Evidence review

Assessment of COVID-19 in primary care:

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

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## Summary of revisions

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<tr>
<td>07/05/2020</td>
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</table>
| 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 poor outcomes  
  *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 death’  
  *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 |
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Introduction

The purpose of this rapid review is to provide NHSScotland with advice on assessment of patients with COVID-19 in primary care.

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. 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 via 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 6.
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.

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

- 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)*

- Characteristics which have been associated with severe disease are older age, male sex and minority ethnic background. 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 pulmonary disease, chronic kidney disease, cancer and solid organ transplantation. *(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 (AT1) antagonists and severe COVID-19 disease but very few studies have investigated this. *(Table 2)*

- The evidence for chronic liver disease as a risk factor is mixed.

- Some evidence is emerging that less advantaged socioeconomic status and frailty are associated with poor outcomes. *(Table 2)*

- Clinical signs which have been found to be associated with severe disease are low oxygen saturation levels, low blood pressure and high respiratory rate. Of these, the strongest evidence relates to oxygen saturation levels. *(Table 3)*

- The evidence base remains too weak and emergent to make definitive recommendations.
1. Signs and symptoms
The intention of this evidence review was to identify any evidence of 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. 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. 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.

Table 1 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. 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 severity of 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. This finding is supported by evidence from outside China where 21 out of 24 patients (88%) in ICU in the US experienced shortness of breath compared with 5% of the first 38 diagnosed cases (of any severity) from eight European countries and 32% of cases confirmed after presenting at an Emergency Department in Italy. There is some evidence that patients may be suffering from hypoxia without showing outward symptoms of shortness of breath.
### Table 1: Prevalence of symptoms in mild/moderate and severe COVID-19

<table>
<thead>
<tr>
<th>Symptoms associated with COVID-19</th>
<th>Prevalence (% of cases - range) from studies outside China</th>
<th>Prevalence (% of cases) from meta-analysis – mainly China&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ICU Hospitalised patients All cases Critical illness Non-critical illness</td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;1-6,8,10&lt;/sup&gt;</td>
<td>88</td>
<td>66–86</td>
</tr>
<tr>
<td>Fever &gt;37.8°C&lt;sup&gt;5,6,8,10,13&lt;/sup&gt;</td>
<td>28–73</td>
<td>24–85</td>
</tr>
<tr>
<td>Dyspnoea&lt;sup&gt;4,6,8,10,14&lt;/sup&gt;</td>
<td>88</td>
<td>11–80</td>
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<tr>
<td>Fatigue&lt;sup&gt;5,11&lt;/sup&gt;</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Cough (sputum)</td>
<td>No evidence found comparing mild/moderate to severe disease</td>
<td>32</td>
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<tr>
<td>Delirium (confusion)</td>
<td>No evidence found comparing mild/moderate to severe disease.</td>
<td></td>
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<tr>
<td>Diarrhoea&lt;sup&gt;6,11&lt;/sup&gt;</td>
<td>-</td>
<td>17–27</td>
</tr>
<tr>
<td>Vomiting/nausea&lt;sup&gt;6,8,11&lt;/sup&gt;</td>
<td>-</td>
<td>8–24</td>
</tr>
<tr>
<td>Myalgia&lt;sup&gt;8,11,14&lt;/sup&gt;</td>
<td>-</td>
<td>34–42</td>
</tr>
<tr>
<td>Chest pain&lt;sup&gt;6,9,14&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anosmia/dysgeusia</td>
<td>No evidence found comparing mild/moderate to severe disease</td>
<td></td>
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<tr>
<td>Headache&lt;sup&gt;6,11&lt;/sup&gt;</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>No evidence found comparing mild/moderate to severe disease</td>
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<tr>
<td>Abdominal pain&lt;sup&gt;6,11&lt;/sup&gt;</td>
<td>-</td>
<td>17</td>
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<tr>
<td>Sore throat&lt;sup&gt;4,6,8-11,14&lt;/sup&gt;</td>
<td>8</td>
<td>18–61</td>
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2. **Prognostic Tools**

A variety of risk prediction scores and tools have been developed, which may have 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 here: [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/](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. However, it has been temporarily endorsed by the Royal College of General Practitioners as a response to COVID-19 [https://elearning.rcgp.org.uk/mod/page/view.php?id=10570](https://elearning.rcgp.org.uk/mod/page/view.php?id=10570)

Five studies of association between comorbidities or risk factors and hospitalisation for COVID-19, severe illness or death were identified<sup>6,12,13,16</sup>. **Table 2** shows the associations noted in these studies as well as ranges of comorbidities/risk factors identified from the wider body of identified studies. A meta-analysis, available as a preprint, summarises findings of 63 association studies of which 57 were from China.<sup>17</sup> Relevant information from this study is also provided in **Table 2**. Not all variables are included in all studies and considerable risks of confounding remain, which may explain the variation in the results reported in these studies. The headings used for the comorbidities/risk factors are those cited in the studies and have not been recategorised for this review.
Table 2: Comorbidities and risk factors associated with COVID-19

<table>
<thead>
<tr>
<th>Comorbidity/risk factor</th>
<th>Description</th>
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| **Age**                | Older age was reported as significantly associated with severe disease in 47 out of 54 studies (87%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China.  

The average age for hospitalisation reported in studies from the US and Italy was 53–68 years, for ICU admission was 63–70 years and for death was 77–81 years. A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death was significantly associated with older age. The hazard ratio (HR) (compared with age 50–59) for age ≥80 was 20.6 (18.7 to 22.7), 70–79 was 6.1 (5.5 to 6.7) and 60–69 was 2.4 (2.2 to 2.7).  

A study examining associations in 5,279 confirmed cases in New York found that older age was the strongest predictor of hospitalisation. Age ≥75 years (odds ratio (OR) 37.9, 95% confidence interval (CI) 26.1 to 56.0) and age 65–74 (OR 8.7, 95% CI 6.7 to 11.2). The association was retained albeit weakly for risk of critical illness after blood test results on admission were included in the analysis: age ≥75 years (OR 2.3, 95% CI 1.6 to 3.4) and age 65–74 (OR 1.7, 95% CI 1.2 to 2.5).  

Other studies of association for settings outside China found mixed results. An unpublished study of 585 cases in US veterans aged 54–75 found age significantly associated with hospitalisation but not ICU admission when laboratory findings were included in the analysis. An unpublished study of 2,653 cases in Italy found that age was significantly associated with both hospitalisation and death. A smaller unpublished Italian study of 411 cases found that older age was significantly associated with death but not admission to ICU. A small US study (n=54) found that older age was significantly associated with hospital admission and pneumonia but not if oxygen saturation levels were included in the analysis.  

**Sex** | Male sex was reported as significantly associated with severe disease in 16 out of 45 studies (36%) which reported on sex in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China.  

In studies from Korea, Europe, Italy, USA and Bolivia, males accounted for 38–67% of cases, 50–63% of hospital admissions, 63–93% of severe disease and 56–74% of deaths.  

A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death was significantly associated with male sex (HR 1.6, 95% CI 1.5 to 1.7). |
A study examining associations in 5,279 confirmed cases in New York found that there was a significant association between male sex and hospitalisation (OR 2.8, 95% CI 2.4 to 3.2) but not critical illness once laboratory results were included in the analysis. Two unpublished studies from settings outside China were identified. A study of 2,653 cases in Italy found that male sex was significantly associated with both hospitalisation and death. Another Italian study, of 411 cases at a single hospital, found that male sex was significantly associated with admission to ICU but not death.

| Ethnicity | There is no mention of ethnicity as a variable of interest in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China. A systematic review of ethnicity reporting in patients with COVID-19 and its relation to clinical outcomes suggested that evidence on ethnicity as a risk factor for disease severity has emerged more slowly than clinical risk factors, in part because studies published in China do not report data disaggregated by ethnicity. Data from the grey literature and preprint articles suggest that those of Black and Asian ethnicities are at increased risk of hospitalisation, admission to the intensive care unit and death. 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. 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. A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death 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. A study of 5,279 cases in New York found no significant association between Asian ethnicity and either hospitalisation (OR 1.29, 95% CI 0.97 to 1.72) or critical illness (OR 1.24, 95% CI 0.82 to 1.90). The same study also found no association between African American ethnicity and hospitalisation and a negative association with critical illness (ie African Americans were less likely to experience critical illness), OR 0.6, 95% CI 0.4 to 0.8. A further preprint study of 585 cases in a US cohort of veterans aged 54–75 found that Black ethnicity was significantly associated with testing positive for COVID-19 but was not associated with hospitalisation or admission to intensive care. |

| Minorit y ethnic background | significantly associated with severe disease. |
### Socioeconomic status

Socioeconomic status significantly associated with poor outcomes

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% vs 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% vs 34.7%).

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).

A recent 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.

### Obesity

Obesity significantly associated with severe disease.

Body mass index (BMI) was reported as significantly associated with severe disease in six out of 11 studies (55%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China.

A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death was significantly associated with obesity. The hazard ratio for BMI of 30–34.9 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 or over was 1.9 (95% CI 1.7 to 2.1) all compared with BMI <30.

One US study (n=5,279) found that obesity was one of the most important factors for hospitalisation after age; BMI >40 kg/m² (OR 2.5, 95% CI 1.8 to 3.4) and BMI 30–40 kg/m² (OR 1.8, 95% CI 1.5 to 2.2). BMI was also associated with critical illness in those with BMI >40 kg/m² (OR 1.7, 95% CI 1.1 to 2.7) but not in those with BMI 30–40 kg/m² (OR 1.1, 95% CI 0.85 to 1.5). An Italian study including 2,653 cases found that obesity was not associated with either hospitalisation or death.

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.

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/m² was independently associated with mortality (adjusted OR 5.1, 95% CI 2.3 to 11.1). For the older population, BMI above 40 kg/m² was also independently associated with mortality to a lesser extent (adjusted OR 1.6, 95% CI 1.2 to 2.3).
<table>
<thead>
<tr>
<th>Smoking</th>
<th>Significantly associated with severe disease.</th>
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<tr>
<td>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. This is supported by a systematic review of peer-reviewed studies carried out by the World Health Organization (WHO) suggesting that smoking is associated with increased severity of disease and death in hospitalised COVID-19 patients. The authors note that although this is likely related to severity, there is no evidence to quantify the risk to smokers of COVID-19-related hospitalisation. A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death 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). Being a current smoker was reported as significantly associated with severe disease in one out of 11 studies (9%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China. In the association studies identified for settings outside China two studies considered smoking. One study of 585 cases in US veterans found no association with hospitalisation or ICU admission. A study of 5,279 cases in New York found a negative association between current smoking and hospitalisation (OR 0.59, 95% CI 0.43 to 0.81) and former smoking and hospitalisation (OR 0.69, 95% CI 0.56 to 0.85) but no association between either risk factor and critical illness. A systematic review including 28 studies concluded that there was low-quality evidence that current and former smoking compared with never smoking is associated with greater disease severity.</td>
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<table>
<thead>
<tr>
<th>Cancer</th>
<th>Significantly associated with severe disease.</th>
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<tr>
<td>Cancer was reported as significantly associated with severe disease in five out of 19 studies (26%) in an unpublished meta-analysis including 17,648 COVID-19 patients, mostly in China. Four of the association studies identified from settings outside China included cancer in their analysis. Three studies found no association with hospitalisation, admission to ICU or death. One study of 2,653 cases in Italy found that cancer was associated with both hospitalisation (HR 1.4, 95% CI 1.1 to 1.7) and death (HR 1.4, 95% CI 1 to 2).</td>
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</table>
A recent large observational study of 10,926 COVID-19 deaths in England distinguished haematological and non-haematological cancer and time since diagnosis. The study found that COVID-19 death 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 5 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 an equivalent risk as individuals without cancer for cancers diagnosed more than 5 years previously.\(^{24}\)

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 presence of 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 4 weeks.\(^{38}\)

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: 1.60, 95% CI 1.03 to 2.47), number of comorbidities (two v none: 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: 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.\(^{39}\)

<table>
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<tr>
<th>Cardiovascular disease</th>
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<tr>
<td>Significantly associated with severe disease.</td>
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Cardiovascular disease (CVD) was reported as significantly associated with severe disease in 16 out of 25 studies (64%) in a large unpublished meta-analysis of mostly Chinese studies.\(^{17}\) After age and ‘at least one comorbidity’, CVD and hypertension had the strongest association.

An Italian study of 411 cases found CVD had a significant association with death but not with ICU admission.\(^{6}\)
**Hypertension**
Hypertension was reported as significantly associated with severe disease in 22 out of 33 studies (67%) and coronary vascular disease in 16 out of 25 studies (64%) in the large unpublished meta-analysis of mostly Chinese studies. After age and any comorbidity these two conditions had the strongest association.

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.

A further US study (n=585) did not find any significant association between hypertension and hospitalisation or critical illness. Two Italian studies (n=2,653 and n=411) found that hypertension was significantly associated with both hospitalisation and death. A fifth study (n=54) found hypertension significant for hospitalisation and acute respiratory distress syndrome (ARDS) but that the significance disappeared if oxygen saturation was included in the analysis.

**Stroke**
Stroke was also reported as significantly associated with severe disease in five out of 12 studies in the systematic review of Chinese studies (42%).

**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.

**Coronary artery disease**
A US study (n=5,279) found no association between coronary artery disease and hospitalisation or critical illness.

**Ischaemic heart disease**
One Italian study (n=2,653) found a significant association between ischaemic heart disease and both hospitalisation and death.

**Arrhythmia**
One Italian study (n=2,653) found a significant association between arrhythmia and both hospitalisation and death.

**Vascular disease**
Two studies (Italy, n=2,653; US, n=585) found no associations between vascular disease and death.

**Hyperlipidaemia**
One study (US, n=5,279) found hyperlipidaemia had a negative association with hospitalisation but found no association with critical illness. Another found no association between dyslipidaemia and hospitalisation or death.
### ACE inhibitors and AT1 antagonists

Four of the association studies identified for settings outside China included ACE-I and AT1 antagonists in their analysis. Three studies found no association with either hospitalisation or severe disease.\(^6,13,23\) One study (Italy, \(n=2,653\)) found that the medication was associated with hospitalisation but not death.\(^16\)

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).\(^40\)

### Chronic kidney disease

**Significantly associated with severe disease.**

Chronic kidney disease (CKD) was reported as significantly associated with severe disease in four out of 14 studies (29%) in an unpublished meta-analysis including 17,648 COVID-19 patients, mostly in China.\(^17\)

Four of the association studies identified from settings other than China included CKD in the analysis. All found some evidence of association with hospitalisation but the picture relating to severe disease and death was more mixed. A study of 5,279 confirmed cases in New York found that CKD had the strongest association with hospitalisation (OR 2.6, 95% CI 1.9 to 3.6) after age and heart failure but was inversely associated with critical illness (OR 0.73, 95% CI 0.55 to 1.0). A study of 2,653 cases in Italy found that CKD was associated with hospitalisation (HR 1.9, 95% CI 1.3 to 2.9) but not death.\(^16\) A US study of 585 cases in veterans aged 54–75 found a significant association for both hospitalisation and ICU admission in univariate analyses which was no longer significant when laboratory results were added to the analysis.\(^13\) An Italian study of 411 cases found renal insufficiency to be associated with both death and ICU admission.\(^6\)

### Chronic liver disease

**Evidence of association is unclear.**

Hepatitis or cirrhosis was reported as significantly associated with severe disease in none of the 14 studies in an unpublished meta-analysis including 17,648 COVID-19 patients, mostly in China.\(^17\) However, a number of studies in China have shown an association between metabolic associated fatty liver disease and severe COVID-19 disease.\(^41-43\)

In contrast, a multicentre retrospective study (\(n=50\)) and a multicentre research network study (\(n=2,780\)) showed that chronic liver disease (particularly cirrhosis) was associated with severe disease in Italy and the US.\(^44,45\)

### Chronic respiratory disease

**Significantly associated with severe disease.**

Chronic obstructive pulmonary disease (COPD) was reported as significantly associated with severe disease in six out of 19 studies (32%) which reported the variable in an unpublished meta-analysis including 17,648 COVID-19 patients, mostly in China.\(^17\) Other respiratory disease was reported as significantly associated with severe disease in two out of seven studies (29%) in the same meta-analysis.
A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death 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 COVID-19 death (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).\(^{24}\)

In unpublished studies from Korea and the USA and one published study from the USA, the prevalence of chronic respiratory disease was 7–15% in cases, 7–17% in hospital admissions, 11–21% in ICU admissions and 17% in patients who died.\(^{8,12,18,46}\)

Four of the association studies identified from settings other than China included pulmonary disease in their analysis. Results of the analysis were mixed. Two studies found no associations. A study of 5,279 confirmed cases in New York found no association between pulmonary disease and hospitalisation or critical illness.\(^{12}\)

A study of 411 cases from one hospital in Italy found pulmonary diseases not to be associated with death or admission to ICU.\(^{9}\)

Two studies (US, n=585; Italy n=2,653) found associations with hospitalisation but not severe disease or death.\(^{13,16}\)

The evidence for asthma as a risk factor for COVID-19 severity is mixed. A large 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.\(^{47}\)

A smaller 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.\(^{48}\)

No associations were found for asthma in the single study which looked at this separately.\(^{13}\)

### Diabetes

<table>
<thead>
<tr>
<th>Significantly associated with severe disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes was reported as significantly associated with severe disease in 13 out of 32 studies (41%) in the unpublished meta-analysis including 17,648 COVID-19 patients, mostly in China.(^{17})</td>
</tr>
</tbody>
</table>

An unpublished population cohort study assessing the risks of hospital death with COVID-19 between 1 March and 11 May 2020 in individuals registered with a general practitioner in England included 263,830 people with a recorded diagnosis of Type 1 diabetes and 2,864,670 people with a recorded diagnosis of Type 2 diabetes. Adjusted for age, sex, deprivation, ethnicity and geographical region, people with Type 1 and Type 2 diabetes had 3.50 (95% CI 3.15 to 3.89) and 2.03 (95% CI 1.97 to 2.09) times the odds, respectively, of dying in hospital with COVID-19 compared with those without diabetes.\(^{49}\)

A further unpublished cohort study by the same authors showed that hyperglycaemia in people with Type 1 or Type 2 diabetes was
Independently associated with increased COVID-19 mortality. Risk of death was significantly higher in those with an HbA1c >58 mmol/mol and increased as HbA1c levels rose.\textsuperscript{50}

A US study with 5,279 cases found a significant association between diabetes and hospitalisation (OR 2.24, 95% CI (1.84 to 2.73) but not critical illness.\textsuperscript{12} Another US study (n=585) found a significant association for hospitalisation but not critical illness.\textsuperscript{13} An Italian study (n=2,653) found that diabetes was significantly associated with death but not admission to ICU.\textsuperscript{16}

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.\textsuperscript{51,52}

An unpublished 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.\textsuperscript{53}

**Frailty**

**Significantly associated with death.**

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 30-day mortality. Adjusted hazard ratios compared with a CFS score of 1–2 (fit and well) were 1.8 (95% CI 1.5 to 2.9) for scores 5–6 and 2.4 (95% CI 1.5 to 3.8) for scores 7–9.\textsuperscript{54}

**Immunosuppressive conditions**

**Significantly associated with death**

A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death 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 1.7, 95% CI 1.3 to 2.2).\textsuperscript{24}

**Solid organ transplants**

**Significantly associated with death**

A recent large observational study of 10,926 COVID-19 deaths in England found that COVID-19 death was significantly associated with organ transplant (HR 3.6, 95% CI 2.8 to 4.5).\textsuperscript{24}

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.\textsuperscript{55-58} In contrast, a US case series of 15 kidney transplant recipients reported outcomes similar to the general population.\textsuperscript{59}
<table>
<thead>
<tr>
<th>Steroids or other immuno-suppressants</th>
<th>Evidence of association is unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunocompromise was considered in only two out of 63 studies of association reported in an unpublished meta-analysis of 17,648 COVID-19 cases, mostly in China. Neither of the studies found that it was significantly associated with severe disease.</td>
</tr>
<tr>
<td></td>
<td>In two studies from the USA (n=2,026,227 and n=5,143) patients on immunosuppressant medications accounted for 3–5% of cases, 6% of hospital admissions and 6–9% of severe disease.</td>
</tr>
<tr>
<td></td>
<td>None of the identified association studies from settings outside China included steroids or immunosuppressants in the analysis.</td>
</tr>
</tbody>
</table>
At least one comorbidity was reported as significantly associated with severe disease in 17 out of 23 (74%) studies which reported the variable in an unpublished meta-analysis including 17,648 COVID-19 patients, mostly in China.\textsuperscript{17} It was second only to age as the variable which was reported as significant in the highest percentage of studies. In studies from Singapore, Korea, Italy and USA patients reported as having at least one comorbidity accounted for 27–29% of cases, 71–89% of hospital admissions, 68–78% of severe disease and 95–99% of deaths.\textsuperscript{4,6,12,18–23}

Only one of the identified association studies included ‘at least one comorbidity’ as a variable. Three other studies looked only at individual comorbidities\textsuperscript{12,13,23} and one used a composite score of comorbidity, the Charlson Comorbidity Index.\textsuperscript{16} A study of 411 cases presenting at an emergency department in Italy found a significant association between any comorbidity and both ICU admission and death.\textsuperscript{8} An Italian study including 2,653 cases found a significant association between the Charlson Comorbidity Index scores of 1 and death and scores of 2 and 3 or more with both death and hospitalisation.\textsuperscript{16} A higher score represents a greater level of comorbidity with 0 representing no comorbid conditions.

### 3. Clinical measures

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

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

| Oxygen saturation | Arterial oxygen saturation (SpO$_2$) was reported as significantly associated with severe disease in four out of five studies (80%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China.\textsuperscript{17} It was unclear whether this was a higher or lower oxygen saturation and what level was investigated. Saturation levels were not given, nor was it explicitly stated that lower oxygen saturation was associated with severe disease, this has been assumed. 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%).\textsuperscript{12} A US study of 585 veterans aged 54–75 found that a 1% reduction in SpO$_2$ was not associated with hospitalisation or admission to ICU.\textsuperscript{13} 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.\textsuperscript{23} |
Respiratory rate
Significantly associated with severe disease.

Respiratory rate was reported as significantly associated with severe disease in six out of 10 studies (60%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China. It is unclear what level was investigated for significance. None of the identified studies of association from settings outside China included respiratory rate in their analysis.

Heart rate
Evidence of association is unclear.

Heart rate was reported as significantly associated with severe disease in one out of seven studies (14%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China. 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.

Systolic blood pressure
Significantly associated with severe disease.

Systolic blood pressure (SBP) was reported as significantly associated with severe disease in two out of five studies (40%) in an unpublished meta-analysis including 17,648 patients with COVID-19, mostly in China. 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.

4. Method of patient consultation

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. Questions like those in the COVID-19 Scottish Primary Care Hub Triage Guide can be asked. Smartphone apps should not be used as oximeters.
5. Sources of further information
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](https://bestpractice.bmj.com/topics/en-gb/3000168/prognosis) and [https://bestpractice.bmj.com/topics/en-gb/3000168/history-exam](https://bestpractice.bmj.com/topics/en-gb/3000168/history-exam)


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


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](http://www.sign.ac.uk)
6. Methodology

6.1 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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Interventions/Exposures</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>People in the community presenting to primary care with potential COVID-19</td>
<td>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 &gt;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.</td>
<td>Disease severity Admission to hospital Admission to ICU Mechanical ventilation Mortality Duration of symptoms Disease progression</td>
<td>Consider method of consultation: telephone, video, face-to-face and whether different assessments need to be considered for each.</td>
</tr>
</tbody>
</table>
6.2 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.

6.2.1 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 which have been subsequently published have been appropriately updated.

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

6.4 Contributors

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6.4.1 Acknowledgments
SIGN is grateful to Dr Beth White, Consultant in Infectious Diseases and Acute Medicine, Queen Elizabeth University Hospital, Glasgow for contributing to the development of the report.
6.5 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.

Dr Neave Corcoran  General Practitioner, NHS Lothian
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In addition to those listed above, the following individuals provided feedback on updated versions of this report.

Professor Tom Evans  Professor of Molecular Microbiology, Institute of Infection, Immunity & Inflammation, University of Glasgow and Consultant Infectious Disease Physician, NHS Greater Glasgow & Clyde
Ms Anne Keane  Public Partner, Healthcare Improvement Scotland, Edinburgh
Professor Gregory Lip  Price-Evans Chair of Cardiovascular Medicine, University of Liverpool
Dr Elaine McNaughton  General Practitioner, Carnoustie Medical Group, Carnoustie
Mr Alan Timmins  Lead Clinical Pharmacist – Acute, NHS Fife

6.6 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
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AT1</td>
<td>angiotensin-II receptor antagonists/angiotensin receptor blockers</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CFS</td>
<td>Clinical Frailty Scale</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>NEWS</td>
<td>National Early Warning Score</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<td>SaO₂</td>
<td>arterial oxygen saturation</td>
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<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
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<tr>
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<td>systolic blood pressure</td>
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<td>Scottish Intercollegiate Guidelines Network</td>
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<td>United States</td>
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<td>WHO</td>
<td>World Health Organization</td>
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References


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