



The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to your question. The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate.

## YOUR QUESTION

The following is our interpretation of the question as stated:

1. [In patients with COVID-19, what patient characteristics will suggest development of severe disease?](#)
2. [In patients with severe COVID-19, what treatments are shown to be most effective in reducing fatality or increasing survival rates?](#)
3. [Which populations have the highest ratio of severe to mild/moderate cases of COVID-19?](#)

## IN A NUTSHELL

Based on data from EU/EEA countries<sup>2</sup>, 32% of the diagnosed cases have required hospitalisation and 2.4% have had severe illness requiring respiratory support or ventilation. The crude fatality rate was 1.5% among diagnosed cases and 11% among hospitalised cases. The likelihood of hospitalisation, severe illness and death increases in persons over 65 years of age and those with defined risk factors including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, compromised immune status, cancer and obesity.

In a systematic review and meta-analysis by Zhao et al.<sup>4</sup>, predictors for disease severity included old age ( $\geq 50$  yrs, odds ratio [OR] = 2.61; 95% CI, 2.29-2.98), male (OR = 1.348, 95% CI, 1.195-1.521), smoking (OR = 1.734, 95% CI, 1.146-2.626) and any comorbidity (OR = 2.635, 95% CI, 2.098-3.309), especially chronic kidney disease (CKD, OR = 6.017; 95% CI, 2.192-16.514), chronic obstructive pulmonary disease (COPD, OR = 5.323; 95% CI, 2.613-10.847) and cerebrovascular disease (OR = 3.219; 95% CI, 1.486-6.972). In terms of laboratory results, increased lactate dehydrogenase (LDH), C-reactive protein (CRP) and D-dimer and decreased blood platelet and lymphocytes count were highly associated with severe COVID-19 [all for  $P < 0.001$ ]. Meanwhile, old age ( $\geq 60$  yrs, RR = 9.45; 95% CI, 8.09-11.04), followed by cardiovascular disease (RR = 6.75; 95% CI, 5.40-8.43) hypertension (RR =



4.48; 95% CI, 3.69-5.45) and diabetes (RR = 4.43; 95% CI, 3.49-5.61) were found to be independent prognostic factors for the COVID-19 related death.

## Q1: In patients with COVID-19, what patient characteristics will suggest development of mild or severe disease?

---

### IRISH AND INTERNATIONAL GUIDANCE

#### What does the Health Protection Surveillance Centre (Ireland) say?

[Health Protection Surveillance Centre. Epidemiology of COVID-19 in Ireland: Report Prepared by HPSC on 06/04/2020<sup>1</sup>](#)

Table 5: Number of confirmed cases of COVID-19 notified to midnight April 4th 2020 by age group and hospital, ICU and vital status, Ireland.

#### What does the European Centre for Disease Prevention and Control say?

[European Centre for Disease Control and Prevention. Rapid risk assessment: coronavirus disease 2019 \(COVID-19\) pandemic: increased transmission in the EU/EEA and the UK \[Eighth update\]<sup>2</sup>](#)

"Based on data from EU/EEA countries, 32% of the diagnosed cases have required hospitalisation and 2.4% have had severe illness requiring respiratory support or ventilation. The crude fatality rate was 1.5% among diagnosed cases and 11% among hospitalised cases. The likelihood of hospitalisation, severe illness and death increases in persons over 65 years of age and those with defined risk factors including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, compromised immune status, cancer and obesity."

---

### POINT-OF-CARE TOOLS

#### What does UpToDate say?

[Coronavirus Disease 2019 \(COVID-19\)<sup>3</sup>](#)

Severe illness can occur in otherwise healthy individuals of any age, but it predominantly occurs in adults with advanced age or underlying medical comorbidities. [The impact of age is discussed elsewhere](#). Comorbidities that have been associated with severe illness and mortality include:



- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Chronic lung disease
- Cancer
- Chronic kidney disease

---

## INTERNATIONAL LITERATURE

### What does the international literature say?

#### **Zhao et al. (2020). Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis<sup>4</sup>**

A total of 30 studies including 53000 patients with COVID-19, were included in this study. The mean age was 49.8 years (95% CI, 47.5-52.2 yrs) and 55.5% were male. The pooled incidence of severity and mortality were 20.2% (95% CI, 15.1-25.2%) and 3.1% (95% CI, 1.9-4.2%), respectively. The predictor for disease severity included old age ( $\geq 50$  yrs, odds ratio [OR] = 2.61; 95% CI, 2.29-2.98), male (OR = 1.348, 95% CI, 1.195-1.521), smoking (OR = 1.734, 95% CI, 1.146-2.626) and any comorbidity (OR = 2.635, 95% CI, 2.098-3.309), especially chronic kidney disease (CKD, OR = 6.017; 95% CI, 2.192-16.514), chronic obstructive pulmonary disease (COPD, OR = 5.323; 95% CI, 2.613-10.847) and cerebrovascular disease (OR = 3.219; 95% CI, 1.486-6.972). In terms of laboratory results, increased lactate dehydrogenase (LDH), C-reactive protein (CRP) and D-dimer and decreased blood platelet and lymphocytes count were highly associated with severe COVID-19 [all for  $P < 0.001$ ]. Meanwhile, old age ( $\geq 60$  yrs, RR = 9.45; 95% CI, 8.09-11.04), followed by cardiovascular disease (RR = 6.75; 95% CI, 5.40-8.43) hypertension (RR = 4.48; 95% CI, 3.69-5.45) and diabetes (RR = 4.43; 95% CI, 3.49-5.61) were found to be independent prognostic factors for the COVID-19 related death.

#### **Steinberg et al. (2020) 'Calculated decisions: COVID-19 calculators during extreme resource-limited situations<sup>5</sup>**

This review discusses the use of clinical prediction scores for pneumonia severity at 3 main decision points to examine which scores may provide value in this unique situation. Initial data from a cohort of over 44,000



COVID-19 patients in China, including risk factors for mortality, were compared with data from cohorts used to study the clinical scores, in order to estimate the potential appropriateness of each score and determine how to best adjust results at the bedside.

### **Verity et al.(2020). Estimates of the severity of coronavirus disease 2019: a model-based analysis<sup>6</sup>**

Using data on 24 deaths that occurred in mainland China and 165 recoveries outside of China, we estimated the mean duration from onset of symptoms to death to be 17.8 days (95% credible interval [CrI] 16.9-19.2) and to hospital discharge to be 24.7 days (22.9-28.1). In all laboratory confirmed and clinically diagnosed cases from mainland China (n=70 117), we estimated a crude case fatality ratio (adjusted for censoring) of 3.67% (95% CrI 3.56-3.80). However, after further adjusting for demography and under-ascertainment, we obtained a best estimate of the case fatality ratio in China of 1.38% (1.23-1.53), with substantially higher ratios in older age groups (0.32% [0.27-0.38] in those aged <60 years vs 6.4% [5.7-7.2] in those aged ≥60 years), up to 13.4% (11.2-15.9) in those aged 80 years or older. Estimates of case fatality ratio from international cases stratified by age were consistent with those from China (parametric estimate 1.4% [0.4-3.5] in those aged <60 years [n=360] and 4.5% [1.8-11.1] in those aged ≥60 years [n=151]). Our estimated overall infection fatality ratio for China was 0.66% (0.39-1.33), with an increasing profile with age. Similarly, estimates of the proportion of infected individuals likely to be hospitalised increased with age up to a maximum of 18.4% (11.0-27.6) in those aged 80 years or older.



## **Q2: In patients with severe COVID-19, what treatments are shown to be most effective in reducing fatality or increasing survival rates?**

### **Oxford University Centre for Evidence Based Medicine (2020). What is the effectiveness and safety of antiviral or antibody treatments for coronavirus?<sup>7</sup>**

54 studies were included in the review: three controlled trials, 10 cohort studies, seven retrospective medical record/database studies, and 34 case reports or series. These studies included patients with severe acute respiratory syndrome (SARs, n=33), middle east respiratory syndrome (MERS, n=16), COVID-19 (n=3), and unspecified coronavirus (n=2). The most common treatment was ribavirin (n=41), followed by oseltamivir (n=10) and the combination of lopinavir/ritonavir (n=7). Additional therapies included broad spectrum antibiotics (n=30), steroids (n=39) or various interferons (n=12). No eligible studies examining monoclonal antibodies for COVID-19 were identified.

---

## **IRISH AND INTERNATIONAL GUIDANCE**

### **World Health Organization (2020). Clinical management of severe acute respiratory infection when COVID-19 is suspected<sup>8</sup>**

[Full document relevant]

---

## **POINT-OF-CARE TOOLS**

### **What does BMJ Best Practice say?**

#### **Coronavirus disease 2019 (COVID-19) Treatment Algorithm<sup>9</sup>**

Severe illness; mild illness with risk factors.

**1st line – hospital admission**

**Plus – infection prevention and control procedures**

**Plus – treatment and care planning**

**Plus – monitoring**

**Adjunct – supportive care**

**Adjunct – empirical antimicrobials**



Treatment recommended for some patients in selected patient groups:  
Patients with severe illness may require continued antimicrobial therapy once COVID-19 has been confirmed depending on the clinical circumstances.

[Adjunct – antipyretic](#)

[Adjunct – antitussive](#)

[Adjunct – antitussive](#)

[Adjunct – advanced oxygen/ventilatory support](#)

[Adjunct – tailor management to comorbidities](#)

[Adjunct – experimental therapies](#)

---

## INTERNATIONAL LITERATURE

[Alhazzani et al. \(2020\). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 \(COVID-19\)<sup>10</sup>](#)

[Poston, J.T., Patel, B.K. and Davis, A.M., 2020. Management of Critically Ill Adults With COVID-19<sup>11</sup>](#)

[Systematic review and critical appraisal of prediction models for diagnosis and prognosis of COVID-19 infection<sup>12</sup>](#)

27 studies describing 31 prediction models were included for data extraction and critical appraisal. We identified three models to predict hospital admission from pneumonia and other events [as a proxy for COVID-19 pneumonia] in the general population; 18 diagnostic models to detect COVID-19 infection in symptomatic individuals; 13 of which were machine learning utilising computed tomography (CT) results; and ten prognostic models for predicting mortality risk, progression to a severe state, or length of hospital stay."



### Q3 Which populations have the highest ratio of severe to mild/moderate cases of COVID-19?

#### [Johns Hopkins University Center for Systems Science and Engineering \(CSSE\). Coronavirus COVID-19 Global Cases](#)<sup>13</sup>

Dashboard outlining total number of cases, deaths and recoveries. See full explanation at Dong et al. (2020). [An interactive web-based dashboard to track COVID-19 in real time](#).<sup>14</sup>

#### [Oxford University Centre for Evidence-Based Medicine \(2020\). Global COVID-19 Case Fatality Rates \[CFRs\]](#)<sup>15</sup>

Our current best assumption as of the 22nd March is the CFR is 0.51%, the lowest end of the current prediction interval and in line with several other estimates.

Evaluating CFR during a pandemic is however a hazardous exercise and high-end estimates should be treated with caution as the H1N1 pandemic highlights that original estimates were out by a factor greater than 10. We now want to draw your attention to the flaws in CFR estimation due to the changing nature of the testing regimes.

Italy: A [change in strategy on Feb 25](#) limited testing to patients who had severe signs and symptoms also resulted in a 19% positive rate [21,157 of 109,170 tested as of Mar 14] and an apparent increase in the death rate—from 3.1% on Feb 24 to 7.2% on Mar 17—patients with milder illness were no longer tested. In the UK, only patients deemed ill enough to require at least one night in hospital met the criteria for a COVID-19 test. Models are also starting to accrue that suggest the number of people infected [is much higher than](#) what testing alone identifies, and that the number infected is much higher in denser populations.

CFRs across countries are, therefore, highly variable, depending on who is tested for what reasons. There is no consistency.



Produced by the members of the National Health Library and Knowledge Service Evidence Team<sup>†</sup>. Current as at 09 March 2020. This evidence summary collates the best available evidence at the time of writing and **does not replace clinical judgement or guidance**. Emerging literature or subsequent developments in respect of COVID-19 may require amendment to the information or sources listed in the document. Although all reasonable care has been taken in the compilation of content, the National Health Library and Knowledge Service Evidence Team makes no representations or warranties expressed or implied as to the accuracy or suitability of the information or sources listed in the document. This evidence summary is the property of the National Health Library and Knowledge Service and subsequent re-use or distribution in whole or in part should include acknowledgement of the service.

The following PICO(T) was used as a basis for the evidence summary:

	COVID-19
	DISEASE SEVERITY
	INDICATORS; PREDICTORS

<sup>†</sup> Ann Madden, Librarian, St. Vincent's University Hospital, Dublin [Author]; Brendan Leen, Regional Librarian, HSE South, St. Luke's General Hospital, Kilkenny [Editor]







- 
- <sup>1</sup> Health Protection Surveillance Centre. Epidemiology of COVID-19 in Ireland: Report Prepared by HPSC on 06/04/2020 <https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/casesinireland/epidemiologyofcovid-19inireland/> Accessed 8<sup>th</sup> April 2020
- <sup>2</sup> European Centre for Disease Control and Prevention. Rapid risk assessment: coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK [Eighth update] <https://www.ecdc.europa.eu/en/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic-eighth-update>.
- <sup>3</sup> UpToDate (2020). Coronavirus Disease 2019 (COVID-19). <https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19#H943884075>.
- <sup>4</sup> Xianxian Zhao, Bili Zhang, Pan Li, Chaoqun Ma, Jiawei Gu, Pan Hou, Zhifu Guo, Hong Wu, Yuan Bai. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. <https://www.medrxiv.org/content/10.1101/2020.03.17.20037572v1>.
- <sup>5</sup> Steinberg E, Balakrishna A, Habboushe J, Shawl A, Lee J. Calculated decisions: COVID-19 calculators during extreme resource-limited situations. *Emerg Med Pract.* 2020;22(4 Suppl):CD1–CD5. Published 2020 Apr 6.
- <sup>6</sup> Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis [published online ahead of print, 2020 Mar 30]. *Lancet Infect Dis.* 2020;S1473-3099(20)30243-7. doi:10.1016/S1473-3099(20)30243-7.
- <sup>7</sup> Rios, P, Radhakrishnan, A, Antony, J, Thomas, SM, Muller, M, Straus, SE, Tricco, A. What is the effectiveness and safety of antiviral or antibody treatments for coronavirus? <https://www.cebm.net/covid-19/effectiveness-and-safety-of-antiviral-or-antibody-treatments-for-coronavirus/>
- <sup>8</sup> World Health Organization (2020). Clinical management of severe acute respiratory infection when COVID-19 is suspected. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
- <sup>9</sup> BMJ Best Practice. Coronavirus disease 2019 (COVID-19) Treatment Algorithm. <https://bestpractice.bmj.com/topics/en-gb/3000168/treatment-algorithm>.
- <sup>10</sup> Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) [published online ahead of print, 2020 Mar 28]. *Intensive Care Med.* 2020;1–34. doi:10.1007/s00134-020-06022-5.
- <sup>11</sup> Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults With COVID-19 [published online ahead of print, 2020 Mar 26]. *JAMA.* 2020;10.1001/jama.2020.4914. doi:10.1001/jama.2020.4914
- <sup>12</sup> Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ.* 2020;369:m1328. Published 2020 Apr 7. doi:10.1136/bmj.m1328
- <sup>13</sup> Johns Hopkins University Center for Systems Science and Engineering (CSSE). Coronavirus COVID-19 Global Cases. <https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>
- <sup>14</sup> Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time [published online ahead of print, 2020 Feb 19]. *Lancet Infect Dis.* 2020;S1473-3099(20)30120-1. doi:10.1016/S1473-3099(20)30120-1.
- <sup>15</sup> Oke, J, Heneghan, C. Oxford University Centre for Evidence-Based Medicine (2020). Global COVID-19 Case Fatality Rates. Jason Oke, Carl Heneghan, <https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/>