reproductive age, pregnant and recently pregnant COVID-19 positive women were less likely to develop symptoms of fever and myalgia. COVID-19 positive patients were more likely to have pre-existing diabetes. The fewer maternal patients presenting with the respiratory symptoms (cough, fever, and shortness of breath) indicate a possibly higher rate of asymptomatic presentation.[61]

In the community based discovery cohort study,[62] the most frequent symptoms in the *hospitalised* COVID-19 positive pregnant women were persistent cough, headache, and anosmia (all 80%), chest pain (73%), sore throat and fatigue (67%). In the *replication cohort*, the most frequent symptoms in the hospitalised COVID-19 positive patients were fatigue (87.5%), cough (84.6%), nausea or vomiting (78.2%), muscle pain (76.2%) and anosmia (75.2%). There were fewer neurological symptoms in hospitalised pregnant versus non-pregnant women and fewer 'skipped meals'. In the replication cohort COVID-19 positive hospitalised pregnant women versus non-pregnant there was more nausea and vomiting and gastrointestinal symptoms. Shortness of breath and nasal congestion were also more common in pregnancy than the non-pregnant.

Non-hospitalised pregnant women who were positive for COVID-19 most commonly reported headache (71.9%), anosmia (62.5%), persistent cough (57.8%), and skipped meals (48.4%).[62]

Maternal outcomes in COVID-19 pregnant and recently pregnant women

Only the Allotey review reported on pregnancy outcomes.[61] Compared to COVID-19 non-pregnant women of reproductive age, COVID-19 positive pregnant/recently pregnant women had higher odds for admission to an ICU (odds ratio (OR) 1.62 [95%CI 1.33 to 1.96%]) and for needing invasive ventilation (OR 1.88 [95%CI 1.36 to 2.60%]). Increased maternal age, high body mass index and pre-existing morbidities such as diabetes or hypertension might be associated with very severe disease. Overall 73 pregnant women (26 studies; 11,580 women) with confirmed COVID-19 died from any cause and 4% (17 studies; 10,901 women) were admitted to ICU, 3% requiring ventilation (13 studies; 10,713 women) and 0.4% requiring extracorporeal membrane oxygenation (9 studies; 1935 women).[61]

The Molteni study of community populations of COVID-19 positive pregnant women also found maternal co-morbidities impacted on severity of the COVID-19 illness: pre-existing lung disease impacted severity most, followed by heart disease then kidney disease and diabetes.[62]

Perinatal outcomes

Only the Allotey review reported on perinatal outcomes. The odds for preterm birth were higher for women with COVID-19 compared to those without (OR 3.0 [95%CI 1.2 to 7.9%]) but no differences were observed in other maternal outcomes. Overall rates of preterm birth were not high (17% [95%CI 13.0 to 21.0%]) and stillbirth (18/2837 offspring; 27 studies [95%CI 0.0 to 0.0%]) and neonatal death rates (6/1728 offspring over 26 studies [95%CI 0.0 to 0.0%]) were very low resulting in negligible risk in women with suspected or confirmed COVID-19. The preterm births might have been medically indicated, as the overall rate of spontaneous preterm births in pregnant women with COVID-19 was similar to rates in women before the pandemic. There was no difference in caesarean section rates in COVID-19 and non-COVID-19 deliveries. Neonates born to women who were COVID-19 positive had a higher risk of admission to the neonatal unit compared to those born to non-COVID-19 women (OR 3.13 [95%CI 2.1 to 4.8%]). There was no difference in rates of stillbirth or neonatal deaths.[61]

Gaps in evidence

Few studies compare risk of severe disease in pregnant and non-pregnant women in similar age groups and pregnancy outcomes in pregnant women with and without COVID-19. Also needed are studies of symptoms by trimester of onset to assess rates of miscarriage and post-partum complications. Only a small number of studies relate to complications of COVID-19 in women in the third trimester, and in multiparous women. Furthermore, studies of intercurrent risk factors such as ethnicity and pregnancy-related conditions (e.g. pre-eclampsia, gestational diabetes) pregnancy outcomes in COVID-19 versus non-COVID-19 patients are also required.

All studies in the Allotey review are of hospital-based populations and none are in primary care or from the general population. The true prevalence of COVID-19 in pregnancy is likely to be lower in community based samples. The Molteni study supports this notion of a much

lower prevalence of COVID-19 positive pregnant patients in the general population with under 1% tested being positive and around 4% suspected cases. More studies in non-hospitalised patients would help confirm this.

Relevance for clinical practice

There is no evidence that COVID-19 positive pregnant women are at any higher risk of increased morbidity or complex symptoms than non-pregnant women but co-morbidities increase risk for severe COVID-19 disease, as they do for COVID-19 infection in the general population.[62]

"Based on existing data…pregnant and recently pregnant women with COVID-19 might manifest fewer symptoms than the general population, with the overall pattern similar to that of the general population."[61]

"The most common symptoms for pregnant women were similar to non-pregnant people, including persistent cough, headache, loss of taste or smell (anosmia), chest pain, sore throat and fatigue. However, there was an increased incidence of gastrointestinal symptoms such as nausea and vomiting in the group of pregnant women who became most severely ill with COVID-19, which could be confused with similar symptoms that are due to the pregnancy itself."[64]

"Emerging comparative data indicate the potential for an increase in the rates of admission to intensive care units and invasive ventilation in pregnant women compared with non-pregnant women. Mothers with pre-existing comorbidities will need to be considered as a high-risk group for COVID-19, along with those who are obese and of greater maternal age".[61]

Age related differences

Paediatric

NCHRAC conclusion 4: Most children with COVID-19 are asymptomatic or have only mild to moderate symptoms. The high proportion of asymptomatic infection in children may contribute to community transmission of the virus. Those children who do develop symptoms have a different symptom pattern to adults, with the most common symptoms being headaches, fatigue, fever, sore throat and cough.

General signs and symptoms in children

Children are more likely to be asymptomatic than adults. One review suggested 95% of children with COVID-19 are asymptomatic or have only mild to moderate symptoms.[65] Similarly, children are less likely than adults to require admission to an intensive care unit[66] and their estimated case fatality rate is 0.08%.[65] The most common route of infection in children appears to be household contacts, with a familial contact being identified in 73.3%[65,66] to 87% [95%CI 77 to 95%][46] of cases. Several reviews note that the rate of asymptomatic infection in children may contribute to community transmission of the virus.[65,66] One review noted a sex imbalance in paediatric community infection: 57% [95%CI 53 to 62%] patients were male.[46]

Using symptom tracker data from the British population the most common symptoms among children <18 years are headaches (55%), fatigue (53%), fever (48%), sore throat (40%) and cough (38%).[63] This is in contrast to adults 18 to 65 years in whom the three most common symptoms are fatigue (82%), headache (73%) and loss of smell (55%).[63] With the exception of headaches, the results from the ongoing population study are similar to those found by Liguoru et al. in children <18 years: fever (51.6%), cough (47.3%), and sore throat (17.9%). A review including people up to the age of 21 years found fever (59.1%), cough (55.9%), rhinorrhoea (20.0%) and myalgia/fatigue (18.7%).[66] Zhang et al.[46] noted that in children <18 years with laboratory confirmed COVID-19, the main symptoms were fever (53%, 95%CI 45 to 61%), cough (39%, 95%CI 30 to 47%), and sore throat or pharyngeal erythema (14%, 95%CI 4 to 28%). Liguoru et al.[65] found the main non-respiratory symptoms in children to be diarrhoea (9.7%), vomiting (7.2%), and fatigue (10.6%). From the systematic reviews it appears the main non-respiratory symptom of COVID-19 for children are fever and fatigue; headaches are only emerging in more contemporary data.

It is interesting to consider the possible reasons underlying the differences in reported symptoms between the ongoing British population study and systematic reviews. The population-based study is an ongoing investigation involving the general population progressively more attuned to the evolving knowledge of non-respiratory effects of COVID-19, while the systematic reviews represent data from case studies and case series earlier in the pandemic, most commonly of patients sufficiently unwell to present to hospital.

Common laboratory abnormalities

Low levels of laboratory abnormalities are seen in children with COVID-19. Liguoro et al.[65] note that less than one fifth (17.1%) show low white blood cell and lympho- or neutropenia. A decreased neutrophil count with PPE of 38% [95%CI 19 to 60%] was noted by Henry et al.[55] as the most significant blood abnormality.

Liguoro et al. found inflammatory indices including C-reactive protein and procalcitonin were elevated in 31.1% children with creatine kinase and liver enzymes altered in 14.5% and 12.4% of patients.[65] Zhang et al. also found an increase in creatine kinase (21% [95%CI 8 to 37%]) and increased lactate dehydrogenase (29%[95%CI 16 to 43%]) and aspartate aminotransferase (18% [95%CI 9 to 28%]).[46] Increased levels of C-reactive protein, procalcitonin, and lactate dehydrogenase were observed in a third review along with elevated creatine kinase-MB in one-third of patients.[55]

The most common chest imaging findings in children with COVID-19 are patchy lesions and ground glass opacity.[66,46] In patients who had chest CT scans, 36% [95%CI 28 to 45%] of patients had normal CT images, 33% had patchy consolidations [95%CI 23 to 43%] and 28% had ground glass opacities [95%CI 18 to 39%].[46] Patchy lesions were also seen in a higher frequency to ground glass opacities in chest radiographs, again normal images was the most frequent result.[66]

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C is a rare but concerning syndrome with manifestations similar to Kawasaki disease. Kawasaki disease is a post-infection medium-large vessel vasculitis that accompanies a febrile muco-cutaneous rash and lymphadenopathy, and which can result in arterial aneurysms. MIS-C is characterised by gastrointestinal symptoms (occurring in 71% of patients, of which abdominal pain was seen in 36%, diarrhoea in 27%, and vomiting in 25%), dermatological (42% of MIS-C cases)[67] and cardiovascular manifestations rather than being dominated by respiratory symptoms (only described in 4.5% of MIS-C cases).[67] Less common extrapulmonary manifestations include transient left ventricular systolic dysfunction, shock, conjunctivitis, swelling of the extremities, oral mucosal changes, cervical lymphadenopathy and markedly elevated inflammatory biomarkers.[68,69]

MIS-C occurs in a small minority of children: estimated at 2 per 100,000 patients <21 years old infected with SARS-CoV-2 who develop severe disease.[70] Radia et al.[67] noted a higher incidence of 783 cases of MIS-C were identified in an estimated 15 million cases of SARS-CoV-2 infection reported worldwide; the review noted that only 362/619 cases documented evidence of current or past infection with SARS-CoV-2 through RT-PCR or serology testing.[67]

MIS-C affects children with a median age of 8 years, whereas Kawasaki disease normally occurs in children less than 5 years of age (median 11 months). Similar manifestations to MIS-C have been described in adults, but only rarely. Children with MIS-C did not typically have antecedent co-morbidity (156/783 identified cases).[67] Admission to intensive care units was required in the majority of cases (531/783 of identified cases) due to physiological impairment, predominantly cardiovascular dysfunction (82% tachycardic and 61% hypotensive).[67]

Older Adults

NCHRAC conclusion 5: Older adults display the same spectrum of illness manifestations as younger people, such as cardiovascular disease, acute respiratory distress syndrome (ARDS), and stroke, but with a higher incidence of severe complications and a higher risk of death.

Older adults are at increased risk of complications and death from COVID-19, with the risk rising exponentially from the age of 50 years.[71] This is probably related to immunosenescence, a progressive, wide-ranging decline in cell-mediated immune function from the age of 50 onward.[72,73] This makes older people more susceptible to infections but also makes vaccines less immunogenic.[74] Generally older people have the same spectrum of illness manifestations as younger people, such as cardiovascular disease, ARDS, and stroke, but with a higher incidence of severe complications and a higher risk of death. Cardiovascular disease, including cardiac and thromboembolic effects, are the most important non-respiratory complications. The incidence of cardiac injury and heart failure are higher in older adults compared to middle aged adults.[75,76] Older people (aged >74 years) had a higher risk of acute cardiac injury, heart failure, skeletal muscle injury and kidney injury compared to those aged 60–74 years.[76,77] Delirium is also significantly more common in older adults with COVID-19.[78] Other neurological manifestations are also more

common, including disturbances of smell and taste, headache, dizziness, ischaemic stroke, haemorrhagic stroke and cerebral venous thrombosis.[29]

Primary care vs. hospital presentations

Primary care presentations

NCHRAC conclusion 6: Knowledge of the epidemiology of the non-respiratory manifestations of COVID-19 in patients not sufficiently unwell to present to hospital is poor. Tiredness, headache, fever, ageusia, and anosmia all appear common. Several large primary care cohort studies are underway that should fill this evidence gap, and primary care data is being collected in Australia but is not yet being consolidated into usable information due to lack of resources to do so.

Of the reviews and studies identified for consideration, none are specified to be in the primary care setting. The prevalence of non-respiratory effects of COVID-19 increases with overall disease severity, at least for some of the manifestations described. As a consequence of only studying patients unwell enough to present to hospital, or not specifying the type of patient studied, the available evidence is of uncertain relevance to a less unwell primary care population.

Primary care specific studies

A search for terms related to primary care and COVID-19 symptoms did return a small number of studies describing symptomatology. A study in Spain of community seroprevalence of COVID-19 in probable and possible cases presenting to primary care revealed that the most common symptoms in both test-positive and test-negative patients were cough, tiredness, headache and fever. Confirmed COVID-positive patients were more likely to have tiredness, cough, fever, ageusia, anosmia and headache.[79] Regression analysis determined that risk factors for a positive test result were fever (>38°C), anosmia, ageusia and contact with a positive patient. The odds ratio for a positive test decreased for men suffering from headache and women with a sore throat and shaking chills.

Another small study surveyed over 800 patients referred by their GP for testing about their symptoms prior to undergoing the COVID-19 nasopharyngeal PCR test.[80] Smell and taste disorders were common (19%–23%) and highly predictive of a positive COVID-19 test. Most common symptoms were: cough (55%), dry throat (47%), headache (44%), and fever (45%).

Upcoming studies

A protocol has been published (April 2020) for a primary care surveillance study that will use weekly anonymised data extracted from the UK's Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) network of 500 general practices in England.[81] This network will enable epidemiological study of COVID-19 or suspected COVID-19 as it presents in community settings. Publications have not yet emerged from this network on non-respiratory symptomatology.

The *COVID-19 Symptom Study* was launched in April 2020 by King's College London in collaboration with Zoe Global Limited, Harvard Medical School, Massachusetts General

Hospital and Stanford Hospital. It aims to track COVID-19 symptoms from over 10 million volunteers worldwide with an app. In time, this data will also provide information about non-respiratory COVID-19 symptoms in a community setting and one paper in pre-print on these findings[62] has been described in the section on pregnancy in this report.

Australian data sources

In Australia there is a particular paucity of research on the epidemiology of the virus in community-based care. The epidemiological picture is likely to differ from that in other countries because community transmission in Australia is low and suspected cases or contacts have been encouraged to attend designated respiratory clinics for testing and evaluation to allow routine primary care to continue for all other patients.[82] However, despite Victoria enduring its second wave (June – October 2020), presentations to primary care for post-diagnosis management of COVID-19 positive patients have received little attention.

The potential to establish a surveillance network of general practices in Australia, along the lines of the RCGP RSC, exists but requires support. As an illustrative example, the Patron (University of Melbourne) network receives anonymised data extracted weekly from over 115 practices around Victoria, over 40 of which were in the hotspot areas for the second wave. This amounts to over 2 million active patients. Since March 2020, over 15,000 COVID-19 tests have been ordered from 63 of the clinics. Pathology test results are imported into the data set, enabling identification of positive cases and pairing these with clinical presentation and outcomes as entered in the electronic record. Hence studies of pre-test probability or presenting symptomatology and clinical course can be conducted. The extraction tool is GRHANITE which creates an anonymous key that can be used to link data to other routinely collected datasets such as Medicare Benefits Schedule, Pharmaceutical Benefits Scheme, and state hospital and emergency departments (email communication, Professor L. Sanci, 21 October 2020).

COVID-19 in patients presenting to hospital

NCHRAC conclusion 7: Most COVID-19 patients (>85%) do not require hospital admission. Of those that do, elderly patients have the longest length of stay (median 11 days). Among patients requiring ICU admission in Australia, mortality is only 15%, substantially lower than comparable figures overseas, for unknown reasons. Patients undergoing surgery whilst affected by COVID-19 have a very high mortality: 20%.

The hospitalisation rate for confirmed cases of COVID-19 in Australia is 13% (based on National Notifiable Disease Surveillance System data).[2] In the period from 17 February 2020, 466 cases of COVID-19 have been admitted to insensitive care units in participating sites; 55% of these patients required mechanical ventilation. The length of stay in hospital of COVID-19 patients in Australia increased with advancing age, with children <18 years staying in hospital a median of 2.5 days and patients >80 years staying in hospital a median of 11 days. Conversely the length of stay in intensive care units was longest in patients <18 years (median 12 days), while for adults >80 years of the median ICU length of stay was 3.5 days (possibly reflecting a higher mortality in this oldest group).[2] Across all age strata, Australian

patients admitted to ICU who required mechanical ventilation had a lower mortality (15%) and longer length of stay (median 16 days for those requiring invasive ventilation) than those in reports from overseas, for unknown reasons.[83]

There is little to no data on attributable mortality and hospital length of stay distinguishing respiratory from non-respiratory effects of COVID-19. Many patients have protean manifestations of the disease, making such a distinction arbitrary and of little value.

A systematic review of 23 studies reporting 2,947 patients found a very high postoperative mortality of 20% [95%CI 15 to 26%] among patients with COVID-19, and a postoperative ICU admission rate of 15% [95%CI 10 to 21%].[84] Thromboembolic disease, pulmonary complications, and infection were the commonest perioperative complications, but the proportion of attributable mortality that was due to these conditions, as opposed to other unspecified effects of SARS-CoV-2 infection in the perioperative period, were not apparent from the studies examined.

Evidence gaps and limitations

NCHRAC conclusion 8: The major evidence gap is in the understanding of the acute non-respiratory effects of COVID-19 in the majority of patients who are not sufficiently unwell to present to hospital. The main consequence of this lack of knowledge is higher risk of community transmission by patients – primarily younger patients – infected with SARS-CoV-2 but who are not diagnosed with the disease.

The major conclusion of this report is that there are currently important deficiencies in the knowledge of the acute non-respiratory effects of COVID-19. These deficiencies have the potential to delay diagnosis of infected patients, enhance disease transmission, and lead to an under-appreciation of the adverse effects of the disease amongst certain population groups (most notably younger people) that might be inappropriately reassured due to their low risk of fatal respiratory disease. The most important evidence gaps are knowledge of the:

- effect of COVID-19 in patients who do not present to hospital
- diagnostic value of identifying certain combinations of signs and symptoms and the order in which they appear
- relationship between overall disease severity and the incidence of acute and chronic non-respiratory effects, and
- subtle acute and chronic non-respiratory (and respiratory) manifestations of COVID-19 that might not yet have been identified. A greater understanding of the pathophysiology of the disease is likely to enhance vigilance for the possibility of such effects.

Australian cohort studies are underway, including those addressing the primary care evidence gap.

NCHRAC recognises that the distinction between acute and long-term non-respiratory effects of COVID-19 might have value for clinicians, but is of little meaning to patients. There is little to suggest that COVID-19 patients recover from their acute illness and then develop different long term effects. Rather, their non-respiratory long-term effects appear to more commonly begin in the acute phase of illness. Consequently, the evidence in this paper must be read in conjunction with that in the NCHRAC paper examining the long-term consequences of COVID-19.

NCHRAC recognises that this review is inherently limited as a summary of the evidence at a single point in time. Several international cohort studies are currently underway based on data that is planned to be continuously updated, including:

- The COVID Symptom Study, based on the ZOE study app (https://covid.joinzoe.com/earlysymptomsdiscoveries)
- The British Association of Dermatologists Covid-19 Skin Patterns study https://covidskinsigns.com/

There are also several "Living systematic reviews" that, while primarily focussed on therapeutic interventions, demonstrate what can be achieved with sufficient resources, for example:

- https://covid-nma.com/, https://www.cochrane.org/coronavirus-covid-19-cochrane-resources-and-news;
- http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx, and
- https://covid19evidence.net.au/

Other considerations

In the course of developing this advice, NCHRAC identified the following considerations that were out of scope for this document, but are important and related considerations:

- Virtually all of the evidence identified has examined COVID-19 in isolation. NCHRAC identified merit in investigating the incidence of non-respiratory effects of COVID-19 in comparison to that observed in other severe viral and infectious disease, in order to understand particular features of the pathogenesis of the disease that could be amenable to specific adjuvant treatment.

- NCHRAC identified the potential utility of understanding the time course of the development of respiratory and non-respiratory effects of COVID-19, relative to each other, as an aid to diagnosis. We identified only one study that has attempted this approach, using limited data.[85] There is merit in exploring this concept in the detailed data available in the primary care databases described in this report.

- NCHRAC acknowledges many of the non-respiratory effects of COVID-19 persist long after the resolution of acute illness, as defined in this report. These effects are described in the separate NCHRAC report "Evidence for the long-term consequences/sequelae of COVID-19".

Attachments

Attachment 1: Membership of the NCHRAC non-respiratory effects working group

Attachment 2: Evidence Review

References

Note: Research papers shared before peer review are identified as pre-prints and are marked with a § in the reference list. Accordingly, they should be interpreted with caution.

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Attachment 1: Membership of the NCHRAC non-respiratory effects working group

About the Committee and the Working Group

About the National COVID-19 Health and Research Advisory Committee

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was established in April 2020 to provide advice to the Commonwealth Chief Medical Officer advice on Australia's health response to the COVID-19 pandemic. NCHRAC provides rapid and evidence-based advice (or expert advice in the absence of evidence) on Australia's health response to the COVID-19 pandemic with the aim of preventing new cases, optimising the treatment of current cases, and assisting in optimising overall health system readiness to deal with the pandemic as it progresses.

Further information on the terms of reference and membership of the Committee is available at: www.nhmrc.gov.au/nchrac. NHMRC is providing secretariat and project support for the Committee. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Working Group Membership

NCHRAC convenes working groups of its members and external experts to deliver its reports. The following NCHRAC members and external experts were involved in the development of this advice:

NCHRAC Members

Professor Michael Reade AM (Chair)

Professor Brendan Crabb AC

Dr Michael Freelander MP

Professor Raina MacIntyre

Mr Daniel Zou

Additional experts

Professor Benjamin Cowie (Doherty Institute)

Professor Anthony Kelleher (Kirby Institute)

Professor Lena Sanci (University of Melbourne)

Associate Professor Timothy Tan (University of New South Wales)

Attachment 2: Evidence Review

Evidence review aims

1. To identify and describe the spectrum of non-respiratory tract COVID-19 signs and symptoms that have been documented at the time of presentation
2. To identify and describe the best available evidence
    a. Confirming that these are signs and symptoms of COVID-19
    b. Quantifying the proportion of all COVID-19 patients that present with each sign or symptom, alone or in combination, at the time of diagnosis
3. To identify the prevalence or incidence of non-respiratory manifestations of COVID-19 during the acute phase of illness.

Methods

The intention was to identify some (but not all) reliable systematic reviews that describe the spectrum of signs, symptoms and/or clinical manifestations of COVID-19. As prospective studies require time to follow patients, and to analyse and report results, it was expected that the evidence included in any systematic reviews identified would largely be observational and retrospective.

Which databases were searched?

The databases PubMed, Europe PMC and medRxiv[b] were searched. Search strings applied in each database aimed to maximise specificity rather than sensitivity. Search terms are provided below.

Search results were downloaded into an Excel spreadsheet and duplicates removed. Titles and abstracts were scanned by one person and articles were included if they were reports of systematic reviews and/or meta-analyses that explored the symptoms of COVID-19, and their prevalence. Articles were excluded if:

- they were not reports of systematic reviews
- they were not clearly related to COVID-19 or acute effects of COVID-19
- the full article was not available (i.e., no full article)
- they were protocols for systematic reviews (i.e., did not include results)
- were exploring risk factors for particular outcomes, or
- were duplicate records.

Full articles were obtained for all potentially relevant and eligible systematic reviews. The manuscript for each shortlisted review was examined and those considered eligible were summarised (Supplements 1–3, below).

What were we looking for?

The aim was to identify published (in peer reviewed literature or as pre-prints) relevant, good quality systematic reviews reporting on the signs and symptoms of COVID-19 and their prevalence or incidence. Systematic reviews were the target in recognition of the large

[b] MedRxiv is a preprint server and its contents have not been peer reviewed at the time of submission.

number of studies that continue to be published on this topic, and the desire to base advice on a body of evidence rather than selected studies, where appropriate.

About the included systematic reviews

To be included, reviews needed to have conducted a search for studies on or after 1st May 2020. Reviews with searches before that date were included if they filled a gap. For example, evaluated the quality of included studies, addressed a specific subgroup (e.g. children or pregnant women), setting, or reported a symptom or manifestation (e.g. cardiovascular effects of COVID-19) not reported in a general systematic review.

The level of certainty in the systematic reviews in this topic is low to very low. Many did not have clearly articulated aims or objectives, or eligibility criteria. Almost all included only retrospective, observational studies with many including single case studies, and most either did not assess the risk of bias in included studies or did not take this bias into account when pooling or interpreting data. None of the general reviews declared their methods *a priori* with a published protocol.

Some systematic reviews pooled data in a meta-analysis and most had often high to very high levels of heterogeneity.

Some reviews do not formally pool data in a meta-analysis, but may simply calculate averages. Calculating averages does not account for the weight of individual studies. However some descriptive data have been provided where meta-analysed data was not available on specific findings of relevance. Unless stated otherwise, values presented in Supplement 3 (below) without confidence intervals are averages.

Results

Eleven general reviews (not focused on a particular type of sign or symptom or population) were included. Only two of these general reviews had registered protocols, six assessed risk of bias and all had at least one element of duplication of study selection or data collection. The study designs included in these reviews were all retrospective and observational.

The remaining 34 systematic reviews were grouped into system based headings. Nine had registered protocols, many (24) assessed risk of bias and 16 duplicated both selection of studies and data extraction.

Additional studies identified by authors as relevant or where they provide more recent data have also been used throughout the paper.

Search terms for systematic reviews

1. PubMed

Date searched: 4th September, 2020

Search terms:

"COVID-19"[Supplementary Concept] AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR ("systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]))

Result: 435 citations

2. PMC Europe

Date searched: 2nd September, 2020

Search terms:

"2019-nCoV" OR "2019nCoV" OR "COVID-19" OR "SARS-CoV-2" OR "COVID19" OR "COVID" OR "SARS-nCoV" and "systematic review" or PUB_TYPE:"Meta-Analysis" and "presenting symptom" or "clinical presentation" or "signs and symptoms" or “symptom dynamics” or “symptom course” or “onset of symptoms”

Result: 772 of which 660 were published in 2020.

3. medRxiv

Date searched: 31st August, 2020

Search term: "covid-19 non-respiratory symptoms systematic review"

Result: 30 citations

Supplement 1

Table 1: Systematic review characteristics

Note: Rows highlighted in grey indicate systematic reviews evaluated that do not add anything to reviews published subsequently, or are current reviews that do not add to (or are of lower quality than) previously published reviews. Reviews published before May 2020 have only been included if they reported data not included in other reviews.

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
General										
Grant	To determine the prevalence of symptoms associated with COVID-19 worldwide	No	Setting: Not specified Adults (>16years) Confirmed: lab confirmed RT PCR		N/A	1st January onwards – no end date (published 23rd June)	Not stated. Excluded case reports, and articles "which failed to disaggregate symptoms in adult and paediatric cohorts"	No	Not reported Yes	Subgroups: country
Nasiri	To provide a comprehensive overview of COVID-19	No	Setting: Not specified Life stage not specified Confirmed: RT-PCR		Meta-analysis of comorbidities included. Table 2 – pooled frequency. • Chronic liver disease • Diabetes • Hypertension • Malignancies • Pulmonary disease • Renal disease • Smoking	29th May	Not specified	Yes (JBI)	Yes Yes	Only included studies for which "raw data" available, although unclear what this means. Reports lab abnormalities and complications and meta-analyses clinical manifestations.
Li	To elucidate regional variations in baseline clinical characteristics, presentation, and factors associated with outcomes in COVID-19 patients	No State "submitted to PROSPERO"	Setting: Not specified Life stage not specified: not paediatric or pregnant women Confirmed: 190 studies PCR, 1 study serum antibody, 9 studies combination of chest CT and PCR tests, 1 study PCR, chest CT, and antibody test, 10 studies not specified		Comorbidities reported: • Chronic heart disease • Chronic liver disease • Chronic lung disease • Chronic renal disease • Diabetes • Hypertension • Malignancy	6th April	Not specified. "Studies of laboratory-confirmed COVID-19 patients with relevant data"	Yes (NOS)	Yes Yes	subgroup analysis by country/region, disease severity, age, gender, sample size, and quality assessment score.
Kaur	To evaluate the epidemiological and clinical characteristics of COVID-19 patients while also highlighting the comorbidities and radiological findings	No	Setting: Not specified Life stage not specified Confirmed: RT-PCR		Comorbidities reported (table 1): • Alcohol consumption • Cerebrovascular disease • CKD • CVD • Diabetes • GI disease • Hep B • HIV • Hypertension • Immunosuppression • Malignancy • Obstructive sleep apnoea	27th April	observational studies, case series, and case reports	No	Yes Yes	

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
					• Organ transplant • Pulmonary disease • Smoking					
Age specific – Older adults ≥60 years										
Neumann-Podczaska	To concisely summarise the clinical features, comorbidities, radiological/laboratory findings, and outcomes in older adults	No	Not specified Older adults (>= 60)		• Autoimmune Disease • Cerebrovascular Disease • Chronic Hepatic Disease • Chronic Lung Disease • Chronic Renal Disease • CVD • Diabetes • Endocrine Disease • Hypertension • Immunocompromised • Malignancy • Neurological Disorder • Osteoporosis • Past surgery • Smoking • Tuberculosis	1st June	Retrospective studies (descriptive, case reports, case series, case control, cross sectional studies) and cohort studies. Excluded studies where age data not reported separately), and studies with <= 2 older patients	Yes (adaptation of STROBE, CERQual)	Yes Yes	
Age specific – Paediatric ≤18 years										
Radia	To evaluate reported cases of MIS-C (Multisystem Inflammatory Syndrome - Children) in children and adolescents	No *	Not stated. Neonates, infants, children, adolescents		• Obesity	30th June	Not stated	No	Yes Yes	*mentions protocol but not registered
Hoang	Review question: What are the clinical presentations of paediatric patients with confirmed COVID-19?	Yes	Not stated. Paediatric (including neonates, children, and teenagers up to 18 years of age)		Not reported	14th May	cross-sectional, case series, and case reports providing clinical signs, imaging findings, and/or laboratory results	Yes (NIH tool)	Yes Yes	CRD42020182261 Patients will be included if SARS-CoV-2 is detected by RT-PCR in nasopharyngeal, throat, blood, or stool samples at any point of their disease course. Explores underlying conditions and coinfections Note: Zhang, Henry, Cui, Ding, Chang, Pei, He Ludvigsson
Liguoro I	To provide a concise and systematic overview of the available evidence on clinical, laboratory, and radiological findings in children with SARS-CoV-2 infection	No	Not stated. Children (0-18)		• Chronic lung disease • Congenital heart disease • Hemato-oncological diseases • Immunosuppressive treatment	1st May	Case reports, case series, and retrospective or observational studies	Yes (JBI)	Not reported Yes	
Henry BM	Aim not stated	No	Not stated RT-PCR confirmed cases of COVID-19 in pediatric patients		Not reported	1st May	case reports, case series, or observational studies that report clear and extractable data on laboratory findings	No	Yes Yes	
Zhang	Review question 1. What are the epidemiological,	Yes	Not stated. Children up to 18 years		Not reported	To 4th May	Randomized trials (baseline data only), observational studies (cross-sectional, cohort and	Yes (NOS)	Yes No	CRD42020178178

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
	demographic, clinical, radiological, and laboratory characteristics of children (up to 18 years of age) with laboratory-confirmed COVID-19? 2. What are the treatments used for children with laboratory-confirmed COVID-19? 3. What the prognosis of children with laboratory-confirmed COVID-19?		All 551 children "were hospitalized or treated in the emergency department"				case-control), case series or case reports, and research letters.			
Cui	Review question To provide a comprehensive and systematic analysis of demographic characteristics, clinical symptoms, laboratory findings and imaging features of coronavirus disease 2019 (COVID-19) in pediatric patients.	Yes	Not stated. Children.		Not reported	To 30th April	Cohort studies, case series and case reports	Yes (NIH)	No Yes	CRD42020191099 Although use of past tense suggests registered post hoc
Pregnancy										
Allotey	To determine the clinical manifestations of covid-19 in pregnant and recently pregnant women, identify the risk factors for complications, and quantify maternal and perinatal outcomes.	Yes	**Setting**: not reported **Life stage**: Pregnant, postpartum and post abortion/miscarriage women with suspected or confirmed COVID-19 infection. **Confirmed**: "We defined women as having confirmed covid-19 if they had laboratory confirmation of covid-19 infection irrespective of clinical signs and symptoms. Women with a diagnosis based only on clinical or radiological findings were defined as having suspected covid-19." "All (77 included) studies tested respiratory samples using RT-PCR to confirm the presence of SARS-CoV-2; 23 studies additionally diagnosed covid-19 based on clinical suspicion."		Figures 3 and 4 • Aguesia • Cough • Diarrohea • Dyspnoea • Fever • Mylagia	26th June	Primary case reports, case series, observational studies or randomised-controlled trials.	Cohort studies (NOS), RCTs (RoB 2) tool, diagnostic accuracy studies (QUADAS-2), and prevalence studies (Hoy et al).	Yes Yes	Registered CRD42020178076 Living systematic review NOTE: there are many systematic reviews of COVID-19 in pregnancy but this is clearly the best and the most current Laboratory findings analysed. Reports neonatal outcomes The most common symptoms reported by pregnant and recently pregnant women with suspected or confirmed covid-19 were fever (40%) and cough (39%); lymphopaenia (35%) and raised C reactive protein levels (49%) were the most common laboratory findings (fig 3). Pre-existing comorbidities, high maternal age, and high body mass index seem to be risk factors for severe covid-19
Ear nose and throat										

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
Agyeman	To estimate the prevalence of olfactory and gustatory dysfunctions (OGDs) among patients infected with COVID-19	No	**Setting:** Not reported **Life stage:** not reported **Confirmed:** "patients with COVID-19 infection with diagnostic confirmation"		None reported	11th May	Not stated. Excluded case series <10 participants	Yes (Murad)	Not stated Yes	Claimed registration of protocol "not feasible" given the urgent need for information to inform clinical decision making" Subgroups (meta-regression): age, sex, assessment method (ie of dysfunction)
Tong JY	To further delineate the global prevalence of olfactory and gustatory dysfunction in COVID-19 patients	No	**Setting:** Not reported **Life stage:** not reported **Confirmed:** reported method used by included studies RT-PCR (7/10); Not reported (3/10, including 1 review that included suspected)	Report olfactory or gustatory dysfunction	None reported	19th April	Not stated. Excluded case reports and reviews/meta-analyses	Yes Adapted from Hoy et al	Yes Yes	
Giorli	To investigate the association between the olfactory dysfunction and the more typical symptoms (fever, cough, dyspnoea) within the Sars-CoV-2 infection (COVID-19) in hospitalized and non-hospitalized patients.	No	**Setting:** not requiring hospitalization **Life stage:** not stated **Confirmed:** reported for each included study (Table 1): RT-PCR or PCR (8/11) Not reported (3/11)		None reported	1st June	Cross-sectional, case-control or retrospective observational studies	No	No No	
Samaranayake	The systematic evaluation of currently reported prodromal symptoms of loss of taste and smell in patients with COVID-19. In particular, to understand the temporality and the periodicity of the appearance of these clinical manifestations in terms of the progress of SARS-CoV-2 infection.	Yes	**Setting:** ambulatory and hospitalized **Life stage:** Adolescent-elderly (≥17-≥80), **Confirmed:** "laboratory confirmed"	Non-severe to severe COVID-19 patients	Co-morbidities (*reported in >1 included studies): • Allergic patients • Asthma • Cancer* • Cardiac ailment* • Cardiac or cerebrovasulcar dis. • Chronic kidney disease • COPD • Dementia • Diabetes* • GERD • Hypertension* • Hypothyroidism • Malignancy • Neurological disorder/depression • Sinusitis	30th May	Cross-sectional studies and retrospective, observational case series	Yes (Hoy)	Yes No	CRD42020183714 Co-morbidity prevalence (% noted only for each study not pooled) reported in 4/8 included studies (Table 1)-
Almufarrij I	To investigate the presence and incidence of audio-vestibular symptoms as a result of coronavirus	Yes	**Setting:** not stated **Life stage:** not stated **Confirmed:** not specified Diagnosed coronavirus (SARS-Cov-2; MERS; SARS) using any diagnostic tool.	Patients diagnosed with hearing loss, tinnitus or dizziness as a result of coronavirus	None reported	5th May	No restrictions	Yes (NIH)	No Yes	CRD42020184932 *no audiovestibular symptoms reported for SARS and MERS so not included based on eligibility criteria

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
			7/7 included studies confirmed COVID-19*							
Cardiovascular										
Porfidia	To evaluate the incidence of VTE in patients admitted for COVID-19 and identify subgroups at high risk	No	**Setting:** Hospitalised **Life stage:** Adults **Confirmed:** Not reported	Studies evaluating the incidence of VTE in COVID-19	None reported	24th June	cohort study or RCT >=10 participant	Yes (non- RCTs using MINORS, RCTs using Cochrane RoB)	Yes Yes	Only looking at VTE, DVT and PE as complications of COVID-19. Considers ICU and general ward patients.
Sabatino	Review questions: • How do pre-existing cardiovascular morbidities or cardiovascular risk factors impact on clinical outcomes in COVID-19 patients? • How do cardiovascular complications impact on survival in COVID-19 patients?	Yes	**Setting:** Hospitalised **Life stage:** not reported **Confirmed:** Other – not specified, only as *confirmed positivity to the SARS-CoV-2 virus*. Method not mentioned.		Reported on cardiovascular comorbidities (grouped, S1 Fig) and risk factors (S2 Fig): • Coronary Artery Disease • Diabetes • Heart Failure • Smoking	11th June	"retrospective studies", case series	Yes QAT-OC/CSS	Yes Yes	CRD42020191650 Clinical outcomes will be analysed in relation to their exposure to pre-existing cardiovascular disease or cardiovascular risk factors. Subgroup: ICU vs not
Cheruiyot	To identify and consolidate data on the incidence of AT in COVID-19 patients	no	**Setting:** Not reported but probably hospitalised **Life stage:** not specified **Confirmed:** RT PCR		Comorbidities reported: • Hypertension • CVD • atrial fibrillation • CKD • COPD • Obesity • Hyperlipidemia • Diabetes • Asthma • Leukemia • Renal tubular acidosis	9th June	case reports/case series/cohort studies	No	No yes	Rapid review
Momtazmanesh	(1) to calculate pooled frequency of newly developed and pre-existing CVD, hypertension, diabetes mellitus, cardiac symptoms as the initial presentations of COVID-19, elevation of cardiac and inflammatory biomarkers, acute hepatic, and renal injury	No	**Setting:** Not reported **Life stage:** Not specified **Confirmed:** Not reported	Report cardiovascular diseases in COVID-19 patients and cardiac biomarkers.	Comorbidities reported: • Hypertension • Diabetes • CVD	21st April	Studies (all types, not review articles) >=10 participants	Yes (NOS)	No Yes	Reports cardiac and inflammatory biomarkers Pre-existing cardiovascular diseases, diabetes, and hypertension. Hypertension was the most common pre-existing comorbidity among COVID-19 patients with a pooled frequency of 29.2% (95% CI 24.7–33.6%), followed by diabetes with a pooled frequency of 13.5% (95% CI 11.5–15.4%). Overall, fewer than one-fifth of patients had pre-existing cardiovascular diseases. The pooled frequency of cardiovascular diseases was estimated at 12.6% (95% CI 10.0–15.2%). Additionally, our analysis on the pooled frequency of heart failure using data of five studies, which had reported pre-existing heart failure,

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
										showed a pooled frequency of 6.3% (95% CI 2.9–9.8%). There was significant heterogeneity in the estimates of pre-existing cardiovascular diseases and hypertension (I2 ≥ 95%).
Shafi	To systematically review the current published literature on the different cardiac manifestations and the use of cardiac-specific biomarkers in terms of their prognostic value in determining clinical outcomes and correlation to disease severity	No	**Setting:** not reported **Life stage:** not reported **Confirmed:** not reported	Studies were included if they had discussed a cardiac manifestation associated with COVID-19, correlation between cardiac-specific biomarkers and the diagnosis or prediction of severity of COVID-19 infection.	Comorbidities reported (Table 2): • Hypertension • Diabetes • CVD • Heart Failure • CVA • CAD • Cardiomyopathy • Hypercholesterolemia	Not reported	Not reported	Yes (NOS)	Yes Yes	
Sawalha	We aim to describe the clinical characteristics and management of currently published COVID-19 myocarditis patients. We also aim to investigate the most common presenting features, workup and outcomes in the reported cases to identify a common pattern to aid in the diagnosis and management.	No	**Setting:** Not reported **Life stage:** not specified **Confirmed:** Not reported		Comorbidities reported (Table 4): • Cardiomyopathy • HTN • Smoking • Other (lymph node TB, allergies)	30th June	Case reports	No	Yes no	
Neurologic										
Uncini	To review reported cases of GBS in SARS-CoV- 2 infection, to clarify the clinical and electrophysiological phenotype, to discuss whether the disease mechanism could be parainfective or postinfective and to speculate on the possible pathogenesis.		**Setting:** any **Life stage:** not reported **Confirmed:** yes • RT-PCR (via nasopharyngeal swab, 85.7%) • Serology (14.3%)		None reported	6th July	Case studies and case series Six (14.3%) patients were admitted to the hospital because of COVID-19 symptoms and developed GBS during hospitalisation; 4 (9.5%) were admitted for COVID-19, discharged and then readmitted because of the onset of neuropathic symptoms; 32 (76.2%) patients presented to the hospital because of neuropathic symptoms.	No	No No	Clinical, lab and imaging findings (Tables 1 and 2) – number (%) only
Di Carlo	To investigate the occurrence of different neurologic symptoms associated with COVID-19 and to assess their rate	No	**Setting:** Not reported **Life stage:** not specified **Confirmed:** laboratory diagnosis		• Hypertension • Diabetes • Cardiovascular disease • Malignancy • Smoking	29th May	cohort studies, case-controls studies, case series	Yes (modified NOS)	Yes No	Secondary objective to compare the results between patients with severe and non-severe infection.

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
De Sanctis	To identify specific clinical features of GBS associated with COVID-19	Yes	**Setting:** not reported **Life stage**: not reported **Confirmed:** reports test result for each patient	patients diagnosed with GBS who tested positive for SARS-CoV-2 infection	Not reported	17th May	Case studies, case series	Yes (GRADE)	No No	Abstract states there was a predefined protocol
Wang	To systematically collect and investigate the clinical manifestations and evidence of neurological involvement in COVID-19	No	**Setting:** Not reported **Life stage:** excluded studies focused on specific populations (eg infants, patients with cancer) **Confirmed:** not reported	Only articles reporting "unspecific neurological symptoms (eg headache, weakness, respiratory failure) were included.	Neurological diseases not specified.	3rd May	Case reports, case series, correspondence with relevant clinical data, retrospective and cross-sectional studies	Yes (NIH case series tool)	No No	
Munhoz RP	To provide a review of the existing data, including epidemiology, pathophysiology, and clinical and laboratory findings of neurological findings in COVID-19.	No	**Setting**: not reported **Life stage:** not reported **Confirmed:** laboratory confirmed cases only		None reported	10th May	Not restricted. Identified case series and case reports.	No	No No	Lab findings
Nazari [pre-print]	To evaluate the CNS presentations in COVID-19 patients	Yes	**Setting:** not specified **Life stage:** adults or children **Confirmed:** positive PCR test		Comorbidities reported Table 4 • Autoimmune diseases • Bacterial co-infection • Cardiovascular diseases • Cerebrovascular diseases • Chronic liver disease • Chronic renal disease • Chronic resp/pulm disease • COPD • Diabetes • Digestive/GI disease • Endocrinology disorder • Hepatitis B • HIV • Hyperlipidaemia • Hypertension • Immunodeficiency • Immunosuppression • Malignancy/Cancer • Smoking • Urinary system disease	20th April	observational studies: cross sectional, cohort, case series.	Yes (NIH)	Yes Yes	CRD42020184456 Several subgroup analyses will be done to compare clinical neurological characteristics of patients in age (<18 years/ ≥18 years), severity (critical or non-critical) or Comorbidities.
Abdullahi	To summarise the evidence on the neurological and musculoskeletal symptoms	No	**Setting:** not reported **Life stage:** adults (excluded children)		Noted not quantified**: • allergic rhinitis • cancer	Published by 17th April	Any study design	Yes (modified McMaster	Yes Yes	Claim not possible to register protocol

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
	of COVID-19, and their prevalence		**Confirmed:** states that in most of the studies, the Chinese national CDC recommended protocol, WHO interim guidance and RT-PCR were used to confirm diagnosis.		• cardiac or cerebrovascular disease • chronic kidney disease • chronic renal failure • COPD • Diabetes • Hepatitis B • History of head trauma • Hypertension • **Immune-suppression** • Malignancy • Neurological disease • Pituitary adenoma • Pregnancy			Critical Review Form)		** *"reviewed studies could not account for whether or not the neurological and musculoskeletal symptoms of COVID-19 are due to the comorbidities and/or the medicines the patients use for the comorbidities."* Refers to NHMRC evidence for each study (p4 and Table 1)
Pinzon	To provide a systematic report of the neurologic characteristics in patients with COVID-19	no	**Setting:** not reported **Life stage:** not reported **Confirmed:** 31/33 studies RT-PCR confirmed 1/33 clinical diagnosis 1/33 not mentioned.	Patients with COVID-19 and a focus on clinical manifestations or symptoms as long as reporting neurologic data	• General comorbidity not specified*** • CVD comorbidity • Cerebrovascular disease (most common) • Muscle pain See Table 1 & Figure 8	8th April	RCTs, cohort studies, case-control studies, cross-sectional studies, case reports and case series	Yes (CEBM)	Yes Yes	Lab findings *** One (limited) study stated that patients with comorbidity on admission were more likely to present with unconsciousness (2.5 vs 1%); another more likely to have muscle pain Pooled prevalence of CVD comorbidity was 8.5% (95% CIs: 4.5–13.5)
Gastrointestinal										
Tariq	To evaluate the prevalence of gastrointestinal (GI) symptoms and mortality in patients with COVID-19	No	**Setting:** Not reported (any setting) **Life stage:** Adults with confirmed COVID-19 infection **Confirmed:** not described "confirmed COVID-19"	report GI symptoms	None reported	7th May	Observational studies	Yes (Mayo clinic)	Yes Yes	Primary analysis: weighted pooled prevalence (WPP) of GI symptoms, occurring any time during the course of illness. Secondary outcomes were the WPPs of mortality in all COVID-19 infected patients and in those with GI symptoms.
Kulkarni	Research question: to assess the incidence of liver dysfunction (elevation in liver chemistries) in COVID-19	Yes	**Setting:** not reported **Life stage:** irrespective of age and gestational status **Confirmed:** not reported		Pre-existing liver disease (and type); severity	24th April	Case reports (>2), case series, letters, observational studies, RCTs and descriptive studies that mentioned liver dysfunction in patients with SARS-CoV-2 infection	Yes AXIS (for cross sectional), IHE (for case series) "Cochrane tool" for RCTs.	No Yes	CRD 42020181962
Kumar	To systematically study the occurrence of liver injury in COVID-19 and also determine the frequency of liver involvement in COVID-19. To identify any differences in frequency of liver dysfunction with varying disease severity, and identify differences in frequency of liver dysfunction.	No	**Setting:** Not reported **Life stage:** All ages. **Confirmed:** excluded if "studies did not have confirmed cases of COVID-19" (not defined)	Report liver function abnormalities, severe and non-severe disease, or underlying liver disease as a comorbidity in patients with COVID-19.	Severity Comorbidities reported (Figs. 4–7): • hepatitis B • fatty live, • total liver disease • chronic liver disease	5th April	Included all studies (any design) >=5 participants	No	Yes No	Results ALT, GGT, AST

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
Sultan S	To summarize international data on the GI and liver manifestations of COVID-19 infection and treatment	No	**Setting:** Hospitalised and outpatients **Life stage:** All ages **Confirmed:** RT-PCR confirmed			5th April	Any studies (prospective or retrospective) that reported on patient characteristics and symptoms of interest	Yes (ROBINS-I)	Yes Yes	Rapid review and guideline Took double counting (1 study published more than once) into account American Gastroenterological Association
Mao	To quantify the effects of COVID-19 on the digestive system	No	**Setting:** Not reported **Life stage:** Not stated (all ages) **Confirmed:** not stated "COVID-19 was diagnosed on the basis of the study criteria, with reference to WHO guidance"	Report gastrointestinal findings	Pooled prevalence estimate of digestive system comorbidities (underlying GI and liver disease) – Supplementary Figure 1	4th April	Excluded case series <10	Yes NIH QAT case series	Yes Yes	Abnormal liver function reported (mean/median, SD) – Supplementary data, Table 4
Eyes										
Sadhu [pre-print]	i) To estimate the prevalence of ocular signs and symptoms among COVID-19 patients, its onset, duration and prognosis ii) To estimate the proportion of patients presenting with conjunctivitis as a first symptom of the disease iii) To estimate the proportion of patients having ocular sample PCR positivity.	No	**Setting:** Not reported **Life stage:** Not stated **Confirmed:** "Clinically or laboratory confirmed". Table 1 specifies sample of included studies: range "new coronavirus pneumonia, clinically confirmed, suspected, cases, patients, lab confirmed, confirmed COVID-19 pneumonia	Studies looking at ocular manifestations among COVID-19 patients	None reported	10th June	Observational studies	Yes (NIH for case series)	Yes Yes	
Inomata T	to determine the clinical and prodromal ocular symptoms in patients with COVID-19	No	**Setting:** Not reported **Life stage**: All ages. **Confirmed**: Not reported	Include patients with COVID-19 demonstrating ocular symptoms.	None reported	7th May	Retrospective studies (cross-sectional, case control, case series, case reports)	No	Yes Yes	Lists inclusion criteria
Renal system										
Yang X	To assess the prevalence of abnormal urine analysis and kidney dysfunction in COVID-19 patients and to determine the association of acute kidney injury (AKI) with the severity and prognosis of COVID-19 patients	No	**Setting**: Not reported **Life stage**: Not stated (all ages) **Confirmed:** Not specified "confirmed COVID-19 patients were included."	Excluded studies not providing useful clinical characteristics or kidney impairment indicators	Not applicable	?? May	Study type not specified. >=10 patients Excluded case reports	No	Yes No	
Kunutsor	to address the following: (i) what are the renal complications associated with COVID-19? (ii) what is the incidence of these complications? and (iii) are patients with pre-existing renal conditions more susceptible to these renal complications?	Yes	**Setting:** not reported **Life stage**: Adults (excl pregnant women) **Confirmed:** not reported	Studies were not included if they did not report on any renal complications	Location (China, USA) Average age (>=60,<60), pre-existing CKD (high / low prevalence)	13th June	Observational studies (prospective cohort, nested case-control, or case-control, retrospective cohort), clinical studies, and randomised controlled trials (RCTs)	Yes (Observational – NOS, RCTs - RoB)	Yes Yes	Registered CRD42020186873
Dermatological										

First author	Aim	A priori methods (protocol)	Population	Other relevant population factors / eligibility criteria	Comorbidity	Search (end) date	Types of study	Risk of bias - Assessed - Tool	Duplication - Study selection - Data extraction	Other
Almutairi	To explore the different types of dermatological clinical manifestations in patients with SARS-CoV-2	No	**Setting:** not reported **Life stage:** adults **Confirmed:** not reported	"The inclusion criteria included discussing enough data on the dermatological symptoms with SARS-CoV-2"	Not reported	Not stated	All studies	Yes (Cochrane RoB)	No No	Defined inclusion criteria after search. RoB is for RCTs of interventions and none of these were identified
Zhao	To gain an in-depth understanding of the COVID-19, we summarized the publications related to the cutaneous manifestations of COVID-19 cases and the ACE2 expression in skin tissues	No	**Setting:** Not reported **Life stage:** not specified **Confirmed:** not reported	Report cutaneous manifestations and expression of ACE2 in skin.	• Diabetes • Hypertension Insufficient information to draw from.	Not stated. Publications before 30th May	Case reports, clinical analysis and fundamental research	No	No No	Lab examinations discussed
Seirafianpour	To present an overview of suggestive skin manifestations of COVID-19	No	Setting: Not reported Life stage: not specified Confirmed: not reported	Report virus or drug-related cutaneous manifestations of COVID-19	None reported	3rd May	All studies	No	No No	

Supplement 2

Table 1: Systematic review results summary grouped by type

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
General				
Grant	24,410 adults	148 articles (number of studies and type not reported)	Systemic: fever, fatigue, myalgia, rigors, arthralgia, rash Respiratory: any cough, dry cough, productive cough, dyspnoea, chest pain, haemoptysis, wheeze ENT: sore throat, rhinorrhoea, vertigo / dizziness, nasal congestion, hyposmia, hypogeusia, otalgia GI: diarrhoea, nausea, vomiting, abdominal pain CNS: headache, confusion, ataxia Eyes: conjunctivitis, ophthalmalgia, photophobia	See Table 1, and Figures 2 and 3
Nasiri	5,057	34 studies 5 case series, 3 correspondence, 23 cross-sectional, 3 research letters	Clinical manifestations and comorbidities: fever, cough, dyspnoea, myalgia/fatigue, sputum production, sore throat, headache, diarrhoea, haemoptysis, anorexia, nausea/vomiting, dizziness, chest tightness, rhinorrhoea, chills. Lab abnormalities and complications Radiological characteristics	Tables 3, 4 and 6
Li	281,461	212 studies	General: fever, chills, fatigue, myalgia, malaise Respiratory: cough, expectoration, rhinorrhoea, chest pain, shortness of breath Gastrointestinal: vomiting, abdominal pain, diarrhoea, anorexia, nausea Neurological: dizziness, headache Clinical course and outcomes: ICU, mortality, shock, mechanical ventilation, hepatic injury, renal injury, cardiac injury	TBC
Kaur	6,635	50 articles observational studies, case series, and case reports	Clinical symptoms: Fever, Cough, Fatigue/Myalgia, ,Sputum, Shortness of breath, Headache/dizziness, sore throat, diarrhoea, chills, nausea/vomiting, nasal congestion, Loss of appetite, rhinorrhoea, chest pain, haemoptysis, Impaired consciousness, rigors, Conjunctival congestion, Impaired taste, Impaired smell, Impaired vision, Ataxia, Seizures. Imaging findings Comorbidities	
Age specific – Older adults ≥60 years				
Neumann-Podczaska	4,965	20 studies	Fever, cough, dyspnoea, fatigue, sputum production, chest tightness, diarrhoea, anorexia, fatigue and myalgia, myalgia, nausea and vomiting	See Tables 1 and 4

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
		All studies retrospective but study type not reported		CERQual assessment Table 5
Age specific – Paediatric ≤18 years				
Radia	783	35 papers Study types not mentioned	Gastrointestinal symptoms (abdominal pain, diarrhoea, vomiting), rashes, respiratory tract symptoms (cough, sore throat), fever.	Table 1
Hoang	7,780	131 8 cross-sectional, 75 case series, 48 case reports	a) clinical signs and symptoms (fever, shortness of breath, etc.), b) imaging characteristics (chest x-ray, CT or MRI), c) laboratory findings (CBC, BMP, LFTs, inflammatory markers, etc), d) hospital course/complications (ICU admission, death, organ failure, intubated, etc.), e) treatments provided (antivirals, hydroxychloroquine, etc.)	Tables 4 and 5
Liguoro I	7480	Sixty-two case reports, case series and cohort studies, and three reviews	Asymptomatic Clinical features (mild, moderate, severe, critical) Common symptoms (fever, cough, sore throat, runny nose, dyspnoea) Extra-respiratory symptoms (diarrhoea, vomiting, fatigue)	Table 2
Henry BM	624 (610 mild, 14 severe)	24	27 laboratory parameters	Table 2
Zhang	551	46 articles 26 case series, 20 case reports	Clinical findings: asymptomatic, fever, >39.0^{0}C, cough Radiological findings Laboratory findings	Table 2
Radia	5829	48 studies	Asymptomatic / mild / moderate Clinical presentation: fever, cough, sore throat, tachycardia, rhinorrhoea, nasal congestion, tachypnea, diarrhoea, vomiting, myalgia or fatigue, hypoxemia, chest pain Laboratory examination Imaging features	
Pregnancy				
Allotey	11,432	77 cohort studies: 55 comparative, 22 non-comparative. A cohort study was defined in this review as “as those that sampled participants on the basis of exposure, followed-up participants over time, and ascertained the outcomes”	Symptoms: fever, cough, dyspnoea, myalgia, ageusia, diarrhoea Laboratory findings: raised WCC, lymphopaenia, thrombocytopaenia, abnormal LFT, raised procalcitonin, raised C reactive protein Radiological findings: ground glass appearance, abnormality on CT Also reports maternal and perinatal outcomes. Timing:	Figure 3

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
		Analysis:		
Ear nose and throat				
Agyeman	8,438	24 studies Study type not reported Analysis: random effects	Olfactory dysfunction Gustatory dysfunction Timing: reported for each study	Figures 2 and 3
Tong JY	1,627	10 studies 1 case control, one case series, 8 cross sectional Analysis: random effects	Olfactory dysfunction Gustatory dysfunction Timing: not reported	Table 1 Figures 2 and 3
Samaranayake	11,054	8 studies 3 Case control, 4 cross sectional, 1 case series Analysis: data not pooled	Clinical signs and symptoms in patients with SARS-CoV-2 infected either pre-symptomatic, or symptomatic COVID-19 related oro-facial muco-cutaneous lesions including: 1. Vesiculo-bullous lesions 2. Sotmatitis (focal and generalised), 3. Salivary gland affections including xerostomia, 4. White or red lesions in oro-facial regions 5. Chemosensory dysfunction: Dysgeusia/ ageusia, 6. Chemosensory dysfunction: hyposmia/anosmia Timing: not reported	Table 1
Giorli	Not reported	11 7 cross-sectional, 1 case control, 3 retrospective observational Analysis: did not pool prevalence	Anosmia Timing: not reported	
Almufarrij I	Not reported	5 case reports and 2 cross-sectional studies Analysis: data not pooled	Audio-vestibular symptoms “Reports of audio-vestibular symptoms in confirmed COVID-19 cases are few, with mostly minor symptoms, and the studies are of poor quality.” Includes a large cross-sectional study of 1420 confirmed COVID-19 cases. Lechien et al.	Table 1

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
			Timing: not reported	
Cardiovascular				
Porfidia	3,487	30 studies Four prospective, 22 retrospective, 4 study design unclear. Analysis:	Pulmonary embolism Venous thromboembolism Deep vein thrombosis Timing:	Table 1 Figures 3, 4 and 5
Sabatino	77,317	21 studies All observational; study type otherwise unclear	Outcomes: • Death • cardiovascular symptoms (complications) and cardiovascular events (myocardial injury, angina, arrhythmias or palpitations, acute heart failure, acute myocardial infarction) during the COVID-19-related hospitalization	Fig S5
Cheruiyot	90	27 studies 5 cohort, 5 case series, and 17 case reports	Arterial thrombosis	
Momtazmanesh	10,898	54 studies in qualitative synthesis - 19 were case reports, case series, or pathological reports - 35 in meta-analysis	• Chest pain/tightness and palpitation as one of the initial manifestations • Newly developed: arrhythmia, acute cardiac injury, heart failure • Elevation of cardiac and inflammatory biomarkers: Interleukin-6, CRP, ESR, serum ferritin, NT-pro BNP, D-Dimer, lactate dehydrogenase, cardiac Tn (I or T), myoglobin, creatinine kinase, creatinine kinase-MB, TNF-α	
Shafi	Data not pooled	61 Details not reported in summary form	• Heart failure and cardiogenic shock • Arrhythmias • Cardiac inflammatory and chronic manifestations (myocardial injury, myocarditis, acute coronary syndromes (ACS), and spontaneous coronary artery dissection (SCAD) • Cardiac-specific biomarkers	multiple
Sawalha	14	14 case reports	Myocarditis	
Neurologic				
Uncini	42	33 papers Analysis: data not pooled	Does not pool data. Reports averages.	Tables 1 and 2
Di Carlo	12,157	19 studies Study type unclear: 12 retrospective, single-centre, 5 multi-centre	Central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures),	Tables 4 and 5

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
		Analysis: method not reported	Peripheral nervous system (PNS) manifestations (taste impairment and smell impairment) Muscular injury manifestations (myalgia, muscular pain, fatigue) Timing: clinical symptoms at presentation	
De Sanctis	18	14 papers 13 case reports, 1 case series Analysis: data not pooled	Does not pool data. Timing: clinical characteristics of GBS during illness, including time from symptom onset.	Tables 3 and 4
Wang	4700	41 Analysis: random effects	Unspecific neurologic manifestations: Headache, myalgia, fatigue, nausea, vomiting, confusion, anorexia, dizziness, malaise, dyspnoea/shortness of breath Specific neurologic manifestations (data not pooled but summarised for each study) Timing: not reported	Figure 2 Table 2
Munhoz RP	Not reported	37 Analysis: data not pooled	Cerebrovascular disease, encephalopathy, Guillain-Barre Syndrome, Anosmia/ageusia, myalgia, headache, other manifestations (ataxia, seizures, dizziness). Results reported as narrative. Timing: not reported	Table 1
Nazari [pre-print]	11,282	64 Analysis: method not reported	General symptoms CNS symptoms: headache, dizziness, headache and/or dizziness, impaired consciousness Timing: presenting symptoms	Table 3
Abdullahi	11,069	60 articles (51 for synthesis) 4 case series, 10 case reports, 46 either cohort or cross-sectional Analysis: data not pooled	Neurological: Headache, dizziness, impaired smell sensation, impaired taste sensation, acute cerebrovascular disease, ataxia, seizure, impaired consciousness, impaired vision. Musculoskeletal: myalgia, back pain, muscle weakness, skeletal muscle injury, arthralgia, facial muscle pain	Figure 2
Pinzon	7,559	33 19 cohort, 10 case series or cross-sectional, 4 case reports	Headache, dizziness, nausea with/without vomiting, cerebrovascular disease, consciousness disturbance, muscle problem, cerebrovascular disease comorbidity	Table 1, Figures 2-8

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
		Analysis: random effects		
Gastrointestinal				
Tariq	12,797	78 studies Twelve studies retrospective cohort studies, 1 prospective cohort study, 1 case-control study, remaining 64 = case series. Risk of bias was high in 48 studies, medium in 24 studies, and low in 6 studies. Analysis: fixed effects	Diarrhoea, nausea/vomiting, loss of appetite, abdominal pain Timing: at onset or at admission to hospital.	
Kulkarni	20,874	107 articles Analysis: random effects	Elevated liver chemistries, ALT, AST, albumin, bilirubin, prothrombin time, ALP, GGT, severe liver injury. Distinguishes between at presentation and during illness. Liver injury during illness, others at presentation.	Figures 4, S8, S11, S12a/b, S13a/b, S13c
Kumar	Not stated	128 papers Analysis: random effects	Abnormalities in liver function Timing: not stated if at presentation or during illness.	
Sultan S	10,890	47 studies Analysis: fixed effects	Diarrhoea, nausea/vomiting, abdominal pain, liver manifestations Timing: Reports timing (eg on presentation) for individual studies.	Entire document
Mao	6,686	35 studies Analysis: fixed and random effects	Loss of appetite, diarrhoea, nausea or vomiting, abdominal pain Abnormal levels of liver markers: elevated ALT, elevated AST, increased bilirubin Timing: at diagnosis.	Figures 5 and 6
Eyes				
Sadhu [pre-print]	1257	14 studies 2 retrospective cross-sectional studies and 12 “prospective cross-sectional studies”. Plus 6 case reports (not in meta-analysis)	Conjunctivitis or conjunctival congestion “The most common associated features along with conjunctivitis include epiphoria, foreign body sensation, chemosis, and itching.”	Table 1 and Figure 2
Inomata T	1533	15 studies	Conjunctivitis (unilateral or bilateral), ocular pain, dry eye and floaters. Eyelid dermatitis and keratoconjunctivitis (1 case each)	Table and Figure 3
Renal system				
Yang X	4,963	24	Elevated serum creatinine, elevated BUN, proteinuria, AKI	Figures 2, 3 and 4

First author	Sample	Types of study included (number by type)	System / symptom / clinical manifestation	Results
		Details of study type not reported		
Kunutsor	17,391	22 21 retrospective cohorts, 1 prospective cohort	Protocol states: Acute kidney injury, Proteinuria, Hematuria, Albuminuria, Kidney transplant, Electrolyte disturbance, Acidosis, Alkalosis, Hyperkalemia Reports: AKI, acidosis, electrolyte disturbance, alkalosis, renal replacement therapy	Figures 3 and 4
Dermatological				
Almutairi	555	7 studies 2 prospective, 3 retrospective, 2 case series Analysis: data not pooled	Erythema / erythematous rash, Urticaria, Vesicular eruptions, Varicella-like exanthema / rash, Chilblain-like lesions, Exanthema Livedo, Necrosis, Red-purple papules, Petechiae Timing: not reported	Table 1
Zhao	507	44 articles 38 case reports and 6 publications of ACE2 expression in skin tissues Analysis: data not pooled. Reports averages.	Erythema, Chilblain like lesions, Urticaria like lesions, Vesicular lesions, Livedo/necrosis, Petechiae, Pruritis Timing: reports time from onset of symptoms to onset of skin manifestations	
Seirafianpour		27 articles 19 case reports, 8 case series Analysis: data not pooled. Describes each study separately.	Refer to tables in article Timing: not reported.	Table 1: case reports Table 2: case series

Supplement 3

Results summary

General and age-specific reviews

Table 1: Summary of signs and symptoms for reviews categorised as general (including by age group: older age (≥60 years) children (≤18years)

System	Signs and symptoms	study prevalence % (95%CI)				≥60	≤18				
		Li	Grant	Nasiri	Kaur	Neumann-Podczaska	Radia (MIS-C)	Hoang	Liguoro I	Zhang	Cui
Asymptomatic	Nil							19.3%	15.1%	18% (11%–27%	20% (14%–26%)
Systemic	Fever	78.8% (76.2%–81.3%)	78% (75%–81%	83.0% (77.5%–87.6%)	80.3%	83.6%	99.5%	59.1%	51.6%	53% (45%–61%)	51% (45%–57%)
	>39.0^{0}C									7% (4%–10%)	
	Fatigue	32.2%	31%			19.9%			10.6%		
	Myalgia	21.3%	17%			4.6%					
	Fatigue/myalgia (weakness)			34.7%	36.5%	8.0%		18.7%		5% (0%–13%)	12% (7%–17%)
	Rigors		18% (13%–22%)		0.36%						
	Arthralgia		11% (8%–14%)								
	Rash		0% (0%–1%)				42.1%	0.25%			
	Chills	15.7% (12.3%–19.7%)		14.3% (3.0%–47.4%)	7.2%						
	Malaise	37.9% (29.5%–47.1%)									

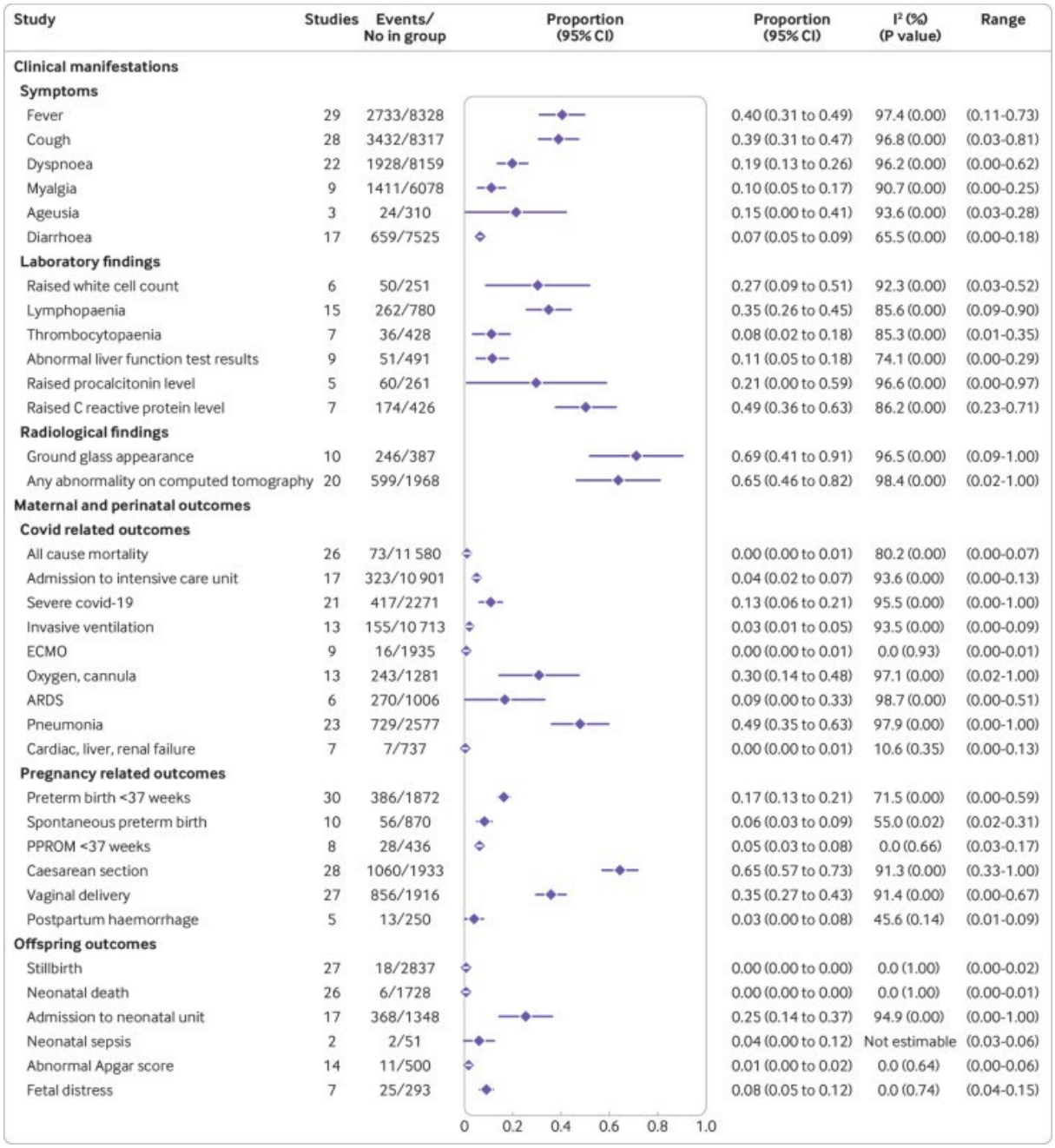
System	Signs and symptoms	study prevalence % (95%CI)				≥60	≤18				
		Li	Grant	Nasiri	Kaur	Neumann-Podczaska	Radia (MIS-C)	Hoang	Liguoro I	Zhang	Cui
Respiratory	Cough (dry or productive)					62.7%	4.5%	55.9%	47.3%	39% (30%–47%)	41% (35%–47%)
	Sputum production					17.7%					
	Dyspnoea					25.5%		11.7%	7.7%		
	Tachypnoea / dyspnoea									8% (2%–15%)	9% (4%–14%)
	Chest pain / tightness					15.3%					3% (0%–5%)
	Haemoptysis										
	Wheeze										
Cardiovascular	Tachycardia										12% (3%–21%)
Gastrointestinal	Diarrhoea	9.5% (7.8%–11.5%)	10% (8%–12%)	5.7% (3.8%–8.6%)	9.4%	13.0%	27.3%		9.7%	8% (3%–14%)	8% (6%–11%)
	Abdominal pain	4.5% (3.3%–6.2%)	4% (2%–7%)				36.4%				
	Diarrhoea / abdominal pain							6.5%			
	Nausea	6.96% (5.3%–9.1%)	6% (3%–10%)								
	Vomiting	4.7% (3.8%–5.8%)	4% (2%–8%)				25.0%		7.2%	2% (0%–5%)	7% (5%–10%)
	Nausea / vomiting			5% (2.3%–10.7%)	5.2%	4.4%		5.4%			
	Anorexia / loss of appetite	13.99%		10.1%	2.0%	8.4%		1.7%			

System	Signs and symptoms	study prevalence % (95%CI)				≥60	≤18				
		Li	Grant	Nasiri	Kaur	Neumann-Podczaska	Radia (MIS-C)	Hoang	Liguoro I	Zhang	Cui
	Decreased oral intake	(10.4%–18.5%)		(1.0%–57.2%)							
Neurological / CNS	Headache	9.7% (8.3%–11.3%)	13% (10%–16%)	11.1% (7.7%–15.7%)						3% (0%–12%)	
	Dizziness	9.4% (7.1%–12.4%)		8.6% (2.5%–26.0%)							
	Headache / dizziness				12.9%			4.3%			
	Confusion		11% (7%–15%)								
	Ataxia		0% (0%–2%)								
	Impaired consciousness				0.38%						
Ear, nose and throat	Sore throat		12% (10%–14%)	14.5% (10.6%–19.5%)	9.6%		4.1%	18.2%	17.9%		16% (7%–25%)
	Pharyngeal erythema							3.3%			
	Sore throat / pharyngeal erythema									14% (4%–28%)	
	Rhinorrhoea	7.5% (5.7%–9.6%)	8% (5%–12%)	9.3% (2.2%–31.0%)	1.1%				7.7%		14% (8%–19%)
	Nasal congestion		5% (3%–7%)		3.1%						17% (6%–27%)
	Rhinorrhoea / nasal congestion							20.0%		7% (3%–14%)	

System	Signs and symptoms	study prevalence % (95%CI)				≥60	≤18				
		Li	Grant	Nasiri	Kaur	Neumann-Podczaska	Radia (MIS-C)	Hoang	Liguoro I	Zhang	Cui
	(nasal symptoms)										
	Vertigo / dizziness		11% (6%–16%)								
	Hyposmia / anosmia (impaired smell)		25% (4%–55%)		0.18%						
	Hypogeusia (impaired taste)		4% (1%–8%)		0.18%						
	Otalgia		4% (1%–11%)								
Eyes	Conjunctivitis (unilateral or bilateral)		2% (1%–4%)								
	Ophthalmalgia		4% (3%–6%)								
	Photophobia		3% (2%–4%)								
	Impaired vision				0.05%						
	Conjunctival congestion				0.29%						

Pregnancy

Table 2: Rates of clinical manifestations of COVID-19 in pregnant women and recently pregnant women with suspected or confirmed COVID-19 and associated maternal and perinatal outcomes (Extracted Figure 3 from Allotey)



Study	Studies	Events/ No in group	Proportion (95% CI)	Proportion (95% CI)	I^2 (%) (P value)	Range
Clinical manifestations						
Symptoms						
Fever	29	2733/8328		0.40 (0.31 to 0.49)	97.4 (0.00)	(0.11-0.73)
Cough	28	3432/8317		0.39 (0.31 to 0.47)	96.8 (0.00)	(0.03-0.81)
Dyspnoea	22	1928/8159		0.19 (0.13 to 0.26)	96.2 (0.00)	(0.00-0.62)
Myalgia	9	1411/6078		0.10 (0.05 to 0.17)	90.7 (0.00)	(0.00-0.25)
Ageusia	3	24/310		0.15 (0.00 to 0.41)	93.6 (0.00)	(0.03-0.28)
Diarrhoea	17	659/7525		0.07 (0.05 to 0.09)	65.5 (0.00)	(0.00-0.18)
Laboratory findings						
Raised white cell count	6	50/251		0.27 (0.09 to 0.51)	92.3 (0.00)	(0.03-0.52)
Lymphopaenia	15	262/780		0.35 (0.26 to 0.45)	85.6 (0.00)	(0.09-0.90)
Thrombocytopaenia	7	36/428		0.08 (0.02 to 0.18)	85.3 (0.00)	(0.01-0.35)
Abnormal liver function test results	9	51/491		0.11 (0.05 to 0.18)	74.1 (0.00)	(0.00-0.29)
Raised procalcitonin level	5	60/261		0.21 (0.00 to 0.59)	96.6 (0.00)	(0.00-0.97)
Raised C reactive protein level	7	174/426		0.49 (0.36 to 0.63)	86.2 (0.00)	(0.23-0.71)
Radiological findings						
Ground glass appearance	10	246/387		0.69 (0.41 to 0.91)	96.5 (0.00)	(0.09-1.00)
Any abnormality on computed tomography	20	599/1968		0.65 (0.46 to 0.82)	98.4 (0.00)	(0.02-1.00)
Maternal and perinatal outcomes						
Covid related outcomes						
All cause mortality	26	73/11 580		0.00 (0.00 to 0.01)	80.2 (0.00)	(0.00-0.07)
Admission to intensive care unit	17	323/10 901		0.04 (0.02 to 0.07)	93.6 (0.00)	(0.00-0.13)
Severe covid-19	21	417/2271		0.13 (0.06 to 0.21)	95.5 (0.00)	(0.00-1.00)
Invasive ventilation	13	155/10 713		0.03 (0.01 to 0.05)	93.5 (0.00)	(0.00-0.09)
ECMO	9	16/1935		0.00 (0.00 to 0.01)	0.0 (0.93)	(0.00-0.01)
Oxygen, cannula	13	243/1281		0.30 (0.14 to 0.48)	97.1 (0.00)	(0.02-1.00)
ARDS	6	270/1006		0.09 (0.00 to 0.33)	98.7 (0.00)	(0.00-0.51)
Pneumonia	23	729/2577		0.49 (0.35 to 0.63)	97.9 (0.00)	(0.00-1.00)
Cardiac, liver, renal failure	7	7/737		0.00 (0.00 to 0.01)	10.6 (0.35)	(0.00-0.13)
Pregnancy related outcomes						
Preterm birth <37 weeks	30	386/1872		0.17 (0.13 to 0.21)	71.5 (0.00)	(0.00-0.59)
Spontaneous preterm birth	10	56/870		0.06 (0.03 to 0.09)	55.0 (0.02)	(0.02-0.31)
PPROM <37 weeks	8	28/436		0.05 (0.03 to 0.08)	0.0 (0.66)	(0.03-0.17)
Caesarean section	28	1060/1933		0.65 (0.57 to 0.73)	91.3 (0.00)	(0.33-1.00)
Vaginal delivery	27	856/1916		0.35 (0.27 to 0.43)	91.4 (0.00)	(0.00-0.67)
Postpartum haemorrhage	5	13/250		0.03 (0.00 to 0.08)	45.6 (0.14)	(0.01-0.09)
Offspring outcomes						
Stillbirth	27	18/2837		0.00 (0.00 to 0.00)	0.0 (1.00)	(0.00-0.02)
Neonatal death	26	6/1728		0.00 (0.00 to 0.00)	0.0 (1.00)	(0.00-0.01)
Admission to neonatal unit	17	368/1348		0.25 (0.14 to 0.37)	94.9 (0.00)	(0.00-1.00)
Neonatal sepsis	2	2/51		0.04 (0.00 to 0.12)	Not estimable	(0.03-0.06)
Abnormal Apgar score	14	11/500		0.01 (0.00 to 0.02)	0.0 (0.64)	(0.00-0.06)
Fetal distress	7	25/293		0.08 (0.05 to 0.12)	0.0 (0.74)	(0.04-0.15)

Ear Nose and Throat

Table 3: Ear Nose and Throat manifestations (reported in ENT-specific reviews)

Manifestation	**Study** Prevalence %; 95%CI	
	Agyeman (Random effects)	**Tong** (Random effects)
Olfactory dysfunction	41.0% (28.5%–53.9%)	52.73% (29.64%–75.23%)
Gustatory dysfunction	38.2% (24.0%–53.6%)	43.93% (20.46%–68.95%)
Studies evaluating olfactory dysfunction using non-validated instruments		36.64% (18.31%–57.24%)
Studies evaluating olfactory dysfunction using validated instruments		86.60% (72.95%–95.95%)

Table 4: ENT signs and symptoms (reported in "general" systematic reviews)

Signs and symptoms	**study prevalence % (95%CI)**				**>= 60**	**<= 18**				
	Li	**Grant**	**Nasiri**	**Kaur**	**Neumann-Podczaska**	**Radia (MIS-C)**	**Hoang**	**Liguoro I**	**Zhang**	**Cui**
Sore throat		12% (10%–14%)	14.5% (10.6%–19.5%)	9.6%		4.1%	18.2%	17.9%		16% (7%–25%)
Pharyngeal erythema							3.3%			
Sore throat / pharyngeal erythema									14% (4%–28%)	
Rhinorrhoea	7.5% (5.7%–9.6%)	8% (5%–12%)	9.3% (2.2%–31.0%)	1.1%				7.7%		14% (8%–19%)
Nasal congestion		5% (3%–7%)		3.1%						17% (6%–27%)
Rhinorrhoea / nasal congestion							20.0%		7% (3%–14%)	

Signs and symptoms	study prevalence % (95%CI)				>= 60	<= 18				
	Li	Grant	Nasiri	Kaur	Neumann-Podczaska	Radia (MIS-C)	Hoang	Liguoro I	Zhang	Cui
Vertigo / dizziness		11% (6%–16%)								
Hyposmia / anosmia (impaired smell)		25% (4%–55%)		0.18%						
Hypogeusia (impaired taste)		4% (1%–8%)		0.18%						
Otalgia		4% (1%–11%)								

Cardiovascular

Table 5: Cardiovascular manifestations

Manifestation	**Study** Prevalence %; 95%CI				
	Porfidia	Sabatino	Cheruiyot	Momtazmanesh	**Cui**[1]
(Acute) heart failure		1.96% (0.94%–3.4%)		23.7% (19.3%–28.0%)	
Acute cardiac injury				25.3% (19.5%–31.1%)	
Angina		10.2% (3.2%–20.5%)			
Arrhythmias or palpitations		18.4% (7.8%–32.3%)			
Arrhythmia				26.1% (5.9%–46.4%)	
Arterial thrombosis			4.4% (2.8%–6.4%)		
Cardiovascular complications		14.1% (10.3%–20.2%[2])			
Chest pain / chest tightness (initial manifestation)				21.8% (8.5%–35.0%)	
Deep vein thrombosis	14% (1%–75%)				
Myocardial infarction		3.5% (2.1%–5.4%)			
Myocardial injury		10.3% (6.7%–14.6%)			
Palpitation (initial manifestation)				9.1% (6.2–%12.1%)	
Pulmonary embolism	12% (2%–46%)				

[1] Cui is a "general" review
[2] See S5 Fig. Cardiovascular complications

Tachycardia					12% (3%-21%)
Venous thromboembolism	26% (6%-66%)				

Table 6: Elevation of cardiac and inflammatory biomarkers (Extracted from Table 1, Momtazmanesh)

Condition	Number of included studies	Total study population (event) number	Pooled estimated prevalence (95% CI)	Test of heterogeneity	
				I^2	*p*
Elevation of cardiac and inflammatory biomarkers					
Interleukin- 6	3	574 (391)	65.9% (55.2%, 76.5%)	86%	<0.001
CRP	12	3227 (2008)	75.4 % (66%, 84%)	99%	<0.001
ESR	3	767 (547)	71.8% (59.0%, 84.6%)	92%	<0.001
serum ferritin	3	538 (375)	70.3% (61.1%, 79.6%)	81%	0.006
NT-pro BNP	7	1047 (311)	46.5% (28.9%, 64.2%)	98%	<0.001
D-Dimer	8	4789 (2050)	41.5% (31.0%, 52.1%)	97%	<0.001
Lactate dehydrogenase	9	2026 (774)	41.0% (28.8%, 53.2%)	97%	<0.001
Cardiac Tn (I or T)	10	1718 (366)	25.3% (17.6%, 33.1%)	94%	<0.001
myoglobin	5	1076 (176)	19.1% (11.6%, 26.6%)	91%	<0.001
Creatine kinase	10	1617 (230)	15.9% (10.5%, 21.3%)	90%	<0.001
Creatine kinase-MB	2	382 (302)	66.2% (6.9%-100.0%[a])	99%	<0.001
TNF-α	2	275(472)	58.3% (53.8%-62.7%)	0%	0.7

Abbreviations: *NT-pro BNP* N-terminal pro B-type natriuretic peptide, *CRP* C-Reactive Protein, *Tn* troponin, *TNF-α* Tumor Necrosis Factor-α

[a]Due to the high heterogeneity the upper limit of 95% CI was higher than 100%

Neurological

Table 7: Neurological manifestations

Manifestation	**Study** Prevalence %; 95%CI											
	Wang	Di Carlo	Nazari [pre-print]	Abdullahi	Pinzon	Li	Grant	Nasiri	Kaur	Hoang	Zhang	Liotta
Cerebrovascular disease (acute)				3% (1%–5%)*	4.4% 1.92%–7.91%)*							
Ataxia							0 (0–2%)*					
Confusion	5.2% (-1.7%–12.2)						11% (7%–15%)					
Dizziness	10% (5.9%–14.2%)	6.1% (5.1%–7.1%)	5.9% (3.7%–8.2%)	10% (3%–19%)*	8.77% (5.02%–13.43%)	9.4% (7.1%–12.4%)		8.6% (2.5%–26.0)				29.7%
Encephalopathy												
Epilepsy												
Fatigue	33.2% (23.1%–43.3%)	24.8% (23.2%–26.4%)										
Fatigue or myalgia		30.5% (25.9%–35.1%)										
Guillain-Barre Syndrome												
Gustatory disorders		52.3% (48.7%–55.8%)		33% (0%–91%)*								15.9%
Headache	9.2% (7.2%–11.2%)	7.5% (6.6%–8.4%)	8.7% (6.8%–10.8%)	12% (9%–15%)	10.9% (8.62%–13.51%)	9.7% (8.3%–11.3%)	13% (10%–16%)	11.1% (7.7%–15.7%)			3% (0%–12%)	37.7%
Headache and / or dizziness			9.8% (7.3%–12.2%)						12.9%	4.3%		

Manifestation	Study Prevalence %; 95%CI											
	Wang	Di Carlo	Nazari [pre-print]	Abdullahi	Pinzon	Li	Grant	Nasiri	Kaur	Hoang	Zhang	Liotta
Impaired consciousness			1.9% (1.0%–2.8%)	2% (1%–2%)*	3.8% (0.16%–12.04%)*				0.38%			
Impaired vision												
Myalgia / muscle injury	16% (12.3%–19.8%)	15.7% (14.4%–17.1%)		19% (16%–23%)	19.2% (15.4%–23.2%)							44.8%
Nausea with/out vomiting					4.6% (3.17%–6.27%)							
Olfactory disorders		46.8% (43.5%–50.2%)		35.0% (0%–94%)*								11.4%
Seizure												

Note: the following reviews report on other neurological outcomes but data from individual studies was not pooled: Wang, De Sanctis, Uncini, Munhoz. Values presented without confidence intervals are averages not calculated in a meta-analysis. An asterisk * denotes a very small number of studies.

Gastrointestinal

Table 8: Gastrointestinal manifestations

	Prevalence reported by systematic reviews focused on GI Pooled prevalence % (95%CI)					
Manifestation	Tariq *(fixed effects)*	Kumar[3] *(random effects)*	Sultan [4] *(fixed effects)*	Mao *(random effects)*	Mao *(fixed effects)*	Kulkarni [5] *(random effects)*
Diarrhoea	12.4% (8.2%–17.1%)	9%	7.7% (7.2%–8.2%)	9% (6%–12%)	8% (8%–9%)	
Abdominal pain	6.2% (2.6% to 10.3%)	4%	3.6% (3.0%–4.3%) Excl China 5.3% (4.2%–6.6%)	3% (2%–5%)	4% (3%–4%)	
Nausea and/or vomiting	9.0% (5.5%–12.9%)	5%	7.8% (7.1%–8.5%) Excl China 14.9% (13.3%–16.6%)	6% (5%–9%)	9% (8%–10%)	
Loss of appetite / anorexia / decreased oral intake	22.3% (11.2%–34.6%)			21% (9%–44%)	23% (22%–25%)	
Severe liver injury (during illness)						10.7% (3%–32.1%)
Acute hepatic injury		23.70% (16.3%–33.1%)				
Elevated liver chemistries						23.1% (19.3%–27.3%)
Elevated liver chemistries (during illness)						24.4% (13.5%–40%)
Elevated ALT		23.28% (19.92%–27.01%)	15.0% (13.6%–16.4%)	18% (13%–25%)	22% (20%–24%)	17.9% (15.3%–21%)
Elevated AST		23.41% (18.84%–28.70%)	15.0% (13.6%–16.5)	21% (14%–29%)	23% (21%–24%)	22.5% (18.1%–27.6%)
Low albumin				6% (3%–11%)	6% (3%–11%)	55% (42.8%–67.6%)
Hyperbilirubinaemia / abnormal bilirubin		10.98%	16.7%	6%	9%	13.4%

[3] Clinical symptoms appear to have been averaged rather than meta-analysed

[4] It is important to note the subgroup differences in this review: e.g. the pooled prevalence of diarrhoea in studies from countries other than China was much higher at 18.3% (95% CI, 16.6%–20.1%); and slightly higher in hospitalised patients at 10.4% (95% CI, 9.4%–10.7%).

[5] This review only included studies that themselves included patients with pre-existing liver disease

	Prevalence reported by systematic reviews focused on GI Pooled prevalence % (95%CI)					
Manifestation	Tariq *(fixed effects)*	Kumar[3] *(random effects)*	Sultan [4] *(fixed effects)*	Mao *(random effects)*	Mao *(fixed effects)*	Kulkarni [5] *(random effects)*
		(6.9%–17.1%)	(15.0%–18.5%)	(3%–13%)	(7%–10%)	(9%–19.4%)
Prothrombin time prolongation						9.7% (4.6%–19.2%)
Elevated ALP		7.48% (3.91%–13.8%)				6.1% (2.4%–14.2%)
Elevated GGT		27.9% (18.2%–40.3%)				21.1% (12.8%–32.9%)

Table 9: Gastrointestinal signs and symptoms (reported in "general" systematic reviews)

Signs and symptoms	**study prevalence % (95%CI)**				**>= 60**	**<= 18**				
	Li	Grant	Nasiri	Kaur	Neumann-Podczaska	Radia **(MIS-C)**	Hoang	Liguoro I	Zhang	Cui
Diarrhoea	9.5% (7.8%–11.5%)	10% (8%–12%)	5.7% (3.8%–8.6%)	9.4%	13.0%	27.3%		9.7%	8% (3%–14%)	8% (6%–11%)
Abdominal pain	4.5% (3.3%–6.2%)	4% (2%–7%)				36.4%				
Diarrhoea / abdominal pain							6.5%			
Nausea	6.96% (5.3%–9.1%)	6% (3%–10%)								
Vomiting	4.7% (3.8%–5.8%)	4% (2%–8%)				25.0%		7.2%	2% (0%–5%)	7% (5%–10%)
Nausea / vomiting			5% (2.3%–10.7%)	5.2%	4.4%		5.4%			
Anorexia / loss of appetite Decreased oral intake	13.99% (10.4%–18.5%)		10.1% (1.0%–57.2%)	2.0%	8.4%		1.7%			

Ophthalmic

Table 10: Ophthalmic manifestations

	Study Prevalence %; 95%CI			
Manifestation	**Sadhu [pre-print]**	**Inomata T**	**Grant**	**Kaur**
Conjunctivitis or conjunctival congestion	5.17% (2.9%–8.04%)			
Conjunctivitis as an initial symptom (subgroup)	0.858% (0.31%–1.67%)			
Conjunctivitis			2% (1%–4%)	
Ocular symptoms		11.2% (5.5%–16.9%)		
Ophthalmalgia			4% (3%–6%)	
Photophobia			3% (2%–4%)	
Impaired vision				5%

Note: Of the 11.2% of patients with COVID-19 exhibiting ocular symptoms in the Inomata review, "unilateral or bilateral conjunctivitis was the leading symptom (86.4%, 38/44 cases), followed by ocular pain (34.4%, 31/90 cases), dry eye (33.3%, 5/15 cases), and floaters (6.7%, 1/15 cases)".

*Figure 1: **A** – Estimated pooled prevalence of conjunctivitis; **B** – Pooled prevalence of conjunctivitis as an initial symptom (extracted Figures 2A and 2B, from Sadhu)*

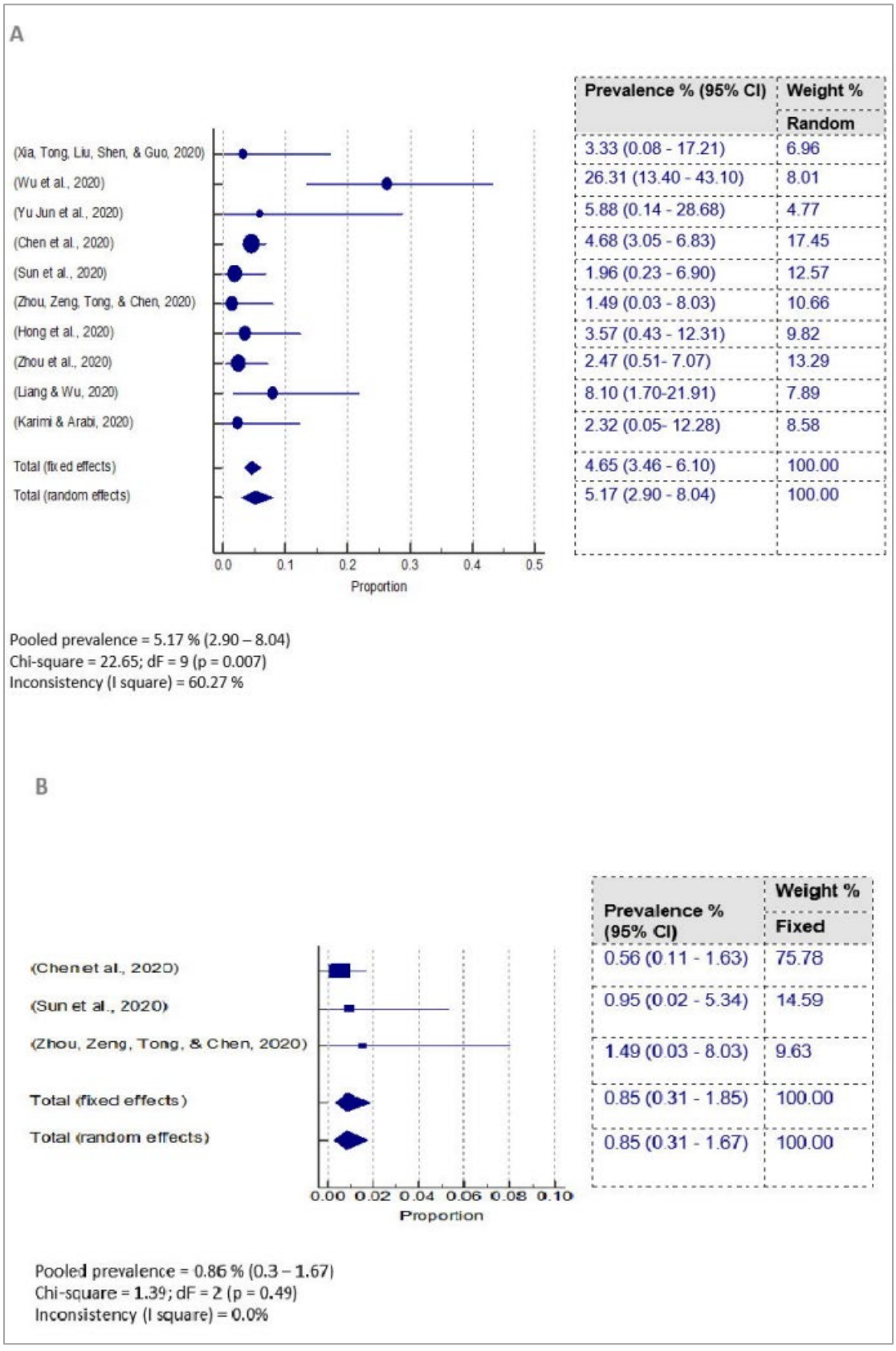
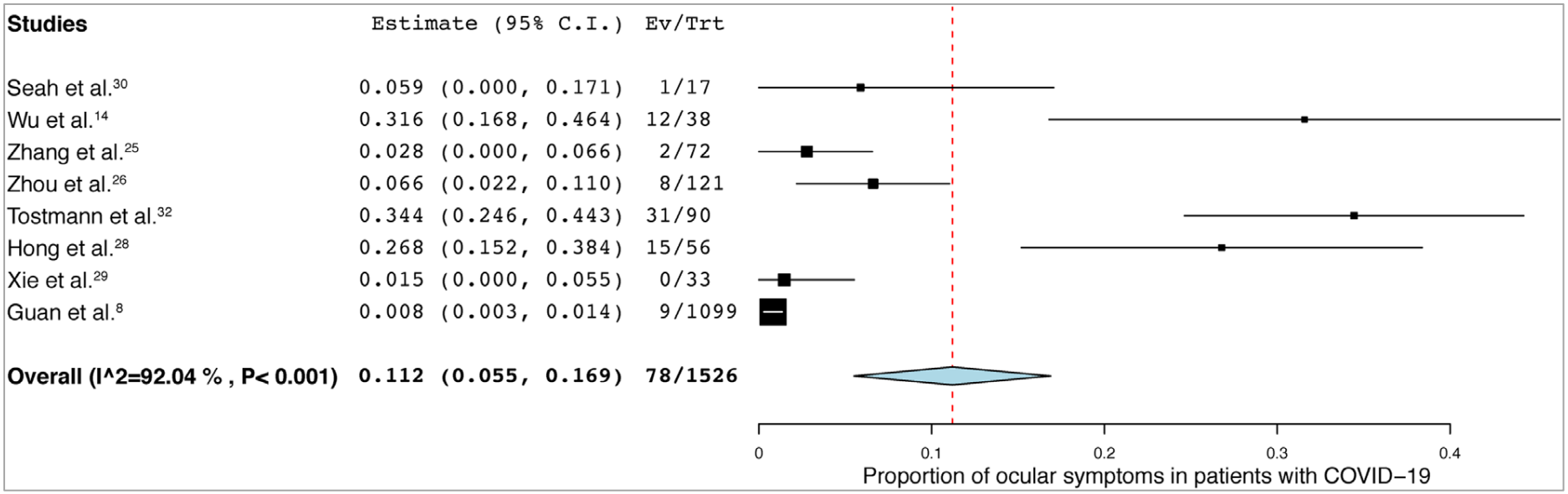


Figure 2: Proportion of ocular symptoms in patients with COVID-19 (Extracted Figure 3, from Inomata)



Renal

Table 11: Renal manifestations

Manifestation	**Study** Prevalence %; 95%CI	
	Kunutsor	Yang X
Acute Kidney Injury (AKI)	11.0% (7.4%–15.1%)	4.5% (3.0%–6.0%)
AKI by COVID-19 severity • Mild-moderate • Severe • Critical		• 1.3% (0.2%–2.6%) • 2.8% (1.4%–4.2% • 36.4% (14.6%–58.3%)
Acidosis	5% (3.2%–7.2%)	
Electrolyte disturbance	12.5% (10.1%–15.0%)	
Alkalosis	6.9% (4.5%–10.6%)	
(continuous) Renal replacement therapy (CRRT/RRT)	6.8% (1.0%–17.0%)	
Elevated serum creatinine		9.6% (5.7%–13.5%)
Elevated BUN		13.7% (5.5%–21.9%)
Proteinuria		57.2% (40.6%–73.8%)

Figure 3: AKI by COVID-19 severity (Extracted Figure 5, from Yang)

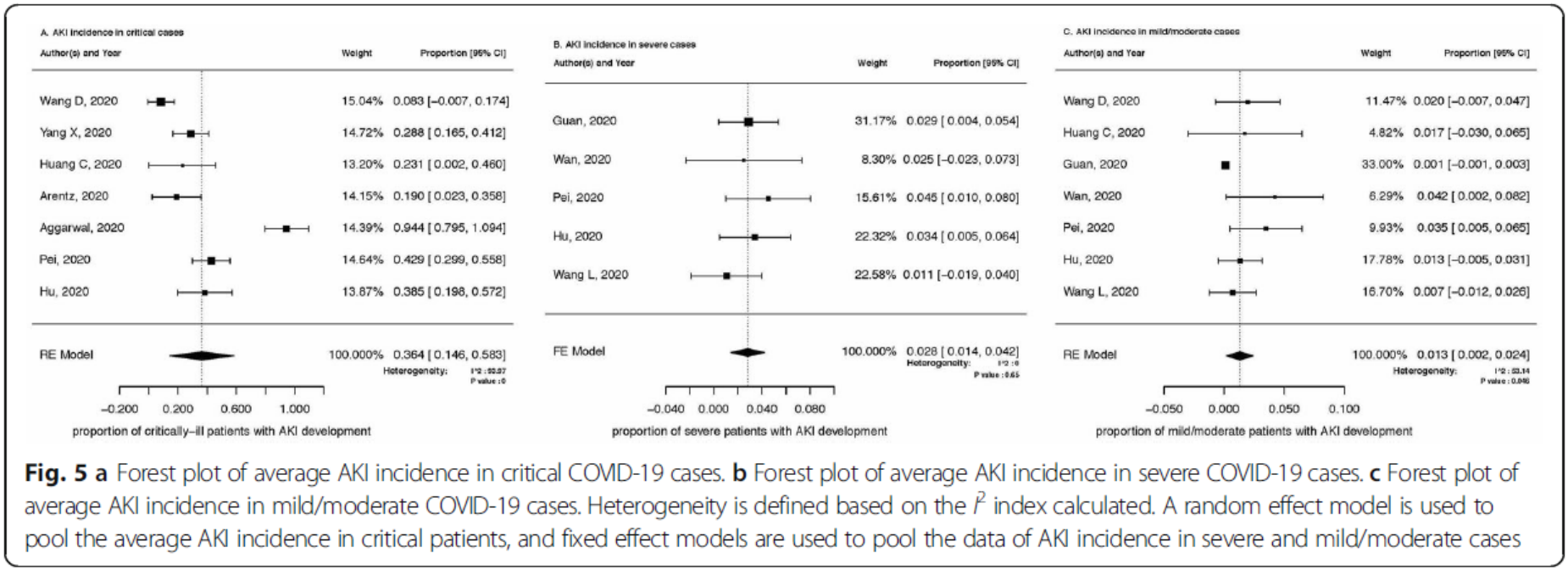


Fig. 5 a Forest plot of average AKI incidence in critical COVID-19 cases. **b** Forest plot of average AKI incidence in severe COVID-19 cases. **c** Forest plot of average AKI incidence in mild/moderate COVID-19 cases. Heterogeneity is defined based on the I^2 index calculated. A random effect model is used to pool the average AKI incidence in critical patients, and fixed effect models are used to pool the data of AKI incidence in severe and mild/moderate cases

Figure 4: Incidence of renal complications in COVID-19 patients (Extracted Figure 3, from Kunutsor)

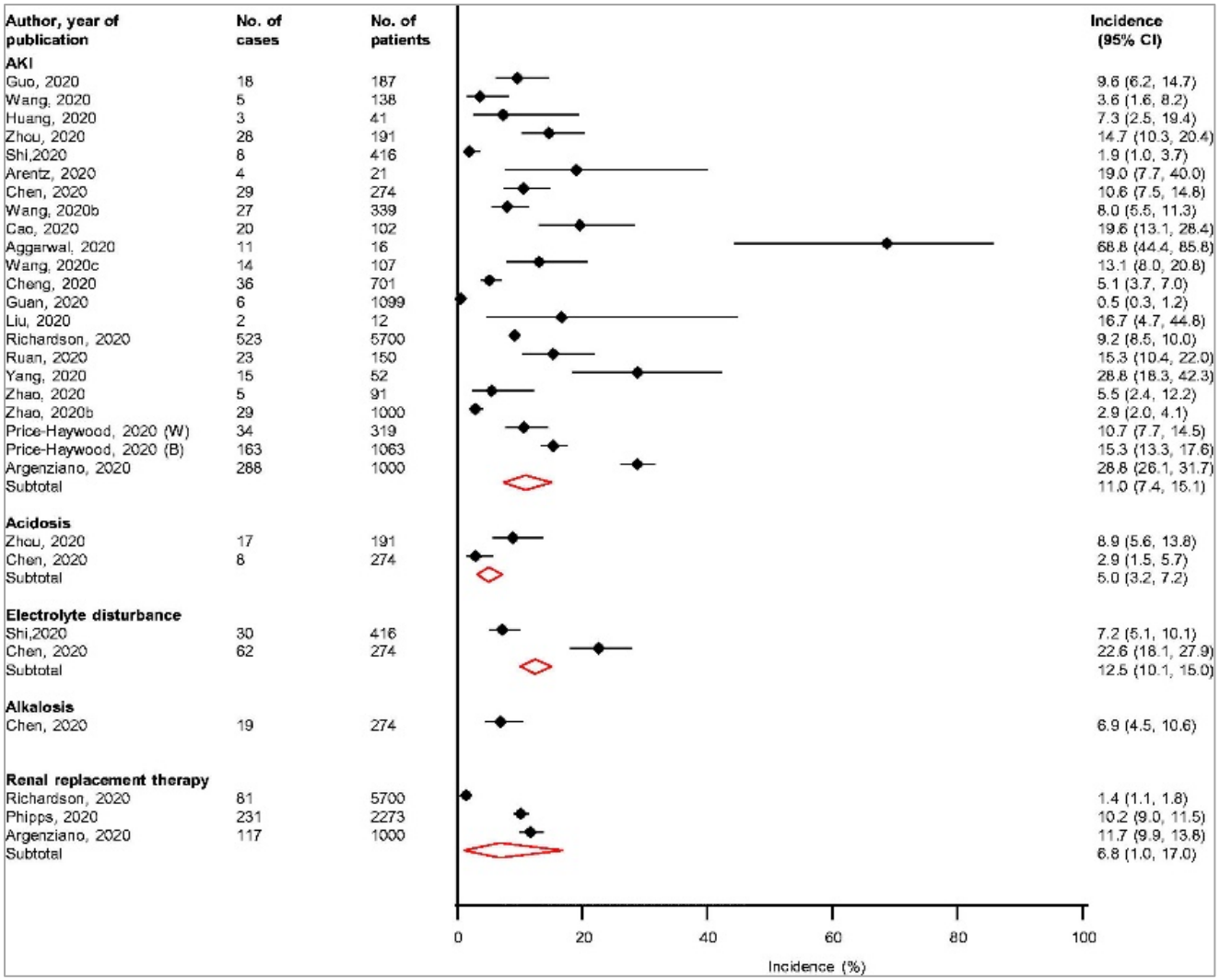
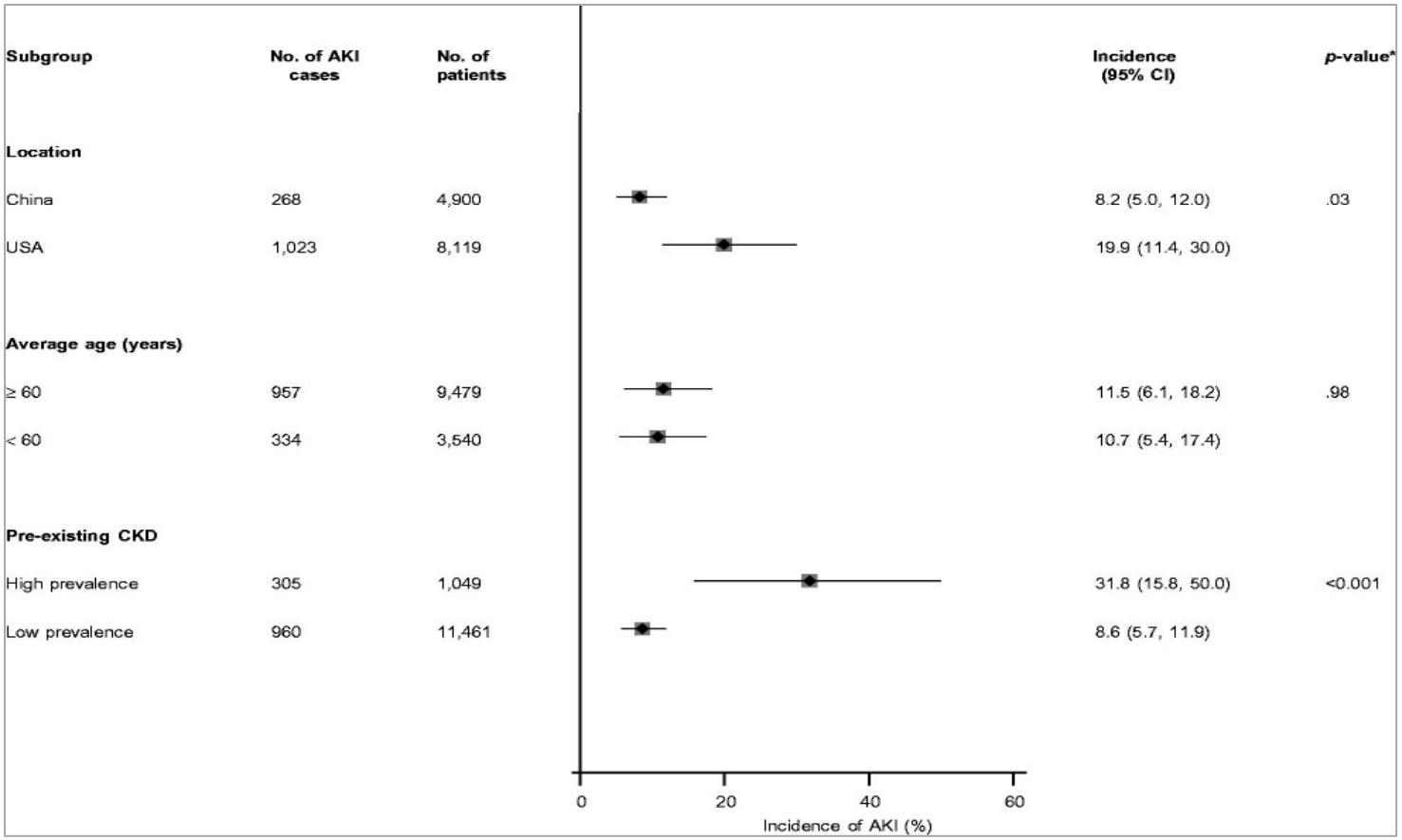


Figure 5: Incidence of AKI in COVID-19 patients by clinically relevant characteristics (Extracted Figure 4, from Kunutsor)



Dermatological

No pooled results available.

Table 22: Summary of skin lesions (Extracted data from Table 1, Zhao)

Mean time of appearance of skin lesions after onset of COVID-19 (range), days	9.92 (1–30)
Cutaneous manifestations (*n* = 507), *n* (%)	
Erythema	224 (44.18%)
Chilblain-like lesions	100 (19.72%)
Urticaria-like lesions	83 (16.37%)
Vesicular	66 (13.02%)
Livedo/necrosis	31 (6.11%)
Petechiae	8 (1.58%)
Accompanied by pruritus	227 (44.77%)
Mean duration of skin lesions, days	9.10