Evidence review

Assessment of COVID-19 in primary care:

the identification of symptoms, signs, characteristics, comorbidities and clinical signs in adults, children and young people, which may indicate a higher risk of progression to severe disease

Date first published: 07/05/2020

Revised: 21/07/2020; 03/02/2021

Publication date of this version: 03/02/2021

Version number: 3

Summary of revisions

Date	Version	Revisions
January 2021	3	**Key findings**: *Occupation as health or social care worker* added as a characteristic significantly associated with severe disease. *Chronic liver disease* – changed from 'evidence of association is unclear' to 'associated with severe disease'. *Severe mental illness, learning difficulties, Down's Syndrome, neurological conditions* and *dementia* added to comorbidities and risk factors associated with severe disease. Advice on *pregnancy* added to key findings. **Section 2**: Previous section 6, *Method of patient consultation*, merged with the section on prognostic tools (section 2). Table 2: Revised to incorporate Scottish and UK data. *Pregnancy*, *occupation, mental illness and learning difficulties* – new categories created. Table 3: Revised to incorporate UK-based studies. Sections 5 and 6: New sections on *signs, symptoms and comorbidities associated with severe COVID-19 in children and young people.*
08/12/2020	2	Hyperlink to COVID-19 Scottish Primary Care Hub Triage Guide updated.
21/07/2020	2	**Key findings**: addition of 'silent' hypoxia, changed 'Asian ethnicity' to 'minority ethnic background', addition of smoking and solid organ transplantation to list of comorbidities/risk factors associated with severe disease, separation of immunosuppressive conditions and immunosuppressive medications, promotion of socioeconomic status and frailty as potentially associated with poor outcomes **Signs and symptoms**: minor text revisions and addition of sentence on 'silent' hypoxia. **Table 2:** In general, addition of new evidence and published revisions to preprint evidence *Socioeconomic status* – changed from no reported evidence to significantly associated with severe disease *Smoking* – changed from 'evidence of association is unclear' to 'significantly associated with severe disease' *Chronic liver disease* – changed from 'has not been associated with severe disease' to 'evidence of association is unclear' *Chronic respiratory disease* – changed 'evidence of association is unclear' to 'significantly associated with severe disease' *Frailty* – addition of 'significantly associated with sever disease' *Immunosuppressive conditions* – new category created *Solid organ transplants* – new category created **Table 3:** published revisions to preprint evidence **Section 6.2.1**: new section added on updates to literature review **Section 6.5**: new peer reviewers contributing to updated version of synthesis added
07/05/2020	1	Original version

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Introduction

The purpose of this rapid review is to provide NHSScotland with advice on assessment of patients with acute COVID-19 in primary care. The review does not address the management of long-term effects of COVID-19.

This guidance is for: general practitioners and primary care teams involved in the assessment of patients presenting with potential COVID-19.

Since the outbreak of coronavirus, there has been an abundance of rapid and systematic reviews published on the diagnosis and management of people with symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, mostly from a secondary care (hospital) perspective. About 80% of people with COVID-19 have symptoms which have been described as mild (no pneumonia manifestations/hospitalisation) or asymptomatic.[1] Others develop severe disease (defined as requiring admission to an intensive care unit (ICU)).

The challenge for primary care practitioners is to identify and triage patients presenting with potential COVID-19, a disease in which the pattern and duration of symptoms is heterogeneous. This is compounded by the need to conduct consultations by telephone or video. In addition, the evidence base is not robust and is subject to change as new evidence emerges.

The COVID-19 Scottish Primary Care Hub Triage Guide lists the common symptoms, and provides red flags for those requiring immediate assessment and yellow flags for those at a higher risk of deterioration (eg certain comorbidities).

We conducted a search for new evidence on prognostic indicators, risk factors and clinical measures to identify people self-managing symptoms of COVID-19 in the community whose symptoms may change or worsen, and therefore may require monitoring or clinical intervention after their initial presentation to primary care. The research question and methodology can be found in section 8.

At the time of update (February 2021), there are several new variants of SARS-CoV-2 which are being investigated for their potential increased transmissibility. It is currently unclear if these variants have any impact on the severity of disease and there has been no evidence which explores the impact of individual variants on disease severity or risk factors.

KEY FINDINGS

Primary care clinicians should consider using the COVID-19 Scottish Primary Care Hub Triage Guide to inform initial consultations with patients presenting with potential COVID-19.

In most patients who develop severe disease, their condition typically deteriorates in the second week of symptoms.

Symptoms, characteristics, comorbidities and clinical signs in adults which may indicate a higher risk of progression to severe disease are as follows:

- The only symptom identified which may distinguish severe disease is shortness of breath/dyspnoea. Some patients with hypoxia may not experience shortness of breath. *(Table 1)*
- The clinical sign most indicative of severe disease is low oxygen saturation. *(Table 3)*
- Characteristics which have been associated with severe disease are older age, male sex, minority ethnic background, and occupation as health or social care worker. Older age is the strongest predictor. *(Table 2)*
- Comorbidities/risk factors most associated with severe disease are smoking, hypertension, cardiovascular disease, diabetes, obesity, stroke, chronic respiratory disease, chronic kidney disease, chronic liver disease, cancer, solid organ transplantation, frailty, severe mental illness, learning difficulties, Down's Syndrome, neurological conditions and dementia. *(Table 2)*
- Rheumatoid arthritis, psoriatic arthritis, lupus and other immunosuppressive conditions are significantly associated with severe disease. There was mixed evidence of any association between steroids, use of immunosuppressant medication, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor type 1 (AT1) antagonists and severe COVID-19 disease but very few studies have investigated this. *(Table 2)*
- Most pregnant women will have asymptomatic or mild disease that will not impact on their pregnancy. The risk of hospital admission with COVID-19 is increased in pregnant women with a minority ethnic background. There is emerging evidence that pregnant women may be at greater risk of severe disease requiring admission to intensive care and/or need for invasive ventilation than non-pregnant women, particularly in the third trimester. COVID-19 may increase the risk of pre-term birth and admission to a neonatal care unit.*(Table 2)*
- Less advantaged socioeconomic status is associated with severe disease. *(Table 2)*
- Severe illness from COVID-19 is less common in children and young people, than adults. While COVID-19 should be considered in children and young people presenting with symptoms, other diagnoses should also be considered. *(sections 5 and 6)*

The evidence base remains too weak and emergent to make definitive recommendations.

1. Signs and symptoms of COVID-19 in adults

The intention of this review was to identify any evidence of signs and symptoms in adults which may differ between mild, moderate and severe disease. The initial scoping of the evidence identified a COVID-19 signs and symptoms tracker which presents severe and non-severe symptoms based on early data from China, https://www.cebm.net/covid-19/covid-19-signs-and-symptoms-tracker/. This was produced by The Centre for Evidence-Based Medicine at the University of Oxford and was based on an unpublished systematic review and meta-analysis.[2] Unpublished studies have not been subject to peer review. We identified a published systematic review and meta-analysis which included 43 studies and 3,600 patients mostly from China.[3] Details of the prevalence of symptoms found in this study are given in Table 1. A review, which includes data from the United Kingdom, found little evidence to differentiate between mild and moderate symptoms and those in a severe condition.[1]

Our initial rapid review *(see section 8)* identified a mixture of published studies and preprints or preliminary reports that included data on signs and symptoms from mixed healthcare settings, primarily in the United States (US) and Italy. Most studies were retrospective, observational studies so are potentially biased and may not be easily generalisable to Scottish primary care practice. Preprint studies have not been subject to peer review. Updates to this review carried out in July 2020 and February 2021 were primarily based on published studies and some of the preprint papers from the initial review that had since been published, however, some of the evidence described is from preprint sources. For these reasons, all reported evidence should be considered low quality and interpreted with caution. Table 1 shows early evidence and includes the results of the review of published and preprint literature comparing symptoms of mild/moderate and severe disease from settings other than China. It compares them to the findings from a systematic review of 43 studies and 3,600 patients mostly from China.[3] In Table 1 the symptoms listed are those which have been identified as associated with COVID-19. For some symptoms we found no evidence comparing that symptom in cases of mild/moderate and severe disease. This is noted in Table 1. It is not always clear in the literature how the authors define severe disease. For the purposes of this review we considered that disease was severe when a patient was admitted to ICU. In Table 1 'all cases' means all diagnosed cases and may include mild, moderate and severe disease. The proportion of those experiencing severe disease as a percentage of the diagnosed cases would be likely to vary depending on the testing policy in place in that setting at the time the data was collected. This may also result in a higher percentage of confirmed cases in subgroups believed to be at risk as they are more likely to have been tested.

The Chinese meta-analysis provides weak evidence that dyspnoea may be an indicator of severe disease as 49% of patients with severe disease experienced dyspnoea compared to 13% of patients with non-severe disease.[3] This finding is supported by evidence from outside China where 21 out of 24 patients (88%) in ICU in the US[4] experienced shortness of breath compared with 5% of the first 38 diagnosed cases (of any severity) from eight European countries[5] and 32% of cases confirmed after presenting at an Emergency Department in Italy.[6] A mixed methods study including a rapid literature review and a consensus building exercise involving UK clinicians and clinical academics found that persistent fever, shortness of breath and muscle aches were the symptoms most associated with severe disease.[7] This study emphasised that the trajectory of dyspnoea is important as acute respiratory distress syndrome (ARDS) may follow quickly from the onset of breathlessness.[8] There is some evidence that patients may be suffering from hypoxia without showing outward symptoms of shortness of breath.[9] This so-called silent hypoxia appears to have a poor prognosis.[10-13] It has been suggested that silent hypoxia may manifest as profound tiredness, but Greenhalgh et al were unable to find published research on this association.[7]

Most patients who deteriorate do so in the second week of symptoms, so it is important to note the date of onset of symptoms and to be alert to the possibility of sudden deterioration.[14] A European study (n=1,420) found that the most prevalent symptoms of mild-to-moderate disease were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%).[15]

Table 1: Prevalence of symptoms in mild/moderate and severe COVID-19 in adults

Symptoms associated with COVID-19	**Prevalence (% of cases - range) from studies outside China**			**Prevalence (% of cases) from meta-analysis – mainly China[3]**	
	ICU	**Hospitalised patients**	**All cases**	**Critical illness**	**Non-critical illness**
Cough[4-6,16-18]	88	66–86	16–37	66	57
Fever >37.8ºC[5,6,16,18-21]	28–73	24–85	20–84	81	71
Dyspnoea[4-6,16,18,22]	88	11–80	5–32	49	13
Fatigue[5,19]	-	33	21	42	34
Cough (sputum)	No evidence found comparing mild/moderate to severe disease			32	31
Delirium (confusion)	No evidence found comparing mild/moderate to severe disease.				
Diarrhoea[16,19]	-	17–27	-	8	4
Vomiting/nausea[6,16,19]	-	8–24	8	-	-
Myalgia[16,19,22]	-	34–42	16	18	21
Chest pain[6,17,22]	-	-	2–4	-	-
Anosmia/dysgeusia	No evidence found comparing mild/moderate to severe disease				
Headache[4-6,19]	8	17	2–16	11	12
Dizziness	No evidence found comparing mild/moderate to severe disease				
Abdominal pain[6,19]	-	17	1	-	-
Sore throat[4-6,16-19,22]	8	18–61	1–8	17	11

2. Diagnostic and prognostic tools

No validated method of measuring breathlessness via tele- or video consultations has been identified. A recommendation based on the consensus of 50 clinicians advises against using the Roth test.[23] A careful history of what patients can and cannot do, compared to what they could and could not do yesterday is likely to be more important.[23] Questions like those in the COVID-19 Scottish Primary Care Hub Triage Guide can be asked. Patient or carer's concern should not be dismissed as anxiety.[7]

Smartphone apps should not be used as oximeters.[7,24] When taking a reading with a pulse oximeter the finger should be warm and, although a low reading is cause for concern, a normal one should not necessarily reassure as young, fit patients in particular can compensate well in the early stages of deterioriation.[7]

A variety of risk prediction scores and tools have been developed, which may be of use in the community. Further research is required for validation and to determine which would be most appropriate in a community setting. A summary is available from the Centre for Evidence-Based Medicine: https://www.cebm.net/covid-19/what-clinical-features-or-scoring-system-if-any-might-best-predict-a-benefit-from-hospital-admission-for-patients-with-covid-19/

As yet, no trials have been conducted to validate the use of the National Early Warning Score (NEWS) or NEWS 2 in the assessment of patients for COVID-19 in primary care.[25] It was temporarily endorsed by the Royal College of General Practitioners as a response to COVID-19 but this has subsequently been withdrawn.[7]

The Remote COVID-19 Assessment in Primary Care (RECAP) score is a currently unvalidated 'early warning score' for the remote assessment of suspected COVID-19 in primary care.[7] Published in November 2020 and based on wide-ranging consultations with UK clinicians and a rapid review of published and preprint literature[26] the score includes twelve items (pulse rate, temperature, fever, respiratory rate, shortness of breath, pulse oximeter reading, tiredness, muscle aches, new confusion, duration of symptoms, shielded list and other risk factors for poor outcome (age, obesity, ethnicity). Each clinical item includes suggested cut-off values and assessment methods which could be used over telephone or video link and where the patient/carer has no access to instruments. The article includes a box describing the clinical course of the deteriorating patient in primary care.[7] Validation is ongoing.[27]

A potential clinical prediction tool has been developed and validated based on the COVID Symptom study app but has been in preprint since June 2020.[28] The article presents six different symptom clusters which may have some prognostic importance. Clusters reported as milder showed predominantly upper respiratory tract symptoms and lack of muscle pain. A cluster associated with gastrointestinal symptoms showed an increased risk of hospitalisation but less need for ventilation. Clusters associated with more severe disease featured early presence of severe fatigue, confusion, skipped meals and early onset of shortness of breath accompanied by chest pain. Frailty was more common in clusters associated with severe disease.[28]

A population-based cohort study using primary care data from over 6 million patients in the UK led to the development and validation of the QCOVID risk prediction algorithm. This algorithm aimed to estimate hospital admission and mortality outcomes from COVID-19 in adults. It is designed for the risk stratification of the population to inform public health policy. It is not suitable for individual risk prediction at the primary care level.[29]

3. Comorbidities and risk factors associated with COVID-19 in adults

Recent evidence includes a number of large studies of the association between comorbidities, risk factors and severe disease. The content of Table 2 is based on two large association studies from England[30] and Scotland.[31] Where these studies are not conclusive or provide insufficient detail, the review has been supplemented with studies from other countries. As these studies are observational considerable risks of confounding remain and results and their interpretation should be treated with caution.

Table 2: Comorbidities and risk factors associated with COVID-19 in adults

Comorbidity/risk factor	
Age **Older age significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with older age. The hazard ratio (HR) (compared with age 50–59) for age ≥80 was 20.6 (confidence interval (CI) 18.7 to 22.7), 70–79 was 6.1 (CI 5.5 to 6.7) and 60–69 was 2.4 (CI 2.2 to 2.7).[30] A case control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe COVID-19 was significantly associated with older age. The odds ratio (OR) associated with a 10-year increase in age was 2.9 for severe disease and 3.7 for fatal disease.[31]
Sex **Male sex significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due COVID-19 was significantly associated with male sex (HR 1.6, 95% CI 1.5 to 1.7).[30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe COVID-19 was significantly associated with male sex. The OR for severe disease was 1.6 for male sex.[31]
Ethnicity **Minority ethnic background significantly associated with severe disease**	Two large UK observational studies (n=78,443 and n=34,986) provided evidence that a minority ethnic background, in particular south Asian ethnicity, was an independent risk factor for poor outcomes.[32,33] Critical care admission was more common in south Asian (OR 1.28, 95% CI 1.09 to 1.52), Black (OR 1.36, 1.14 to 1.62), and other minority ethnic groups (OR 1.29, 1.13 to 1.47) compared with the white group, after adjusting for age, sex and location.[33] The odds ratios remained broadly unchanged after adjusting for deprivation and comorbidities. Patients from ethnic minorities were younger and had fewer comorbidities (except diabetes) than patients from the white group.[33] An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with Black (HR 1.5, 95% CI 1.3 to 1.7), south Asian (HR 1.4, 95% CI 1.3 to 1.6) and mixed ethnicity (HR 1.4, 95% CI 1.1 to 1.8) compared with white ethnicity. The associations were adjusted for comorbidity, age, sex but not adjusted for employment or housing density.[30]

	A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found no statistically significant association of ethnicity with severe COVID-19. The authors note that case numbers from ethnic minority backgrounds were very small so confidence intervals were wide.[31]
Pregnancy **Significantly ssociated with severe disease**	*Factors associated with hospital admission* A UK cohort study of 427 pregnant women admitted to hospital for COVID-19 found that 233 (56%) were from Black or other ethnic minority groups. Each of four categories of non-white ethnicity (Asian, Black, Chinese/other and mixed) were associated with two to four fold increased risk of admission to hospital with COVID-19 in an observed over expected analysis based on estimated total number of maternities in each group. This analysis also found increased risk of hospital admission with BMI >25 and age ≥35. Most women did not have severe illness, and most were admitted in the third trimester of their pregnancy.[34] *Outcomes for pregnant women compared with non-pregnant women* A living systematic review and meta-analysis with literature search to June 2020 identified 77 studies examining aspects of COVID-19 disease in pregnant women.[35] Most studies were on women who required visits to hospital, including for childbirth. This limits the generalisability of findings. The overall rate of COVID-19 diagnosis in pregnant women attending or admitted to hospital for any reason was 10% (95% CI 7% to 14%; 26 studies, 11 432 women). Where universal screening was in place the rate was 7%, whilst for settings with testing based on symptoms it was 18%. The rate of COVID-19 positivity was 5% across asymptomatic study participants. Three quarters (74%) of the pregnant women with COVID-19 in the universal screening population were asymptomatic.[35] Where pregnant women with the disease have symptoms the pattern is similar to that of the general female population with the most common symptoms being fever (40%) and cough (39%). When compared with non-pregnant women (of reproductive age) pregnant women were less likely to report symptoms of fever (OR 0.43, 95% CI 0.22 to 0.85; 5 studies, 80,521 women) and myalgia (OR 0.48, 95% CI 0.45 to 0.51; 3 studies, 80,409 women).[35] When compared with non-pregnant women with COVID-19 the odds of admission to ICU (OR=1.62, 95% CI 1.33 to 1.96) and need for invasive ventilation (OR 1.88, 95% CI 1.36 to 2.60) were higher in pregnant women (4 studies, 91,606 women). These data depend greatly on a large US dataset.[36] After adjusting for age, ethnicity and underlying comorbidities, the relative risk (RR) for admission to intensive care was 3.0 (95% CI 2.6 to 3.4). The RR for requiring invasive ventilation was 2.9 (95% CI 2.2 to 3.8).

	When compared with non-pregnant women, factors associated with increased risk of severe COVID-19 were age ≥35 (4 studies), BMI >30 (3 studies), chronic hypertension (2 studies) and pre-existing diabetes (2 studies). A case control study from France examined the risk of ICU admission in 83 pregnant women with COVID-19 at ≥20 weeks gestation with 107 non-pregnant controls matched for age, diabetes, hypertension and asthma. ICU admission was 2.38% in the control group and 11.08% in the pregnant COVID-19 case group (p=0.024).[37] *COVID pregnancy outcomes compared with non-COVID pregnancy outcomes* The odds of pre-term birth were higher in pregnant women with COVID-19 when compared with pregnant women without COVID-19 (OR 3.0, 95% CI 1.15 to 7.85; 2 studies, 339 women).[35] One study (n=1,121) with historical controls reported that babies born to women with COVID-19 had an increased risk of admission to a neonatal unit (OR 3.13, 95% CI 2.05 to 4.78).[35] This same study reported no statistically significant increase in stillbirths, neonatal deaths, or fetal distress. Apgar scores were not reduced.
Socioeconomic status **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with living in the most deprived quintile (HR 1.8, 95% CI 1.7 to 1.9) compared with the least deprived quintile. The associations were adjusted for comorbidity, age, sex but not adjusted for employment or housing density.[30] A large case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with socio-economic deprivation (RR 0.5, 95% CI 0.5 to 0.6) for least deprived quintile compared to most deprived.[31] A national audit of demographics, activity and outcomes for patients with laboratory-confirmed COVID-19 disease admitted to Scottish ICUs between 1 March and 20 June 2020 reported that a greater proportion of patients in the highest quintile of deprivation was admitted to ICU than patients in the lowest quintile (24.4% *v* 16.2%). Overall estimated 30-day mortality for all patients admitted to ICU was 38.7%, with a higher estimate of death among those in the highest quintile of deprivation compared with those in the lowest quintile (48.7% *v* 34.7%).[38] In Scotland, the age-standardised rate of deaths involving COVID-19 between 1 March 2020 and 30 June 2020 in the most deprived quintile (124.1 per 100,000 population) was 2.1 times higher than in the least deprived quintile (60.5 per 100,000 population).[39] A study using UK Biobank data found those living in the least advantaged quartile to be at greater risk of being tested, testing positive and testing positive in hospital.[40]

Occupation **Occupation as health or social care worker significantly associated with severe COVID-19**	*Occupation and severe COVID-19* A UK cohort study (BIOBANK, with exposure ascertainment from 2006-2010) included 120,075 participants aged 49 to 64.[41] Of these, 29.3% were classified as essential workers (healthcare (9%), social and education (11.2%) and 'other' (9.1%)). White participants made up 92.2% of the sample, south Asians 2.6% and Black participants 2.7%. Woman and ethnic minority participants were more likely to be employed in essential occupations. In comparison with non-essential workers, healthcare workers (n=10,478) had a greater risk of severe COVID-19 as measured by hospitalisation or death, (RR 7.43, 95% CI 5.52 to 10.00). This association remained when adjusted for age, gender, country of birth, ethnicity socioeconomic factors of deprivation, education, shift work, health conditions and lifestyle factors. Similarly, social care workers (n=5,297) had a higher risk when compared with non-essential workers, (RR 2.46, 95% CI 1.47 to 4.14). Transport workers within the sub-category of 'other' essential workers (n=3,279) also had a higher risk of severe COVID-19 (RR 2.20, 95% CI 1.21 to 4.00) but this association was not statistically significant when adjusted for socioeconomic status (RR 1.66, 95% CI 0.91 to 3.01). There were no strong associations between occupation and severe COVID-19 observed for police, food or education workers. Men, south Asian and Black ethnic groups, those with socioeconomic disadvantage and the least educated groups had higher risk of severe COVID-19 compared with women, white British, those with socioeconomic advantage and degree educated groups. Shift work and manual work were associated with a higher risk of severe COVID-19 as were being overweight or obese or being a previous smoker.[41] *Occupation and testing positive for COVID-19* A prospective cohort study in the UK and USA using data from the COVID Symptom Study app (n=2,810,103, 93.5% from the UK) compared the risk of a positive COVID-19 test amongst front-line healthcare workers with that of people from the general community from late March to late April 2020.[42] The prevalence of COVID-19 was 2,747 per 100,000 for front-line healthcare workers which was significantly higher than for the people in the general community, 242 cases per 100,000. When adjusted for the effect of increased probability of testing in the healthcare population the adjusted HR for a positive test for the UK group was 3.43 (95% CI 3.18 to 3.69). *Occupation and anti-SARS-CoV-2 antibodies in healthcare workers* A cross sectional study examined the seroprevalence of anti-SARS-CoV-2 antibodies amongst 10,662 staff employed at a UK hospital in May 2020 and volunteering to be tested.[43] When compared with doctors, seroprevalence (10.3%) was significantly higher for nurses/healthcare assistants (13.7%). South Asian and Black nurses had significantly higher rates of seropositivity than their white colleagues (17.7% *v* 11%). Amongst doctors, seropositivity decreased with increasing seniority with the highest

	rates amongst foundation year doctors (25.9%) and the lowest rates amongst consultants (7.7%). *Occupation and deaths due to COVID-19* In records of deaths due to COVID-19 in Scotland to 30 November 2020, the occupation category with the highest age standardised rate per 100,000 of population was for process, plant and machine operatives (37.7).[39] This compared to the rate of 15.6 for the 350 deaths across all occupations. Those whose death certified occupation related to the category of elementary occupations (which includes construction workers and cleaners) had the next highest rate of 25.9. The corresponding rate for healthcare workers was 8.5 and for social care workers it was 24.3. People in professional occupations had the lowest death rate (2.9 per 100,000).
Obesity **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with obesity. The HR for body mass index (BMI) of 30–34.9 kg/m^2 was 1.1 (95% CI 1.0 to 1.1), 35–39.9 was 1.4 (95% CI 1.3 to 1.5) and 40 kg/m^2 or over was 1.9 (95% CI 1.7 to 2.1) all compared with BMI <30 kg/m^2.[30] Obesity may be particularly strongly associated with poorer outcomes in younger patients. Another study which included 3,615 COVID-19–positive symptomatic patients presenting to an academic hospital in New York found that patients aged < 60 years with a BMI ≥35 were 2.2 (95% CI, 1.7 to 2.9) and 3.6 (95% CI, 2.5 to 5.3) times more likely to be admitted to acute and critical care than patients in the same age category who had BMI < 30.[44] A further unpublished study in New York included 572 patients aged 50 or below and 2,843 patients aged over 50 with confirmed COVID-19. For the younger population, BMI above 40 kg/m^2 was independently associated with mortality (adjusted OR 5.1, 95% CI 2.3 to 11.1). For the older population, BMI above 40 kg/m^2 was also independently associated with mortality to a lesser extent (adjusted OR 1.6, 95% CI 1.2 to 2.3).[45] A small study carried out in several US hospitals found a significant inverse correlation between age and BMI, in which younger individuals admitted to hospital were more likely to be obese.[46] A prospective multicentre cohort study of 77 pregnant women with confirmed COVID-19 infection who were admitted to 12 Italian maternity hospitals reported that increased pregestational BMI was associated with severe disease.[47] See the section on pregnancy for further information.

Smoking **Significantly associated with severe disease**	A meta-analysis of 19 peer-reviewed papers showed that smoking is associated with disease progression and severe disease, with smokers having 1.91 times the odds of progression in COVID-19 severity compared with people who never smoked.[48] A systematic review of peer-reviewed studies carried out by the World Health Organization (WHO) suggested that smoking is associated with increased severity of disease and death in hospitalised COVID-19 patients. The authors note that although likely related to severity, there is no evidence to quantify the risk to smokers of COVID-19-related hospitalisation.[49] A recent large observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with former smoking (HR 1.2, 95% CI 1.1 to 1.2) but not current smoking (HR 0.9, 95% CI 0.8 to 1).[30]
Cancer **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England distinguished haematological and non-haematological cancer and time since diagnosis. The study found that death due to COVID-19 was significantly associated with both types of cancer. For recently diagnosed haematological cancer the HR was 2.8 (95% CI 2.1 to 3.8) reducing to 1.6 (95% CI 1.4 to 1.9) if diagnosed more than five years previously. For non-haematological cancers the HR was 1.7 (95% CI 1.5 to 2) for cancer diagnosed within a year reducing to a risk equivalent to that of individuals without cancer, for cancers diagnosed more than five years previously.[30] There is emerging evidence that the association between cancer and COVID-19 severity is more nuanced and cannot be described simply in the context of the presence of a cancer diagnosis alone. A prospective cohort study from the UK Coronavirus Cancer Monitoring Project which included 800 patients admitted to hospital over a 5-week period with a diagnosis of cancer and symptomatic COVID-19 reported that 226 patients (28%) died. Risk of death was significantly associated with older patient age (OR 9.42, 95% CI 6.56 to 10.02), male sex (OR 1.67, 95% CI 1.19 to 2.34) and the presence of other comorbidities such as hypertension (OR 1.95, 95% CI 1.36 to 2.80) and cardiovascular disease (CVD) (OR 2.32, 95% CI 1.47 to 3.64). After adjusting for age, gender, and comorbidities, chemotherapy in the previous 4 weeks was not significantly associated with mortality from COVID-19 disease compared with patients with cancer who had not received recent chemotherapy (OR 1.18, 95% CI 0.81 to 1.72). There was no significant effect on mortality for patients who received immunotherapy, hormonal therapy, targeted therapy or radiotherapy within the previous four weeks.[50] A further cohort study which included 928 patients with active or previous cancer and a confirmed diagnosis of COVID-19 in the USA, Canada and Spain reported independent association between the following factors and death (all odds ratios partially adjusted): increased age (per 10 years; OR 1.84, 95% CI 1.53 to 2.21), male sex (OR 1.63, 95% CI 1.07 to 2.48), smoking status

	(former smoker *v* never smoked: OR 1.60, 95% CI 1.03 to 2.47), number of comorbidities (two *v* none: OR 4.50, 95% CI 1.33 to 15.28), active cancer (progressing *v* remission: 5.20, 95% CI 2.77 to 9.77), and receipt of azithromycin plus hydroxychloroquine (*v* treatment with neither: OR 2.93, 95% CI 1.79 to 4.79; authors note that confounding by indication cannot be excluded). Ethnicity, obesity, cancer type, type of anticancer therapy, and recent surgery were not associated with mortality.[51] A rapid review of evidence by Alberta Health Authority found that patients with active haematological malignancies and lung cancers appear to be at increased risk of severe disease compared to other malignancies. Relapsing or progressive cancer, functional impairment, lymphopenia <0.5/L (at baseline), and severe hypogammaglobulinemia < 4g/L (at baseline particularly in in multiple myeloma) are associated with an increased risk of severe COVID-19 in active cancer patients with moderate-high strength associations from unmatched observational cohorts.[52] The Alberta Health Authority review found two unmatched cohort studies that showed no association with COVID-19 severity in analysis of chemotherapeutic treatment within four weeks of COVID-19 diagnosis.[52] A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that blood cancer was significantly associated with contracting COVID-19 and subsequent hospitalisation and death. The same study found that respiratory tract cancer was significantly associated with hospitalisation in men and death in women. Any chemotherapy in the last 12 months or radiotherapy in the last six months were significantly associated with both death and hospitalisation for both sexes.[29]
Cardiovascular disease **Significantly associated with severe disease**	*Chronic heart disease* A large observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with chronic heart disease (HR 1.2, 95% CI 1.1 to 1.2).[30] A large case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with non-ischaemic heart disease (RR 1.3, 95% CI 1.2 to 1.5).[31] *Ischaemic heart disease* A large case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was not significantly associated with ischaemic heart disease (RR 1.1, 95% CI 0.98 to 1.2).[31] One Italian study (n=2,653) found a significant association between ischaemic heart disease and both hospitalisation and death.[53]

	Coronary artery disease A US study (n=5,279) found no association between coronary artery disease and hospitalisation or critical illness.[20] *Coronary heart disease* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that coronary heart disease was significantly associated with death for both men and women but hospitalisation only for women.[29] *Hypertension* A large observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly negatively associated with high blood pressure or diagnosed hypertension (HR 0.9, 95% CI 0.8 to 0.9).[30] In an unpublished meta-analysis of 27,713 patients mostly in China, hypertension was reported to increase the odds of severe COVID-19 disease (OR 2.14, 95% CI 1.82 to 2.51).[54] One study of 5,279 confirmed cases in New York found an association between hypertension and hospitalisation (OR 1.78, 95% CI 1.49 to 2.12) but no association with critical illness.[20] A further US study (n=585) did not find any significant association between hypertension and hospitalisation or critical illness.[20,21] Two Italian studies (n=2,653 and n=411) found that hypertension was significantly associated with both hospitalisation and death.[6,53] A fifth study (n=54) found hypertension significant for hospitalisation and ARDS but that the significance disappeared if oxygen saturation was included in the analysis.[55] *Stroke* A large observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with stroke or dementia (HR 2.2, 95% CI 2.1 to 2.3).[30] Stroke was also reported by the unpublished meta-analysis of 27,713 patients mostly in China, to increase the odds of severe COVID-19 disease (OR 3.08, 95% CI 1.95 to 4.88).[54] *Thromboembolism* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that thromboembolism was significantly associated with contracting COVID-19 and subsequent hospitalisation or death for both men and women.[29] *Myocardial infarction* A retrospective cohort study of 31,941 people who died from COVID-19 in the US found that myocardial infarction was significantly associated with mortality (OR 1.97, 95% CI 1.64 to 2.35).[56]

	Heart failure One Italian (n=2,653) and one US study (n=5,279) found significant associations between heart failure and hospitalisation, critical illness or death.[20,53] *Congestive heart failure* In an unpublished meta-analysis of 27,713 patients mostly in China, congestive heart failure was reported to not increase the odds of severe COVID-19 disease (OR 2.18, 95% CI 0.47 to 10.06).[54] A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that congestive heart failure was significantly associated with contracting COVID-19 and subsequent hospitalisation and death for both men and women.[29] A retrospective cohort study of 31,941 people who died from COVID-19 in the US found that congestive heart failure was significantly associated with mortality (OR 1.42 95% CI 1.21 to1.67).[56] *Atrial fibrillation* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that atrial fibrillation was significantly associated with contracting COVID-19 and subsequent hospitalisation and death.[29] *Peripheral vascular disease* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that peripheral vascular disease was significantly associated with contracting COVID-19 and subsequent hospitalisation and death for both men and women.[29] *Hyperlipidaemia* One study (US, n=5,279) found hyperlipidaemia had a negative association with hospitalisation but found no association with critical illness.[20] Another found no association between dyslipidaemia and hospitalisation or death.[53] In an unpublished meta-analysis of 27,713 patients mostly in China, hyperlipidaemia was reported not to increase the odds of severe COVID-19 disease (OR 1.46, 95% CI 0.42 to 5.12).[54] *Congenital heart disease* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that congenital heart disease was not significantly associated with contracting COVID-19 and subsequent hospitalisation and death for either men or women.[29] *ACE inhibitors and AT1 antagonists* Four of the association studies identified for settings outside China included ACE-I inhibitors and AT1 antagonists in their analysis.

	Three studies found no association with either hospitalisation or severe disease.[6,21,55] One study (Italy, n=2,653) found that the medication was associated with hospitalisation but not death.[53] A meta-analysis of nine studies involving 3,936 patients with hypertension found that use of ACE inhibitors and AT1 antagonists was not significantly associated with severe disease but was significantly associated with reduction in mortality, (OR 0.57, 95% CI 0.38 to 0.84).[57]
Chronic kidney disease **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with chronic kidney disease. The study distinguished estimated glomerular filtration rate (eGFR) 30-60, HR 1.3 (95% CI 1.3 to 1.4) and eGFR <30, HR 2.5 (95% CI 2.3 to 2.7).[30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with chronic kidney disease or being a transplant recipient (RR 2.9, 95% CI 2.1 to 3.9).[31] A rapid review of evidence by Alberta Health Authority found that severe COVID-19 outcomes in patients on haemodialysis appeared to be associated with previously defined risk factors (age, co-morbidities), and severe symptoms at onset. One study identified patients with a greater length of time on haemodialysis to be at increased risk of mortality.[58]
Chronic liver disease **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with chronic liver disease HR 1.7 (95% CI 1.5 to 2.0).[30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with liver disease (RR 1.9, 95% CI 1.3 to 2.8).[31] A retrospective cohort study of 31,941 people who died from COVID-19 in the US found that mild and moderate /severe liver disease were significantly associated with mortality (mild OR 1.26 , 95% CI 1.00 to 1.59, moderate/severe OR 2.62. 95% CI 1.53 to 4.47).[56]
Chronic respiratory disease **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with respiratory disease (excluding asthma) (HR 1.6, 95% CI 1.5 to 1.7). Asthma with recent oral corticosteroid use was significantly associated with death due to COVID-19 (HR 1.1, 95% CI 1.0 to 1.3) but in individuals with asthma without this use there was no significant association (HR 1, 95% CI 0.9 to 1).[30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with chronic airway disease or asthma (RR 1.5, 95% CI 1.4 to 1.7).[31]

	The evidence for asthma as a risk factor for COVID-19 severity is mixed. A population-based cohort study using data from the UK Biobank (n=492,768) reported that adults with asthma had a higher risk of severe COVID-19, which was driven by the increased risk in patients with non-allergic asthma (adjusted OR 1.48, 95% CI 1.15 to 1.92). In contrast, the risk of severe COVID-19 was not significantly elevated in patients with allergic asthma.[59] A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that chronic obstructive pulmonary disease (COPD) was significantly associated with contracting COVID-19 and subsequent hospitalisation and death for both men and women. Asthma and rare lung conditions including cystic fibrosis were significantly associated with hospitalisation but not death. Pulmonary hypertension was significantly associated with hospitalisation in both sexes but death only in women.[29] A US cohort study (n=935) indicated that asthma was associated with longer intubation time in hospitalised patients but not hospitalisation, intubation, duration of hospitalisation, ARDS or death.[60] No associations were found for asthma in the single study which looked at this separately.[21]
Diabetes **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England distinguished diabetes with hemoglobin Ac1 (HbA1c) above and below 58 mmol mol^{-1} and diabetes with no recent measure. It found that death due to COVID-19 was significantly associated with all diabetes with those patients with HbA1c below 58 mmol mol^{-1} having the lowest risk (HR 1.3, 95% CI 1.2 to 1.4). Those with HbA1c equal to or above 58 mmol mol^{-1} had a HR of 1.9 (95% CI 1.8 to 2.1) and those without a recent measurement (HR 1.9, 95% CI 1.7 to 2.1).[30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with both type 1 (RR 1.6, 95% CI 1.1 to 2.3) and type 2 diabetes (RR 1.4, 95% CI 1.3 to 1.6).[31] Studies have demonstrated an association between a range of diabetes parameters (including admission blood glucose, glucose coefficient of variation, median blood glucose, median in-hospital glucose level, maximum blood glucose and minimum blood glucose) and disease severity and mortality in patients. Hyperglycaemia was an independent risk factor for progression to critical cases and/or death among non-critical cases.[61,62] A retrospective cohort study of 453 patients admitted to hospital with COVID-19 in Wuhan, China showed that patients with newly-diagnosed diabetes had the highest risk of all-cause mortality compared with patients with known diabetes, hyperglycaemia and normal glucose.[63]

Frailty **Significantly associated with severe disease**	A prospective observational study of 1,564 patients in 10 UK and one Italian hospital found that Clinical Frailty Scores (CFS) 5–6 (mildly and moderately frail) and 7–9 (severe and very severe frailty or terminal illness) were significantly associated with 90-day mortality. Compared with CFS 1–2, the adjusted HRs for time from hospital admission to death were 1.55 (95% CI 1.00 to 2.41) for CFS 3–4, 1.83 (1.15 to 2.91) for CFS 5–6, and 2.39 (1.50 to 3.81) for CFS 7–9.[64] A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that osteoporotic fracture was significantly associated with contracting COVID-19 and subsequent hospitalisation and death for both men and women.[29]
Immunosuppressive conditions **Significantly associated with severe disease**	*Immune deficiency or suppression* A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with immune deficiency or suppression (RR 1.7, 95% CI 1.1 to 2.5).[31] A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that rheumatoid arthritis and systematic lupus erythematosus were significantly associated with contracting COVID-19 and subsequent hospitalisation for both sexes and death for women. The same study found that sickle cell disease or other severe immunodeficiency, motor neurone disease, multiple sclerosis, myaesthenia gravis or Huntingdon's disease were significantly associated with hospitalisation and death for both sexes.[29] *Auto-immune diseases* A rapid review of evidence by Alberta Health Authority found that the presence of certain risk factors in these conditions appear to be associated with severe COVID-19 outcomes. However, epidemiological studies have not routinely addressed differences in disease type routinely (eg patients with systemic lupus erythematosus (SLE) are likely to be at higher risk of complications) and other subtleties in therapy or co-morbidities.[52] *Inflammatory bowel disease* A rapid review of evidence by Alberta Health Authority found that active inflammatory bowel disease (IBD) and corticosteroid use are associated with an increased risk of severe COVID-19 outcomes.[52] *Psoriasis* A rapid review of evidence by Alberta Health Authority found no published cohort data assessing outcomes of COVID-19 in patients with psoriasis.[52] *Systemic rheumatic diseases* A rapid review of evidence by Alberta Health Authority found that systemic rheumatic diseases (SLE, connective tissue diseases (CTD), inflammatory myositis, sarcoidosis, Raynaud's

	phenomenon), prednisone >10mg/day, and co-morbidities (interstitial lung disease and chronic kidney disease) were associated with an increased risk of severe COVID-19 outcomes.[52] *Rheumatoid arthritis, psoriatic arthritis or lupus* An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with rheumatoid arthritis, psoriatic arthritis or lupus (HR 1.2, 95% CI 1.1 to 1.3) and other immunosuppressive conditions (HR 2.2, 95% CI 1.7 to 2.9).[30] *Multiple sclerosis* A rapid review of evidence by Alberta Health Authority found that increased disability and progressive multiple sclerosis were associated with increased risk of severe COVID-19 outcomes.[52]
Steroids or other immuno-suppressant medications Evidence of association is unclear	*In patients with cancer* See separate section above. *In organ transplant recipients* See separate section below. *In rheumatic disease* A case series of 600 individuals with rheumatic disease and COVID-19 from 40 countries found that there was increased risk of disease severity with corticosteroid use, most likely at doses >10mg/day prednisone equivalent (OR 2.05, 95% CI 1.06 to 3.96) and decreased risk of hospitalisation with anti-tumour necrosis factor (TNF) use (OR 0.40, 95% CI 0.19 to 0.81).[65] No association was found between hospitalisation and conventional disease modifying drugs (with or without Janus kinase (JAK) inhibitors), non-steroidal anti-inflammatory drugs (NSAIDs) or anti-malarials.[65] *Immunosuppressant medication* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that 4 or more scripts for immunosuppressant medication in the past six months was not significantly associated with contracting COVID-19 and subsequent hospitalisation or death for either men or women.[29] *Leukotriene antagonists or long acting beta agonists* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that four or more prescriptions for leukotriene antagonists or long acting beta agonists in the past six months was not significantly associated with contracting COVID-19 and subsequent death for either men or women but was significantly associated with hospitalisation for women.[29] *Corticosteroids* A rapid review of evidence by Alberta Health Authority found that there appeared to be increased risk of disease severity with

	corticosteroid use, most likely at doses >10mg/day prednisone equivalent.[52] *Oral steroids* A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that oral steroids were significantly associated with contracting COVID-19 and subsequent hospitalisation or death for both men and women.[29] *Immune checkpoint inhibitors* A rapid review of evidence by Alberta Health Authority found that there was conflicting information from three observational cohorts and further information was needed.[52] *Conventional synthetic disease modifying antirheumatic drugs* (csDMARDs) *(eg methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, 5-aminosalicylic acid)* A rapid review of evidence by Alberta Health Authority found in unmatched cohort studies, csDMARDs were not associated with risk of COVID-19 severity.[52] *Biologic disease modifying antirheumatic drugs (bDMARDs) (including TNF inhibitors, IL inhibitors and B-cell depleting therapies)* A rapid review of evidence by Alberta Health Authority found that there did not appear to be an association with risk of high COVID severity overall and bDMARD use. It also found that from unmatched cohort studies that there may be reduced severity of COVID-19 with bDMARD use.[52] *Targeted synthetic disease modifying antirheumatic drugs (tsDMARDs) (including JAK inhibitors)* A rapid review of evidence by Alberta Health Authority found from unmatched cohort studies that there did not appear to be an association with risk of severe disease.[52] *Disease modifying therapies used in the treatment of multiple sclerosis* A rapid review of evidence by Alberta Health Authority found from unmatched cohort studies that there did not appear to be an association with risk of severe disease.[52]
Solid organ transplants **Significantly associated with severe disease**	A large observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with organ transplant (HR 3.5, 95% CI 2.8 to 4.5).[30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with chronic kidney disease or being a transplant recipient (RR 2.9, 95% CI 2.1 to 3.9).[31] Other evidence on solid organ transplants as a risk factor for severe COVID-19 disease is mixed. A number of small case

	studies and cohort studies from China, the US and the UK have reported that individuals with solid organ transplants may be at higher risk of severe illness or complications, more rapid clinical progression, and a prolonged clinical course compared with the general population, due to chronic immunosuppression and the presence of co-existing conditions.[66-69] In contrast, a US case series of 15 kidney transplant recipients reported outcomes similar to the general population.[70] A rapid review of evidence by Alberta Health Authority found that in solid organ transplant recipients, transplant specific factors (eg organ transplanted, time post-transplant, level of immunosuppression) were not associated with risk of COVID-19 severity (although age, gender, and co-morbidities were associated with COVID-19 severity among patients with solid organ transplants).[52] A rapid review of evidence by Alberta Health Authority found that there was no published evidence on COVID-19 severity in patients receiving induction level doses of anti-rejection therapies.[58] In patients receiving maintenance therapies evidence was mixed. Anti-rejection therapies were not associated with mortality in a global cohort of transplant patients but mycophenolate was associated with a composite severe disease outcome in a small cohort (n=111) of liver transplant patients. The majority of patients in this cohort were male, older and had significant co-morbidities so there is a risk of confounding.[52]
Neurological conditions **Significantly associated with severe disease**	An observational study of 10,926 deaths due to COVID-19 in England found that death due to COVID-19 was significantly associated with stroke or dementia (HR 2.2, 95% CI 2.1 to 2.3) and other neurological conditions (HR 2.6, 95% CI 2.4 to 2.8) [30] A case-control study of 4,272 severe COVID-19 cases and 36,948 controls in Scotland found that severe disease was significantly associated with neurological conditions (except epilepsy) or dementia (RR 2.0, 95% CI 1.8 to 2.2).[31] A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that dementia, epilepsy and cerebral palsy were significantly associated with contracting COVID-19 and subsequent hospitalisation and death for men and women. Parkinson's Disease was significantly associated with hospitalisation for both sexes but only with death for men.[29] A retrospective cohort study of 31,941 people who died from COVID-19 in the US found that dementia was significantly associated with mortality (OR 1.29, 95% CI 1.07 to 1.56, p=0.008).[56]

Severe mental illness **Significantly associated with severe disease**	A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that severe mental illness was associated with contracting COVID-19 and subsequent hospitalisation and death for both men and women.[29]
Learning difficulties including Down's Syndrome **Significantly associated with severe disease**	A population-based cohort study using primary care data from over 6 million patients in the UK with 4,384 deaths and 10,776 hospital admissions found that learning difficulties were associated with contracting COVID-19 and subsequent hospitalisation and death for both men and women. The odds ratios of death for individuals with Down's Syndrome were found to be high compared to those without any learning difficulties; OR for death in men 9.8 (95% CI 4.6 to 20.8) and in women OR 32.6 (95% CI 18.1 to 58.4).[29]
Multimorbidity **Significantly associated with severe disease**	A literature review[71] identified a study from China (n=1,590) which investigated the association between burden of comorbidity and risk of dying during hospitalisation for COVID-19. The risk of dying during hospitalisation for those ≥65 years was 2.7 times higher for those with two or more chronic conditions compared with those ≥65 years without comorbidities. The review also identified a cross-sectional study of 1,591 COVID-19 patients who had been hospitalised in Italy. The OR for death due to COVID-19 increased as Charlson Comorbidity Index (CCI) score increased, reflecting age and number of co-morbidities. In this study, survivors had a mean CCI score of 2.63+/- 0.05 compared with non-survivors score of 4.37+/-0.14 (p=0.0001).[71] Data from a retrospective observational study in Italy reported that those without multimorbidity (defined as ≥2 conditions) were 20 times more likely to survive during hospitalisation.[72] A US study reported that multimorbidity as defined by the CCI had a stronger relationship with mortality than nearly all individual comorbid conditions in patients with COVID-19.[73] The complex relationship between age, particular combinations of pre-existing conditions (and their treatment) and the risk of COVID-19 related death was explored in one analysis with the authors suggesting that multimorbidity itself should be considered a risk factor over and above the additive effects of the individual conditions.[74]

4. Clinical measures

Table 3 details clinical measures that were investigated for association with disease severity in the studies identified in the review.

Table 3: Clinical measures considered for identifying symptoms of COVID-19

Oxygen saturation **Significantly associated with severe disease**	Low oxygen saturation levels (<93%) were reported as significantly associated with severe disease in six out of eight studies (75%) in an unpublished meta-analysis including 27,713 patients with COVID-19, mostly in China.[54] The authors did not conduct a meta-analysis on this outcome. Three of the identified studies of association from settings outside China included oxygen saturation in their analysis. Results were mixed. One study examining associations in 5,279 confirmed cases of COVID-19 in New York found that oxygen saturation at levels <88% and 88–92% were associated with the risk of critical illness compared with levels >92% (OR 3.67, 95% CI 2.78 to 4.8 at <88% and OR 1.49, 95% CI 1.18 to 1.90 at 88–92%).[20] A US study of 585 veterans aged 54–75 found that a 1% reduction in arterial oxygen saturation (SpO_2) was not associated with hospitalisation or admission to ICU.[21] The final study of 54 patients in California found that SpO_2 was significantly associated with hospitalisation and development of pneumonia and ARDS but not admission to ICU.[55] A UK-based mixed methods study which included a rapid review of the literature and an extensive consensus building exercise among UK clinicians suggested that oxygen levels of 94–95% are of clinical concern and a level of 93% or below would require urgent referral.[7] The same study suggests that a fall of 2% after a 40-step exercise test would be of clinical concern and a fall of 3% requires urgent referral. The 40 step test should not be undertaken without clinical supervision if a patient's resting pulse oximetry reading is abnormal (below 96%). For patients without access to a pulse oximeter the same study recommends that profound tiredness or fatigue such that the patient is noticeably more tired doing usual activities or struggling to get out of bed indicate clinical concern and being unable to speak because of tiredness suggests urgent referral.[7]
Respiratory rate **Significantly associated with severe disease**	A respiratory rate of > 30/min was reported as significantly associated with severe disease in 11 out of 15 studies (73%) in an unpublished meta-analysis including 27,713 patients with COVID-19, mostly in China.[54] The authors did not conduct a meta-analysis on this outcome. A recent UK based mixed methods study which included a rapid review of the literature and an extensive consensus building exercise among UK clinicians suggested that a respiratory rate of 21–24 was of some clinical concern, 9–11 or 25–29 of greater concern and eight or less or 30 or more requiring urgent referral.[7] If respiratory rate could not be measured, breathlessness walking

	room to room or getting out of a chair could be considered of clinical concern and severe breathing difficulty or inability to complete sentences at rest as requiring urgent referral.[7] The trajectory of breathlessness is also considered important with worse breathlessness than before being of clinical concern and significant deterioration in the last hour requiring urgent referral.[7]
Heart rate Evidence of association is unclear	Heart rate was reported as significantly associated with severe disease in two out of 13 studies (15%) in an unpublished meta-analysis including 27,713 patients with COVID-19, mostly in China.[54] The authors did not conduct a meta-analysis on this outcome and it is unclear what level of increase was investigated for significance. An Italian study of 2,653 cases found a small negative association with increased heart rate and hospitalisation but no association with admission to ICU.[53] A UK-based mixed methods study which included a rapid review of the literature and an extensive consensus building exercise among UK clinicians suggested that a heart rate of 41–50 or 91–130 beats per minute is of clinical concern and that a heart rate under 40 or over 130 if unexplained would suggest urgent referral.[7]
Systolic blood pressure Evidence of association is unclear	Systolic blood pressure (SBP) was reported as significantly associated with severe disease in five out of nine studies (56%) in an unpublished meta-analysis including 27,713 patients with COVID-19, mostly in China.[54] The authors did not conduct a meta-analysis on this outcome and it is unclear whether this was higher or lower SBP and what level was investigated for significance. Of the identified studies of association in settings outside China, one US study (n=585) found that a 5 mm Hg decrease in SBP was associated with hospitalisation (OR 1.1, 95% CI 1 to 1.2) but not with ICU admission.[21]

5. Signs and symptoms of COVID-19 in children and young people

This section is based on an evidence summary developed by UpToDate®[75] which was updated in November 2020.[75] Key systematic reviews and UK and European studies cited by UpToDate® are referenced for information.[76-83] Additional references and information from the Royal College of Paediatrics and Child Health (RCPCH) are incorporated.[80]

In Scotland, from the start of the outbreak to 17 January 2021, there were 21,455 test-positive cases of COVID-19 in children aged up to 19 years. This equates to approximately 13.1% of all test-positive cases in Scotland. At 17 January 2021 there had been a total of 137 COVID-19-related hospital admissions for children aged 0 to 4. For children aged 5–14 there had been 80 admissions and for young people aged 15–19 the total number of admissions was 84. Children aged 19 and under comprised 1.52% of COVID-19 hospital admissions. At 11 January 2021 one death with COVID-19 noted on death certificate had been recorded for a child aged 14 or under.

Children of all ages can get COVID-19.[84] In a European multicentre cohort study (n=582) the age distribution of children with confirmed COVID-19 infection in contact with tertiary, secondary or primary care was: <1 year 29%, 1–5 years 21%, 5–10 years 16% and 10–18 34%. Neonates (age <1 month comprised 7% of the cohort).[76]

There is preliminary evidence that children have lower susceptibility to infection with the virus than adults, with teenagers more susceptible than younger children.[81,85]

Clinical findings are diverse. Fever and cough are the most common symptoms in children. Other symptoms include shortness of breath, myalgia, rhinorrhoea, sore throat, nausea and vomiting, headache, abdominal pain, diarrhoea and loss of smell or taste.[77,78] Gastrointestinal symptoms may occur without respiratory symptoms. Less commonly reported symptoms include thoracic pains, somnolence, febrile convulsions, lower limb pains and ocular manifestations consistent with viral conjunctivitis.[80] Skin manifestations may be associated with COVID-19 in children but these are not well characterised. Reddish purple nodules on the distal digits similar in appearance to chilblains are described predominantly in children and young adults, although an association with COVID-19 has not been clearly established.[86-88]

There appears to be little in the way of clinical signs in children to differentiate COVID-19 from other childhood respiratory virus infections, and COVID-19 has been detected in combination with other viral and bacterial infections.[80] The Royal College of Paediatrics and Child Health (RCPCH) has issued national guidance for the management of children with bronchiolitis and lower respiratory tract infections during COVID-19 (https://www.rcpch.ac.uk/resources/national-guidance-management-children-bronchiolitis-during-covid-19#background)

Whilst most children have asymptomatic, mild, or moderate disease and recover within one to two weeks of disease onset, severe cases of COVID-19, including fatal cases, have been reported.[77,89,90]

In a systematic review of data published on 7,480 children <18 years of age with laboratory-confirmed COVID-19 infection, information about symptoms and severity was available for 1,475.[77] Among these, 15% of cases were asymptomatic, 42% were mild, 39% were moderate (eg clinical or radiographic evidence of pneumonia without hypoxemia), 2% were severe (eg dyspnoea, central cyanosis, hypoxaemia), and 0.7% were critical (eg acute respiratory distress syndrome, respiratory failure, shock). There were six deaths in the entire study population (0.08%).

The RCPCH has produced a case definition for the paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[91] A UK retrospective observational study of 78 cases meeting the RCPCH definition and admitted to paediatric intensive care units (PICU), reported that fever (100% of patients), shock (87%), abdominal pain (62%), vomiting (63%), and diarrhoea (64%) were common presenting features.[92] Rash was seen in 45% of patients and conjunctivitis in 29% of patients. Only 3% of patients had co-morbidities which would have been expected to require secondary care and 78% had no known co-morbidities. The study authors note the absence of significant respiratory involvement. This is also indicated in a systematic review of 783 international cases.[93]

6. Comorbidities and risk factors associated with severe COVID-19 in children and young people

Although children with underlying medical conditions are at increased risk for severe disease than children without underlying conditions, robust evidence associating specific pre-existing conditions with severe COVID-19 in children is limited.[76-83] The RCPCH note that children may be at higher risk of requiring PICU admission if they are medically complex; have long-term dependence on technological support including tracheostomy; have developmental delay, have genetic abnormalities, have respiratory co-morbidity, have cardiac co-morbidity or are obese. Children who have been admitted to PICU have been seen in two peaks - premature babies and those under one month of age and older children who are more commonly diagnosed with PIMS-TS.[80]

Children from Black, Asian, and other minority ethnic groups appear to be disproportionately over-represented in the group of children admitted to hospital.[75,80]

7. Sources of further information

Guidance and further information on management, care and service delivery in relation to COVID-19 is signposted from the Scottish Intercollegiate Guidelines Network (SIGN) website: www.sign.ac.uk

For up-to-date information on signs, symptoms and prognosis of COVID-19, the following websites provide summaries of new evidence which are updated frequently:

BMJ Best practice: https://bestpractice.bmj.com/topics/en-gb/3000168/prognosis and https://bestpractice.bmj.com/topics/en-gb/3000168/history-exam

Centre for Evidence-Based Medicine, University of Oxford, provides rapid reviews of research, categorised under ‘Signs and Symptoms’, ‘Symptom Assessment’ and ‘Diagnostic Tests’: https://www.cebm.net/oxford-covid-19-evidence-service/

National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/covid-19

UptoDate: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-clinical-features-diagnosis-and-prevention#H3432457140

8. Methodology

8.1 Key question

This rapid review is based on a structured key question that defines the target population, the intervention or exposure under investigation and the outcomes used to measure efficacy, effectiveness, or risk. This question formed the basis of the literature search.

In people presenting in primary care with potential COVID-19, which are the best predictors of adverse outcomes, such as hospitalisation and ventilation therapy?

Population	Interventions/Exposures	Outcomes	Notes
People in the community presenting to primary care with potential COVID-19 For search purposes include all people presenting with potential COVID19 including hospital-based studies given lack of studies in the population of interest.	Sociodemographic factors: age, sex, ethnicity, socioeconomic status. Health-related behaviours: smoking, alcohol intake Clinical information: comorbidities, current medications, previous medical history, BMI, blood pressure, signs on clinical examination (temperature, pulse, respiratory rate), onset of new symptoms (eg cough, temperature >37.8°C, fatigue, sputum, shortness of breath, muscle aches, sore throat, headache, chills, nasal congestion, nausea, diarrhoea) development of symptoms, symptom progression, symptom duration, combination of symptoms.	Disease severity Admission to hospital Admission to ICU Mechanical ventilation Mortality Duration of symptoms Disease progression	Consider method of consultation: telephone, video, face-to-face and whether different assessments need to be considered for each.

8.2 Literature review

A topic exploration was conducted to identify relevant guidance, systematic reviews and rapid reviews, using a broad internet search including, but not exclusively, the following websites:

BMJ Evidence, Center for Disease Control and Prevention, Cochrane Library, Dynamed, MAGICApp, McMasterforum, Medrxiv, NICE, Oxford Centre for Evidence Based Medicine, TRIP database, Uptodate, WHO.

A systematic search was conducted for primary sources of evidence using Medline and Embase. MedRXiv was searched for preprints added up to and including 24 April 2020. No quality assessment was carried out as all evidence is likely to be low quality given that only early data is available.

8.2.1 Updates to the literature review

A rapid scoping search was carried out between 18–23 June 2020 using BMJ Best Practice (https://bestpractice.bmj.com/topics/en-gb/3000168/history-exam) as the source. All references which were cited as preprints in the original version of this synthesis and have been subsequently published have been updated.

For the February 2021 update a search was conducted in November 2020, using the sources listed above, along with a search for primary literature and systematic reviews in PubMed LitCOVID, and a search with a focus on UK studies in Medline.

The evidence review in children and young people was based on an evidence summary developed by UpToDate®[75] which was updated in November 2020.

8.3 Updating the review

Scoping searches for new evidence will be conducted every six months. The review will be updated if new evidence emerges that changes the current conclusions.

8.4 Contributors

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8.5 Peer review

General practitioners, an epidemiologist, and a lay representative were invited to comment on a draft version of this report, to consider the interpretation of the evidence and feasibility for practice.

SIGN is grateful to these experts for their contribution.

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In addition to those listed above, the following individuals provided feedback on updated versions of this report.

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8.6 Editorial review

As a final quality check, the report was reviewed by an editorial group, as follows:

Dr Roberta James	*Programme Lead, SIGN*
Dr Safia Qureshi	*Director of Evidence, Healthcare Improvement Scotland*
Professor Angela Timoney	*Chair of SIGN*

Abbreviations

ACE	angiotensin-converting enzyme
ARDS	acute respiratory distress syndrome
AT1	angiotensin-II receptor type 1 (angiotensin receptor blockers)
BMI	body mass index
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CTD	connective tissue diseases
CVD	cardiovascular disease
DMARDs	disease modifying antirheumatic drugs
eGFR	estimated glomerular filtration rate
HbA1c	hemoglobin A1c
HR	hazard ratio
IBD	Inflammatory bowel disease
ICU	intensive care unit
IL	interleukin
JAK	Janus kinase
NEWS	National Early Warning Score
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal anti-inflammatory drugs
OR	odds ratio
PICU	paediatric intensive care unit
PIMS-TS	paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2
RCPCH	Royal College of Paediatrics and Child Health
RECAP	Remote COVID-19 Assessment in Primary Care
RR	relative risk
SaO_2	arterial oxygen saturation
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SIGN	Scottish Intercollegiate Guidelines Network
SLE	systemic lupus erythematosus
TNF	Tumour necrosis factor
US	United States
WHO	World Health Organization

References

1 Michelen M, Jones N, and Stavropoulou C. In patients of COVID-19, what are the symptoms and clinical features of mild and moderate cases? [cited 20 Apr 20]. Available from url: https://www.cebm.net/covid-19/in-patients-of-covid-19-what-are-the-symptoms-and-clinical-features-of-mild-and-moderate-case/

2 Zhao X, Zhang B, Li P, Ma C, Gu J, Hou P, et al. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. medRxiv;2020.03.17.20037572

3 Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect 2020.

4 Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020.

5 Spiteri G, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. Euro Surveill 2020;25(9):2000178.

6 Benelli G BE, Canetta C, La Piana G, Merli G, Scartabellati A, et al. SARS-COV-2 comorbidity network and outcome in hospitalized patients in Crema, Italy. medRxiv 2020;20053090.

7 Greenhalgh T, Thompson P, Weiringa S NA, Husain L, Dunlop M, Rushforth A, Nunan D, de Lusignan S, Delaney B. What items should be included in an early warning score for remote assessment of suspected COVID-19? qualitative and Delphi study. BMJ open diabetes research & care 2020 10(11):e042626

8 Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46(6):1099-102.

9 Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia is Baffling to Physicians. Am J Respir Crit Care Med 2020;202(3):356-60.

10 Chauhan V, Galwankar SC, Yellapu V, Perez-Figueroa IJ, Stawicki SP. State of the Globe: The Trials and Tribulations of the COVID-19 Pandemic: Separated but Together, Telemedicine Revolution, Frontline Struggle against "Silent Hypoxia," the Relentless Search for Novel Therapeutics and Vaccines, and the Daunting Prospect of "COVIFLU". J Glob Infect Dis 2020;12(2):39-43.

11 Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.

12 Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19. Am J Emerg Med 2020;38(10):2243 e5- e6.

13 Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med 2020;46(5):837-40.

14 Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. Bmj 2020;368:m1182).

15 Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 2020;288(3):335-44.

16 Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(15):458-64.

17 Park PG, Kim CH, Heo Y, Kim TS, Park CW, Kim CH. Out-of-Hospital Cohort Treatment of Coronavirus Disease 2019 Patients with Mild Symptoms in Korea: an Experience from a Single Community Treatment Center. J Korean Med Sci 2020;35(13):e140.

18 Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020.

19 Escalera-Antezana JP, Lizon-Ferrufino NF, Maldonado-Alanoca A, Alarcón-De-la-Vega G, Alvarado-Arnez LE, Balderrama-Saavedra MA, et al. Clinical features of cases and a cluster of Coronavirus Disease 2019 (COVID-19) in Bolivia imported from Italy and Spain. Travel Medicine and Infectious Disease. 2020;Apr 2:101653.

20 Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.

21 Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT, Skanderson M, et al. Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years. medRxiv 2020:2020.04.09.20059964.

22 Easom N, Moss P, Barlow G, Samson A, Taynton T, Adams K, et al. Sixty-eight consecutive patients assessed for COVID-19 infection: Experience from a UK Regional infectious diseases Unit. Influenza Other Respir Viruses 2020;14(4):374-9.

23 Greenhalgh T, Kotze K, Van Der Westhuizen HM. Are there any evidence-based ways of assessing dyspnoea (breathlessness) by telephone or video. [cited 20 Apr 20]. Available from url: https://www.cebm.net/covid-19/are-there-any-evidence-based-ways-of-assessing-dyspnoea-breathlessness-by-telephone-or-video/

24 Tarassenko L and Greenhalgh T. Question: Should smartphone apps be used as oximeters? Answer: No. [cited 20 Apr 20]. Available from url: https://www.cebm.net/covid-19/question-should-smartphone-apps-be-used-as-oximeters-answer-no/

25 Greenhalgh T, Treadwell J, Burrow R, Roberts N. NEWS (or NEWS2) score when assessing possible COVID-19 patients in primary care? [cited 20 Apr 20]. Available from url: https://www.cebm.net/covid-19/should-we-use-the-news-or-news2-score-when-assessing-patients-with-possible-covid-19-in-primary-care/

26 Nunan D BJ, Mahtani K, et al. . COVID-19 signs and symptoms tracker. [cited 07 Jan 21]. Available from url: https://www.cebm.net/covid-19/covid-19-signs-and-symptoms-tracker/

27 Delaney B. RECAP Project. [cited 7 Jan 21]. Available from url: https://imperialbrc.nihr.ac.uk/research/covid-19/covid-19-ongoing-studies/recap/

28 Sudre Carole H LK, Lochlainn Mary Ni, Varsavsky Thomas, Murray Benjamin, Graham Mark S, et al. Symptom clusters in Covid19: A potential clinical prediction tool from the COVID Symptom study app. medRxiv 2020;2020.06.12.20129056.

29 Clift AK, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 2020;371:m3731.

30 Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature 2020;584(7821):430-6.

31 McKeigue PM, Weir A, Bishop J, McGurnaghan SJ, Kennedy S, McAllister D, et al. Rapid Epidemiological Analysis of Comorbidities and Treatments as risk factors for COVID-19 in Scotland (REACT-SCOT): A population-based case-control study. PLoS Medicine / Public Library of Science 2020;17(10):e1003374.

32 Alaa AM, Qian Z, Rashbass J, Pinto KG, Benger J, van der Schaar M. Ethnicity and Outcomes of COVID-19 Patients in England. NHS Digital; 2020. [cited 7 July 2020]. Available from url: https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/ethnicity-and-outcomes-of-covid-19-patients-in-england

33 Harrison EM, Docherty AB, Barr B, Buchan I, Carson G, Drake TM, et al. Ethnicity and outcomes from COVID-19: the ISARIC CCP-UK prospective observational cohort study of hospitalised patients. SSRN Electronic Journal 2020.

34 Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107.

35 Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:m3320.

36 Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–October 3, 2020. Morbidity and Mortality Weekly Report 2020;69(44):1641.

37 Badr DA, Mattern J, Carlin A, Cordier AG, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at >/=20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol 2020;223(5):764-8.

38 Scottish Intensive Care Society Audit Group report on COVID-19. Public Health Scotland; 2020. [cited 14 July 2020]. Available from url: https://beta.isdscotland.org/media/4916/2020-07-08_sicsag_report.pdf

39 Deaths involving coronavirus (COVID-19) in Scotland. National Records of Scotland; 2020. [cited 15 July 2020]. Available from url: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/weekly-and-monthly-data-on-births-and-deaths/deaths-involving-coronavirus-covid-19-in-scotland

40 Niedzwiedz CL, O'Donnell CA, Jani BD, Demou E, Ho FK, Celis-Morales C, et al. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. BMC Medicine 2020;18(1):160.

41 Mutambudzi M, Niedwiedz C, Macdonald EB, Leyland A, Mair F, Anderson J, et al. Occupation and risk of severe COVID-19: prospective cohort study of 120 075 UK Biobank participants. Occup Environ Med 2020.

42 Martin CA, Patel P, Goss C, Jenkins DR, Price A, Barton L, et al. Demographic and occupational determinants of anti-SARS-CoV-2 IgG seropositivity in hospital staff. J Public Health (Oxf) 2020.

43 Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health 2020;5(9):e475-e83.

44 Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis 2020;71(15):896-7.

45 Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Severe Obesity as an Independent Risk Factor for COVID-19 Mortality in Hospitalized Patients Younger than 50. Obesity 2020;28(9):1595-99.

46 Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet 2020;395(10236):1544-5.

47 Savasi VM, Parisi F, Patanè L, Ferrazzi E, Frigerio L, Pellegrino A, et al. Clinical Findings and Disease Severity in Hospitalized Pregnant Women With Coronavirus Disease 2019 (COVID-19). Obstetrics & Gynecology 2020;136(2):252-8.

48 Patanavanich R, Glantz SA. Smoking Is Associated With COVID-19 Progression: A Meta-analysis. Nicotine & Tobacco Research 2020;22(9):1653-55.

49 Smoking and COVID-19: Scientific Brief. World Health Organization; 2020. [cited 7 July 2020]. Available from url: https://www.who.int/publications/i/item/smoking-and-covid-19

50 Lee LYW, Cazier JB, Starkey T, Turnbull CD, Team UKCCMP, Kerr R, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet (London, England) 2020;395(10241):1919-26.

51 Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet (London, England) 2020;395(10241):1907-18.

52 Alberta Health Services. Topic: Is being immunosuppressed (in its various forms) associated with increased likelihood of recognized COVID-19 and/or increased disease severity? Alberta: Alberta Health Services; 2020. [cited 20 Jan 21]. Available from url: https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-sag-immunosuppression-and-covid-19-risk-rapid-review.pdf

53 Rossi G, Marino P, Formisano M, Venturelli D, Vicentini F, Grilli M, et al. Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the Province of Reggio Emilia, Italy. medRxiv 2020:2020.04.13.20063545.

54 Pigoga JL, Friedman A, Broccoli M, Hirner S, Naidoo AV, Singh S, et al. Clinical and historical features associated with severe COVID-19 infection: a systematic review. medRxiv 2020:2020.04.23.20076653.

55 Rubin SJS, Falkson SR, Degner NR, Blish C. Clinical characteristics associated with COVID-19 severity in California. Journal of Clinical and Translational Science 2020:1-4.

56 Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. PLoS Med 2020;17(9):e1003321.

57 Guo X, Zhu Y, Hong Y. Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension. Hypertension 2020;76(2):e13-e4.

58 Alberta Health Services. Topic: What risk factors (such as age, medical conditions, or lifestyle factors) are associated with the development of severe outcomes in COVID-19? [cited Available from url: https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-sag-risk-factors-for-severe-covid-19-outcomes-rapid-review.pdf

59 Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Jr., Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. J Allergy Clin Immunol 2020;146(2):327-9.

60 Mahdavinia M, Foster KJ, Jauregui E, Moore D, Adnan D, Andy-Nweye AB, et al. Asthma prolongs intubation in COVID-19. J Allergy Clin Immunol Pract 2020;8(7):2388-91.

61 Singh AK, Singh R. Does poor glucose control increase the severity and mortality in patients with diabetes and COVID-19? Diabetes & metabolic syndrome 2020;14(5):725-7.

62 Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ open diabetes research & care 2020;8(1):e001476.

63 Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab 2020;22(10):1897-906.

64 Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health 2020;5(8):e444-e51.

65 Gianfrancesco M HK, Al-Adely S, et al. . Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Annals of the Rheumatic Diseases 2020;79(7):859-66.

66 Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. Kidney international 2020;97(6):1076-82.

67 Latif F, Farr MA, Clerkin KJ, Habal MV, Takeda K, Naka Y, et al. Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019. JAMA cardiology 2020:e202159.

68 Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2020;20(7):1800-8.

69 Zhu L, Gong N, Liu B, Lu X, Chen D, Chen S, et al. Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China. European urology 2020;77(6):748-54.

70 Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York. Journal of the American Society of Nephrology 2020;31(6):1150.

71 Tisminetzky M, Delude C, Hebert T, Carr C, Goldberg RJ, Gurwitz JH. Age, Multiple Chronic Conditions, and COVID-19: A literature review. J Gerontol A Biol Sci Med Sci 2020.

72 Marengoni A, Zucchelli A, Vetrano DL, Armellini A, Botteri E, Nicosia F, et al. Beyond chronological age: Frailty and multimorbidity predict in-hospital mortality in patients with coronavirus disease 2019. J Gerontol A Biol Sci Med Sci 2020.

73 King JT, Jr., Yoon JS, Rentsch CT, Tate JP, Park LS, Kidwai-Khan F, et al. Development and validation of a 30-day mortality index based on pre-existing

medical administrative data from 13,323 COVID-19 patients: The Veterans Health Administration COVID-19 (VACO) Index. PLoS One 2020;15(11):e0241825.

74 Fernández-Niño JA, Guerra-Gómez JA, A JI. Multimorbidity patterns among COVID-19 deaths: proposal for the construction of etiological models. Rev Panam Salud Publica 2020;44:e166.

75 Deville J, Song E, Ouellette C. Coronavirus disease 2019 (COVID-19): Clinical manifestations and diagnosis in children. [cited Available from url: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-clinical-manifestations-and-diagnosis-in-children?topicRef=128190&source=see_link

76 Gotzinger F, Santiago-Garcia B, Noguera-Julian A, Lanaspa M, Lancella L, Calo Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020;4(9):653-61.

77 Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. European journal of pediatrics 2020;179(7):1029-46.

78 Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine 2020.

79 Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatrica 2020;23:23.

80 Royal College of Paediatrics and Child Health (RCPCH). COVID-19 - research evidence summaries. [cited Available from url: https://www.rcpch.ac.uk/resources/covid-19-research-evidence-summaries#at-risk-groups

81 Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 disease severity risk factors for pediatric patients in Italy. Pediatrics 2020;146(4).

82 Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020;370:m3249.

83 Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health 2020.

84 de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. The Lancet Infectious Diseases 2020;20(9):1034-42.

85 Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. JAMA Pediatr 2020.

86 Andina D, Noguera-Morel L, Bascuas-Arribas M, Gaitero-Tristan J, Alonso-Cadenas JA, Escalada-Pellitero S, et al. Chilblains in children in the setting of COVID-19 pandemic. Pediatr Dermatol 2020.

87 de Masson A, Bouaziz J-D, Sulimovic L, Cassius C, Jachiet M, Ionescu M-A, et al. Chilblains is a common cutaneous finding during the COVID-19 pandemic: a retrospective nationwide study from France. Journal of the American Academy of Dermatology 2020;83(2):667-70.

88 Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol 2020;183(1):71-7.

89 Mehta NS, Mytton OT, Mullins EWS, Fowler TA, Falconer CL, Murphy OB, et al. SARS-CoV-2 (COVID-19): What Do We Know About Children? A Systematic Review. Clinical Infectious Diseases 2020;71(9):2469-79.

90 Mantovani A, Rinaldi E, Zusi C, Beatrice G, Saccomani MD, Dalbeni A. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. Pediatr Res 2020.

91 Royal College of Paediatrics and Child Health (RCPCH). Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. London: RCPCH; 2020. [cited 12 Jan 2021]. Available from url: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

92 Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health 2020;4(9):669-77.

93 Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatric respiratory reviews 2020:S1526-0542(20)30117-2.