Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Categorisation of 'extremely medically vulnerable' groups who may be at risk of severe illness from COVID-19: evidence review

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

List of abbreviations used in this report

BMI	body mass index
CCC19	COVID-19 and Cancer Consortium
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	disease associated with the SARS-CoV-2 virus
EAG	expert advisory group
ECDC	European Centre for Disease Prevention and Control
HIQA	Health Information and Quality Authority
HPSC	Health Protection Surveillance Centre
HR	hazard ratio
HSE	Health Service Executive
ICU	intensive care unit
NPHET	National Public Health Emergency Team

OR	odds ratio
PARP	Poly (ADP-ribose) polymerase
PCR	polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCID	severe combined immunodeficiency
SIGN	Scottish Intercollegiate Guidelines Network
TERAVOLT	The Thoracic Cancers International COVID-19 Collaboration
UK	United Kingdom
US	United States
WHO	World Health Organization

Review of the evidence for categorisation of 'extremely medically vulnerable' groups who may be at risk of severe illness from COVID-19

Key points

- SARS-CoV-2 is a highly infectious virus, which has caused tens of millions of cases of COVID-19, and over one million deaths, globally.
- The Health Protection Surveillance Centre (HPSC) and Health Service Executive (HSE) have categorised groups of individuals as 'extremely medically vulnerable', who may be at highest risk of severe illness from COVID-19.
- The groups included were based upon Public Health England's definitions, which were originally based on those groups at highest risk of complications from influenza. As the pandemic has progressed, and more evidence is available, the composition of these groups needs to be reviewed.
- This scoping review investigated the evidence underpinning those defined as 'extremely medically vulnerable', from international organisations, evidence syntheses and primary literature.
- Eight international organisations reported the underpinning evidence that informed the categorisation of groups at highest risk of severe illness.
- Four systematic reviews and meta-analyses and one rapid review provided evidence relevant to two groups defined as extremely medically vulnerable; people aged 70 years or older (n=4) and people with specific cancers (n=1).
- A total of 24 primary research studies were identified that provided evidence on six extremely medically vulnerable groups: people aged 70 years and older (n=9); solid organ transplant recipients (n=4); people with specific cancers (n=18); people with severe respiratory conditions (n=2); people on immunosuppression therapies sufficient to significantly increase risk of infection (n=1); and patients with end-stage renal failure or dialysis patients (n=3).
- All reviews and eight of nine primary studies that explored the relationship between age and risk of severe illness from COVID-19 were consistent in reporting a significantly increased risk of severe illness in those aged 70 years and older.
- Three of the four studies on organ transplantation reported a significantly increased risk of mortality in transplant patients with COVID-19, compared with those who had not had a transplant.

- Evidence on patients with cancer (from one systematic review and meta-analysis) together with evidence from 18 primary studies (six of these 18 studies were included in the systematic review) were inconclusive. The most consistent finding was that among cancer patients, those receiving chemotherapy (compared to those who are not) are at a significantly increased risk of severe illness due to COVID-19.

- A small number of primary studies of people with severe respiratory conditions, on immunosuppression therapies sufficient to significantly increase risk of infection, with end-stage renal failure or on dialysis, consistently demonstrated that these conditions were associated with a significantly increased risk of severe illness from COVID-19. Although consistent in their findings, the evidence is of low certainty due to the small number and nature of the studies; these results should be interpreted with caution.

- Of the extremely medically vulnerable groups included in this evidence summary, no evidence (from systematic or rapid reviews or primary studies) was identified for people with rare diseases and inborn errors of metabolism or women who are pregnant with significant heart disease. There is a lack of data relating to paediatric populations.

- A number of groups (cardiovascular disease, type 1 diabetes, type 2 diabetes, chronic liver disease, chronic obstructive pulmonary disease, chronic kidney disease, HIV infection with low CD4 counts, obesity, severe obesity, stage B Child Pugh score cirrhosis, motor neuron disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia or hemiplegia, primary cerebral malignancy, progressive cerebellar disease) are included in the highest risk category of guidance from international organisations; these are included in the Irish guidance as 'high risk' rather than 'very high risk'. Risk classification varies across organisations and may be not directly comparable. Four groups (pregnant women and their unborn children, those with dementia, those who smoke and adults with Down syndrome) were identified that are not included within Irish guidance.

- Overall, evidence was available for six of eight 'extremely medically vulnerable' groups listed by the HPSC and HSE; the strongest evidence supports inclusion of those aged 70 years and older. The review did not identify evidence for people with rare diseases and inborn errors of metabolism or pregnant women with significant heart disease. Given the rarity of certain conditions and likely ongoing shielding of certain patient groups, an absence of evidence should not be interpreted as an absence of true association.

Review of the evidence for categorisation of 'extremely medically vulnerable' groups who may be at risk of severe illness from COVID-19

The Health Information and Quality Authority (HIQA) has developed a series of evidence summaries to inform advice from HIQA to the National Public Health Emergency Team (NPHET). The advice takes account of expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group. This evidence summary relates to the following policy question outlined by NPHET.

> Based on the available international evidence, is the current definition of what constitutes 'extremely medically vulnerable' (that is, those who were previously asked to cocoon) in relation to COVID-19 appropriate?

This evidence summary was developed to address the following research question that was formulated to inform the above policy question:

> What is the evidence underpinning the categorisation of 'extremely medically vulnerable' groups, that is, persons who may be at risk of severe illness from COVID-19?

Background

On 11 March 2020, the WHO declared the coronavirus (COVID-19) outbreak a global pandemic. As of 30 November 2020, there have been in excess of 63 million cases and almost 1.5 million deaths from laboratory-confirmed cases of COVID-19 worldwide.[(1)] Data from early in the course of the pandemic showed that while all age groups are susceptible to infection with SARS-CoV-2, older adults and those with specific medical conditions are at an increased risk of severe illness.[(2)] In the United Kingdom (UK), those regarded as being at an increased risk of morbidity and mortality from influenza were classified as being clinically vulnerable to COVID-19.[(3)] Moreover, it was determined that an additional category, termed the 'clinically extremely vulnerable', may have an even higher risk of complications or fatality due to COVID-19 illness.[(3)]

Similarly, in Ireland, the Health Protection Surveillance Centre (HPSC) and Health Service Executive (HSE) differentiate between those at high risk of severe illness from COVID-19 and those at very high risk.[(4)] The latter are referred to as extremely medically vulnerable and include:

1. People aged 70 years or over.

2. Solid organ transplant recipients.
3. People with specific cancers:
    a. people with cancer who are undergoing active chemotherapy, or people who are undergoing radical radiotherapy for lung cancer
    b. people with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment
    c. people receiving immunotherapy or other continuing antibody treatments for cancer
    d. people having other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors
    e. people who have had bone marrow or stem cell transplants in the last six months, or who are still taking immunosuppression drugs.
4. People with severe respiratory conditions including cystic fibrosis, severe asthma, pulmonary fibrosis/lung fibrosis/interstitial lung disease and severe chronic obstructive pulmonary disease (COPD).
5. People with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell).
6. People on immunosuppression therapies sufficient to significantly increase risk of infection.
7. Women who are pregnant with significant heart disease, congenital or acquired.[4]

Additionally, the HSE include those on dialysis as being at very high risk of severe illness.[5] As the pandemic has progressed, and more data become available, there is a need to review the groups included in the extremely medically vulnerable category, to ensure it accurately reflects the latest evidence. The aim of this review is to summarise the evidence underpinning the categorisation of extremely medically vulnerable groups, that is, people who may be at risk of severe illness from COVID-19.

Methods

This evidence summary followed a scoping review methodology due to the wide range of vulnerable groups for consideration. For this scoping review, the processes outlined in HIQA's protocol (available here) were followed.

Briefly, four document categories were included in this review:

- public health guidance and policy documents
- reviews
- primary research studies

- international disease registries.

Individual documents were subject to inclusion and exclusion criteria as per the protocol specifications:

- public health guidance and policy documents were included if they provided evidence sources underpinning the recommendations made. Guidance and policy documents were sought from a defined list of organisations as detailed in the review protocol. These organisations were chosen based on their established authority relating to public health guidance, as assessed in previous reports conducted by HIQA, and their likely transferability to the Irish setting from the point of view of health services research and pandemic management. Underpinning evidence sources cited by organisations (that is, reviews and primary research studies) were screened for inclusion in this review.
- epidemiological reviews of risk factors were selected for inclusion subject to several criteria, including that at least one 'extremely medically vulnerable' risk group, as outlined by the HPSC and HSE, were included in the review, and where the outcomes examined included severe illness from COVID-19.
- primary research studies were identified from within public health guidance and policy documents; due to time constraints associated with the production of this review, a general search and analysis of primary research studies was not completed.
- evidence from international disease registries was included where the registry study results compared those who are SARS-CoV-2 positive and develop severe illness to those who are SARS-CoV-2 positive and do not develop severe illness.

The evidence contained within this summary relates to extremely medically vulnerable groups. Therefore, when identifying public health guidance, the data included in this evidence summary were limited to those groups defined, by the organisation reporting the guidance, as being at the highest risk. For the purposes of this evidence summary, severe illness from COVID-19 is defined as that requiring admission to an intensive care unit (ICU) or mechanical ventilation, or resulting in death. While there is potential for some variation in admission practices, there is general consensus on criteria for admission to ICU and mechanical ventilation. In contrast, criteria for hospitalisation can vary substantially, so use of this an indicator would introduce considerable bias. Firstly, the indication for hospitalisation has changed significantly over the course of the pandemic, with most confirmed cases being hospitalised at the beginning of the pandemic for isolation purposes regardless of disease status. As the pandemic has evolved and the impact on resources has been realised, the indication for admission to hospital has been amended, with

hospitalisation typically being reserved for moderate to severe cases of COVID-19.[6] Secondly, the indication for hospitalisation differs between jurisdictions and depends largely on the availability of resources. Healthcare systems with sufficient capacity may choose to care for all patients within the hospital setting, whilst those with limited capacity may not be able to do so.[6] To mitigate this potential bias, we have not included hospitalisation as an indicator of severe illness due to COVID-19.

The results of this report comprise a summary of relevant evidence underpinning the categorisation of 'extremely medically vulnerable' groups (that is, people who may be at risk of severe illness from COVID-19) by public health authorities, as identified from literature published between 1 January 2020 and 12 October 2020.

Results

The results are presented in three main sections as follows:

- 'Search Results': a descriptive summary of the range of relevant documents identified, including the sources of evidence used to inform public health guidance and policy documents
- 'Evidence underpinning extremely medically vulnerable groups': a summary of the evidence provided within the documents, presented separately for each of the eight groups considered to be extremely medically vulnerable according to guidance from the HPSC and HSE.
- 'Methodological quality of included studies': a quality appraisal of the documents included.

Search results

Public health guidance and policy documents

Guidance and policy documents from 22 organisations were reviewed. However, among these, only eight organisations reported the underpinning evidence that informed the categorisation of groups at highest risk (that is, extremely medically vulnerable) of severe illness due to COVID-19, and were therefore selected for inclusion in this review. Guidance was included from: Alberta Health Services (Canada);[7] the US Centers for Disease Control and Prevention (CDC);[8] the Danish Health Authority;[9] the Federal Public Service Health, Food Chain Safety and Environment (Belgium);[10] the Norwegian Institute of Public Health;[11] Public Health England;[12] Health Protection Scotland;[13] and Government of France.[14] These guidance documents have been updated since they were first issued, with update dates ranging from 5 May to 15 November. An overview of the groups at highest risk of severe illness from COVID-19, as currently defined by public health guidance and

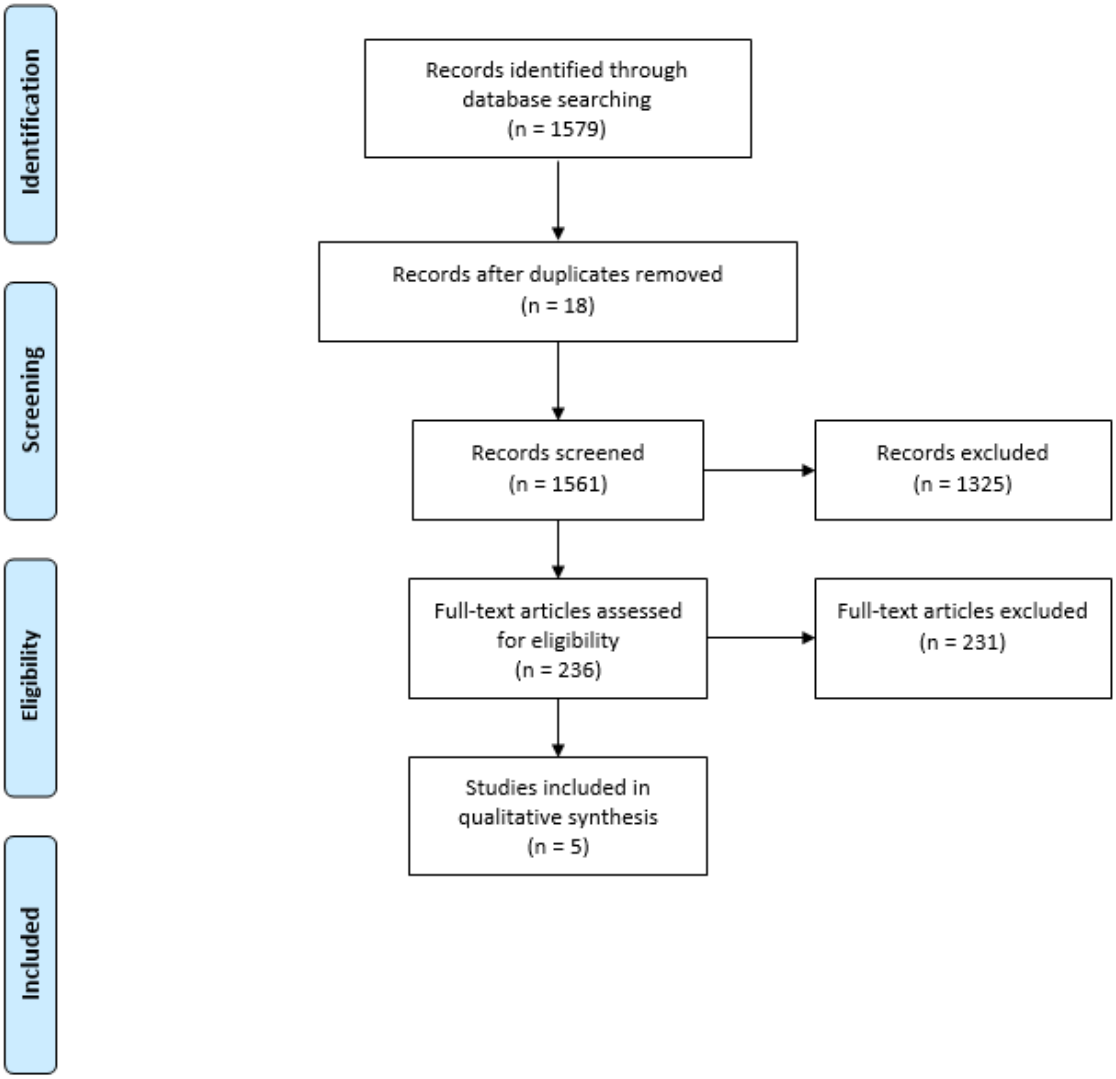
policy documents, and the evidence provided by the organisations authoring the guidance, is presented in Appendix 1.

Alberta,[15] Denmark,[16] Belgium[17] and Norway[18] conducted rapid reviews on risk factors for severe illness from COVID-19; Belgium describe their review as a 'factsheet'. In October 2020, the Haut Conseil de la Santé Publique (le HCSP) in France[19] published updated advice on the risk factors for severe COVID-19. The advice took consideration of national epidemiological data, epidemiological data from three systematic reviews,[20-22] two population studies (both of which are included in this report),[23, 24] seven observational studies,[25-31] one cross-sectional study,[32] three CDC Morbidity and Mortality Weekly Reports,[33-35] as well as previous advice they had issued on this topic.[36-38] In the US, the CDC publish evidence tables covering the medical conditions included in groups considered to be at increased risk.[39] Updates to these tables of underlying medical conditions are based on published reports, articles in press, non-peer-reviewed pre-prints and internal data available between 1 December 2019 and 16 October 2020.[39] Public Health England and Health Protection Scotland based their risk groups on a subset of the at-risk group eligible for the annual influenza vaccine. This subset, developed by the Chief Medical Officer of England, was said to be based on the evidence available on COVID-19, knowledge of other infectious respiratory diseases, and taking a precautionary approach. A rapid review was also conducted by Scottish Intercollegiate Guidelines Network (SIGN) with an update published in July 2020.[40] The aim of the SIGN review was to identify risk factors for severe illness of COVID-19 to be used by primary care teams in Scotland. They reported that the risk factors most associated with severe illness from COVID-19 are smoking, hypertension, cardiovascular disease, diabetes, obesity, stroke, chronic pulmonary disease, chronic kidney disease, cancer and solid organ transplantation; and concluded that the evidence base was too weak to make definitive recommendations.[40]

Systematic and rapid reviews

The collective search up until 12 October 2020 resulted in 1,579 citations; following removal of duplicates 1,561 citations were screened for relevance, with 236 full-texts assessed for eligibility and 231 subsequently excluded. See Figure 1 for a PRISMA flow diagram of the reviews included in this evidence summary. Accordingly, five reviews were identified for inclusion in this evidence summary, of which there were four systematic reviews and meta-analyses,[41-44] and one rapid review.[45] Two reviews were published in July 2020,[42, 44] one in September 2020[43] and two were published as pre-prints.[41, 45] The reviews were from Italy,[42] Spain,[44] Germany,[41] Canada[45] and China.[43] The extremely medically vulnerable groups investigated by the included reviews were those aged 70 years or older[41, 42, 44, 45] and patients with cancer.[43] An overview of the characteristics of reviews included in this evidence summary is presented in Appendix 2.

Figure 1. PRISMA flow diagram of included systematic and rapid reviews



Primary research studies

Primary research studies were identified from included guidance and policy documents, full-text screening of systematic and rapid reviews and forward citation of all included studies. Using the inclusion and exclusion criteria used for identification of systematic and rapid reviews, 24 studies (23 published between April 2020 and October 2020 and one pre-print at the time of writing) were included in this evidence summary. Of the studies included, six were conducted in the US,[46-51] five were multinational,[52-56] four were from the UK,[23, 24, 57, 58] two each were from China,[59, 60] Spain,[61, 62] France[63, 64] and Italy,[65, 66] and one from Denmark.[67] The extremely medically vulnerable groups investigated in the included primary studies included: those aged 70 years and older;[24, 46, 48, 50, 51, 61, 63, 65, 67] solid organ transplant recipients;[23, 24, 55, 67] people with cancer;[23, 24, 47, 49, 51-54, 56-64, 66] people

with severe respiratory conditions;[23, 24] people on immunosuppression therapies sufficient to significantly increase risk of infection;[23] and people with end-stage renal failure or on dialysis.[23, 24, 51] An overview of the characteristics of primary studies is presented in Appendix 3.

International disease registries

International disease registries were identified from the included primary studies. Of the 24 primary studies, four international disease registries were identified. Garassino et al.[56] used data from the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry. This registry is a global consortium designed to gather information on patients with thoracic cancer infected with COVID-19, regardless of therapies administered. The initiative currently involves more than 100 investigators worldwide.

Kuderer et al.[53] used data from the COVID-19 and Cancer Consortium (CCC19) registry database, established on 15 March 2020.[68] The aim of this registry is to explore the clinical characteristics and course of illness among patients with COVID-19 who have a current or past diagnosis of cancer. The CCC19 registry consists of anonymous data on patients aged 18 years or older with a current or past history of haematological malignancy or invasive solid tumour and either a laboratory-confirmed SARS-CoV-2 infection or a presumptive diagnosis of COVID-19.[68]

Webb et al.[55] used data from two online registries, the COVID-Hep registry,[69] and the SECURE-Cirrhosis registry;[70] the former encourages reports from worldwide with the latter collating data from the Americas, China, Japan and Korea. These registries are working collaboratively to define the impact of COVID-19 on patients with chronic liver diseases and post-liver transplantation and explore how factors such as age, comorbidities and immunosuppression impact COVID-19 outcomes.

Evidence underpinning extremely medically vulnerable groups

The following sections present evidence for the classification of extremely medically vulnerable groups in the international literature. This evidence is summarised separately for each of the eight groups considered to be extremely medically vulnerable according to guidance from the HPSC and HSE (see Background, above). Within each group, evidence is presented according to the literature source: public health guidance, systematic or rapid reviews, primary studies, or international disease registries.

Aged 70 years and older

Of the guidance included in this evidence summary, six organisations specified older age as a contributor to the highest risk of severe illness from COVID-19. Alberta

Health Services specify those aged 70 years and older[7] as being at highest risk. This was based on findings from a rapid review (updated on 21 August 2020) conducted by Alberta's Scientific Advisory Group (SAG).[15] The aim of the review was to identify the risk factors (such as age, medical conditions or lifestyle factors) associated with the development of severe outcomes in COVID-19. It included 12 systematic reviews, 11 prospective cohort studies, 37 retrospective studies, and 6 case series.[15] The authors concluded that there is consistent evidence to suggest that increasing age has a consistent and high strength association with hospitalisation and death from COVID-19, but a low to moderate strength association with ICU admission. The association is strongest in people older than 65 years and is enhanced in the presence of additional comorbidities.[15]

The Norwegian Institute of Public Health conducted a rapid review on the association between several factors (age, sex, gender, race or ethnicity, deprivation, body mass index (BMI), underlying comorbidities, smoking habits, and medicine use) and severe illness due to COVID-19.[18] This review, published on 15 November 2020, excluded studies that only reported univariate analysis and studies with a sample size less than 5,000 laboratory confirmed cases. A total of five studies were included. The authors concluded that age was associated with increased risk for severe illness, with a dose response relationship between increasing age and increasing risk for ICU treatment; age was also found to be the strongest predictor of death.[18] Accordingly, those classified as being at highest risk were persons aged 80 years and older with or without any chronic conditions, persons aged 66-80 years with one medical condition, or those aged 50-65 with two or more medical conditions.[11]

The French public health agency, HCSP, concluded on the basis of the included national and international epidemiological data and the literature underpinning their advice, that those aged 65 years and older are at increased risk of severe illness from COVID-19; they specify that those aged 70 years and older are at the highest risk.[14] The Belgian public health agency specify those aged 65 and older, as being at highest risk;[10] this is based on two retrospective cohort studies conducted in China.[71, 72] A non-systematic literature review (published on 23 September 2020) conducted by the Danish Health Authority, explored the risk factors associated with hospitalisation, including admission to the intensive care unit, and death as a result of COVID-19.[16] Subsequently, they include any person aged 65 and older that has at least one of an identified list of chronic conditions.[9]

While not including a specific age-cut-off point, the US CDC notes that the risk for severe illness from COVID-19 increases with age, highlighting that eight of ten COVID-19 deaths reported in the US have occurred in adults aged 65 years and older. The greatest risk for severe illness is noted to be among those aged 85 or

older[8] Public Health England and Health Protection Scotland do not include an age-related group in the highest risk category; see Appendix 1.

Of the five reviews included in this evidence summary, four of these pooled evidence relating to increased age and death from COVID-19;[41, 42, 44, 45] and all four reported a significant association between increased age and death. Bonanad et al. reported an increased risk of death across five countries (China, US, UK, Spain and Italy) in those aged 70-79 years compared to those aged 60-69 years (odds ratio (OR) 2.62, 95% confidence interval (CI) 2.18 – 3.15) and for those aged 80 years and older compared to those aged 70-79 years (OR 1.60, 95% CI 1.36 – 1.88). Figliozzi et al. also compared those aged 70 years and older and reported an increased risk of death in this age group compared to younger subjects (OR 13.19, 95% CI 7.72 - 22.55).[42] Villalobos et al. pooled results from the US, Italy, Spain, England, Belgium and Germany and compared the risk of death of those aged 70 years and older to those aged 50 years old or younger, and reported that those aged 70 years and older had a significantly increased risk of death;[41] see Appendix 2 for ORs and 95% CIs for each country. Wingert et al. reported the risk of death in those aged 70 years and older, 75 years and older and 80 years and older compared to those aged 45 years or younger. They concluded that the relative increase in risk of mortality is approximately 5-10% with each increased year of age;[45] see Appendix 2.

Of the 24 primary studies included in this evidence summary, ten reported relevant outcomes for those aged 70 years and older. Albiges et al. reported on data from 178 cancer patients at the Gustave Roussy Cancer Centre (France) from 24 March 2020 to 29 April 2020.[63] Univariate analysis for overall survival showed that patients aged 70 years or older had an increased risk of mortality when compared to those under 70 years (hazard ratio (HR) 2.13, 95% CI 1.04-4.36).[63] García-Suárez et al. included data on patients with hematologic malignancies and COVID-19 confirmed by a polymerase chain reaction (PCR) test, from 22 regional health service hospitals and five private healthcare centres in Madrid; this included outpatient centres covering a population of 6.6 million inhabitants.[61] Data were collected from 28 February 2020 to 25 May 2020, and in total, 697 patients were included. After adjusting for age, sex, comorbidities, haematological malignancy and recent active cancer therapy, the rate of mortality in those aged 70-79 years and those aged ≥80 years was significantly higher compared with those aged 18-49 years (adjusted HR 5.20, 95% CI 2.12-12.8, and HR 10.1, 95% CI 4.03-25.4, respectively).[61]

Gottlieb et al. used data from Rush University Medical Center in Chicago, Illinois. These data, relating to 8,673 COVID-19 patients, were collected from 4 March 2020 to 21 June 2020.[51] Relative to those aged 19-44 years, no difference in ICU admission was observed in those aged 65-74 years (adjusted OR 1.01, 95% CI 0.67-1.52) or in those aged 75 years and older (adjusted OR 0.81 95% CI 0.51-1.28);

covariates included in the analysis were unclear.[51] Rossi et al. used data from a local health authority from the Reggio Emilia province of Northern Italy.[65] Data for 2,653 individuals were collected from 27 February 2020 to 3 April 2020. Compared with those aged 50 years or younger, there was an increased risk of death for those aged 71-80 years (adjusted HR 9.1, 95% CI 4.0-20.6) and those aged 81 years or older (adjusted HR 27.8, 95% CI 12.5-61.7), following adjustment for age, sex, Charlson Comorbidity Index and place of birth.[65] Petrilli et al. used data from a single academic medical centre in New York City and Long Island, collected between 1 March 2020 and 8 April 2020, with a follow-up through to 5 May 2020.[48] In a sample of 5,279 individuals who tested positive for SARS-CoV-2, age was associated with an increased risk of critical illness in those aged 65-74 years and those aged 75 years and older, compared with those aged 19-64 years;[48] OR 2.88, (95% CI 2.09 - 4.0) and OR 3.46, (95% CI 2.46 - 4.8), respectively. These groups also had an increased risk of death compared to those aged 19-64 years; HR 6.99, (95% CI 4.34 - 11.27) for those aged 65-74 years and HR 10.34, (95% CI 6.37 - 16.79) for those aged 75 years and older; covariates were not reported.[48]

Ioannou et al. used data from the US Department of Veterans Affairs (VA) national health care system. Patients who tested positive for SARS-CoV-2 between 28 February and 14 May 2020 (n=10,131) were followed up through 22 June 2020.[46] Compared with those aged 18-49 years, the risk of mechanical ventilation was significantly higher in those aged 65-79 years (adjusted HR 4.32, 95% CI 2.88-6.47) and in those aged ≥80 years (adjusted HR 3.98, 95% CI 2.54-6.24).[46] Older age was also significantly associated with increased risk of mortality. Compared with those aged 18-49 years, the increased risk in those aged 65-79 years was represented by an adjusted HR of 27.47 (95% CI 13.48-55.99); in those aged ≥80 years the adjusted HR was 60.80 (95% CI 29.67-124.61). Analyses of outcomes were adjusted for a large range of socio-demographic characteristics, comorbid conditions and symptoms.[46] Rentsch et al. also used data from the US Department of VA national health care system.[50] Data were collected from 8 February 2020 to 4 May 2020, with 30-day follow-up. Of the 2,420 individuals who tested positive for SARS-CoV-2, 284 died within 30 days. The age (at baseline) adjusted OR for those aged 70-79 years compared to 60-69 years was 2.01, 95% CI 1.45-2.80, whilst age (at baseline) adjusted OR for those aged ≥80 years compared to 60-69 years was 5.52, 95% CI 3.79-8.02;[50] ORs adjusted for age at baseline and baseline comorbidity are reported in Appendix 3.

In the UK, the OpenSAFELY study group used national primary care health records to examine risk factors. These data includes laboratory-confirmed COVID-19 cases as well as clinically suspected cases; data were collected from 1 February 2020 to 5 May 2020 for 17.2 million adults.[24] As with other studies included in this evidence summary, increased age was associated with an increased risk of death. Compared

with those aged 50-59 years, and adjusting for sex, the risk of death was increased for those aged 70-79 years (adjusted HR 8.62, 95% CI 7.84-9.46) and those aged ≥80 years (adjusted HR 38.29, 95% CI 35.02-41.87).[24] Following adjustment for age, body mass index (BMI), smoking, an index of deprivation, and comorbidities, these associations remained, though the magnitude of the associations decreased (adjusted HRs decreased to 6.07 for those aged 70-79, and to 20.6 for those aged ≥80 years).

Reilev et al. investigated the risk factors for death due to COVID-19 in a nationwide cohort comprising 11,122 confirmed COVID-19 cases in Denmark between 7 February 2020 and 19 May 2020.[67] During this period there were 577 COVID-19-related deaths registered. Multiple regression analysis was conducted adjusting for age, sex and total number of comorbidities. Compared with those aged 50-59, a significant increase in all-cause mortality was observed for those aged 70-79 years years (adjusted OR 15.2, 95% CI 8.7-26.3), 80 to 89 years (adjusted OR 29.9 95% CI 17.2 – 51.9) and age 90 years and older (adjusted OR 90.2 95% CI 50.2 – 162.2).[67] The authors noted the correlation between age and comorbidities and that no increase in mortality was observed until the age of 80 years or older;[67] see Appendix 3.

Solid organ transplant recipients

England,[12] France,[14] Norway[11] and Scotland[13] list solid organ transplant recipients as being at highest risk of severe illness from COVID-19. Public Health England state that this recommendation is based on the scientific evidence and clinical advice of the Chief Medical Officers.[73] Health Protection Scotland states that this group includes people who have had a transplant of heart, lung, stomach or other part of intestine, liver and kidney, as the medication taken to stop rejection of the transplanted organ poses an increased risk.[13] The rapid review by SIGN, updated on 21 July 2020, includes those who have had a solid organ transplant in their highest risk category. This recommendation was primarily based on evidence from a recent large observational study of deaths in England found that COVID-19 death was significantly associated with organ transplant;[40] this study[24] (by Williamson et al.) is included in the primary studies identified by this current review. The CDC include solid organ transplant recipients that are in an immunocompromised state as being at an increased risk of severe illness from COVID-19; this is based on seven case series and one meta-analysis.[39] Organisations in Alberta, Belgium, Denmark and France do not include this group; see Appendix 1.

None of the identified reviews provided evidence relating to those who have had solid organ transplants; however, three primary studies included evidence for this group. Clift et al. used data from the QResearch database, comprising 1,205 general

practices in England with linkage to COVID-19 test results, Hospital Episode Statistics and death registry data.[23] The aim of the study by Clift et al. was to derive and validate a risk prediction algorithm (QCOVID) to estimate hospital admission and mortality outcomes from COVID-19 in adults. The multivariate analysis (adjusted for age, BMI, deprivation, ethnic group, permanent abode, and a range of conditions and treatments) showed that transplant patients had a significantly increased risk of death compared to those who had never had a kidney transplant: adjusted HR 7.84, 95% CI 3.38-18.17 for women, and adjusted HR 3.20, 95% CI 1.62-6.33 for men.[23] Moreover, for those who had any solid organ transplant (excluding kidney and bone marrow) there was also an increased risk of death in women adjusted HR 1.46, 95% CI 0.36-5.92 and men adjusted HR 1.72, 95% CI 0.71-4.21; although neither were statistically significant.[23] After adjusting for age and sex, Reilev et al. reported an increased risk of mortality in organ transplant patients compared to those who had not (adjusted OR 3.4, 95% CI 1.7 – 6.6); however after also adjusting for the total number of comorbidities, this difference was no longer statistically significant (adjusted OR 2.0, 95% CI 0.8 – 5.1).[67] Webb et al. utilised data from two collaborative international registries, the COVID-Hep registry,[69] and the SECURE-Cirrhosis registry.[70] They reported that while those who had solid organ transplants were more likely to be admitted to ICU, there was no increased risk of death (28 deaths reported out of 151 transplant patients); following adjustment for age, sex, creatinine concentration, obesity, hypertension, diabetes and ethnicity. The absolute risk difference for the outcome of death was 1.4% and was not statistically significant 95% CI (-7.7 to 10.4).[55] Conversely, based on the UK OpenSAFELY registry data collected between 1 February 2020 and 5 May 2020, Williamson et al. reported an increased risk of death in a cohort of 20,001 transplant patients.[24] When adjusted for age and sex, the adjusted HR was 6.00, 95% CI 4.73-7.61, and when adjusted for age, BMI, smoking, an index of deprivation and comorbidities, the adjusted HR was 3.53, 95% CI 2.77-4.49;[24] see Appendix 3.

People with specific cancers

Alberta Health Services includes people with any malignant cancer except non-melanoma skin cancer as being at high risk of severe COVID-19.[7] This recommendation was based on the rapid review conducted by the Alberta scientific advisory group (SAG). Regarding cancer and risk of severe illness due to COVID-19, the group concluded that, on its own, cancer appears to have a low strength association with severe COVID-19, but that it is a synergistic factor with age, sex, and other comorbidities.[15] The Norwegian Institute of Public Health identifies people with active cancer and those with ongoing or recently discontinued treatment for cancer, especially immunosuppressive therapy, radiation therapy to the lungs, or chemotherapy as being at high risk of severe COVID-19.[11] This recommendation was informed by the rapid review conducted by the Norwegian Institute of Public

Health[18] and based upon evidence from a prospective cohort study by Petrilli et al..[48]

The cancer groups listed as being at high risk by Public Health England[12] and Health Protection Scotland[13] largely overlap with Irish guidance with respect to the types of cancer included.[4] These groups include: people with cancer undergoing active chemotherapy; people with lung cancer who are undergoing radical radiotherapy; those who have cancers of the blood or bone marrow at any stage of treatment (including leukaemia, lymphoma or myeloma); those receiving immunotherapy or other continuing antibody treatments for cancer; those receiving specialised cancer treatments that can affect the immune system otherwise, such as protein kinase inhibitors or PARP inhibitors; and those who have had bone marrow or stem cell transplants in the last six months or who are still taking immunosuppression drugs as a result of such transplants. The list of cancer groups included by Scotland has been informed by the evidence available on COVID-19, knowledge of other infectious respiratory diseases and taking a precautionary approach.[74] Moreover, the authors of the SIGN review reported that the emerging evidence 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.[40]

In contrast, the CDC includes all people with cancer with no further distinction made.[8] France include those with active cancer undergoing treatment (excluding hormone therapy)[14] and national public health organisations in Belgium and Denmark do not include these risk groups. Whilst Belgium do not include people with cancer in their highest risk group, they do regard them as 'special populations';[17] see Appendix 1.

Of the evidence included in this evidence summary, one systematic review and meta-analysis[43] (updated 28 June 2020) provided evidence relating to individuals with specific cancers. Wang and Huang identified 17 studies, nine of which were included in the meta-analysis;[43] six[49, 53, 56, 57, 59, 60] of the 17 included studies also met the inclusion criteria for this evidence summary. Overall, there was no significant correlation between anti-cancer therapy and the risk of mortality in cancer patients with COVID-19 (OR 1.33, 95% CI 0.84–2.10).[43] Following investigation of treatment types, no statistically significant correlation was shown between any anti-cancer therapy (including surgery, chemotherapy, targeted therapy, immunotherapy, and radiotherapy) and the risk of death events in cancer patients with COVID-19. However, in a subgroup analysis (stratified by treatment time) cancer patients who received chemotherapy within the previous 28 days had a significantly increased risk of death (OR 1.45, 95% CI 1.10–1.91); this was not statistically significant in those who had received chemotherapy within the previous 40 days (OR 0.56, 95% CI 0.27-1.13);[43] see Appendix 2.

A total of 18 primary studies provided evidence relating to people with specific cancers and the increased risk of severe illness from COVID-19. Typically, studies reported data for cancer patients relative to non-cancer patients, or for cancer patients actively undergoing treatment versus cancer patients not undergoing active treatment. Within the 18 studies, treatments for which outcomes were reported included chemotherapy (n=9),[23, 49, 52, 54, 56, 57, 60, 61, 63] non-specific cancer treatment (n=6),[53, 54, 57-59, 64] immunotherapy (n=6),[23, 49, 52, 54, 57, 63] monoclonal antibody therapy (n=2),[47, 61] hormonal therapy (n=2),[54, 57] bone marrow or stem cell transplantation (n=2),[23, 62] radiotherapy (n=1)[23] and corticosteroid treatment (n=1).[23] All of the studies reported outcomes based on data collected prior to 30 June 2020. The most consistent finding was the increased risk of death associated with those undergoing chemotherapy (studies reporting this finding were based on data collected from 1 January 2020 until 30 April 2020); findings were inconsistent for the other treatments identified. See Appendix 3 for the associated effect measures and 95% CIs for each cancer treatment.

Of the studies that reported outcomes for people with specific cancer, two utilised data from international disease registries. Garassino et al.[56] used data from the (TERAVOLT) registry, to explore the effect of COVID-19 on patients with thoracic malignancies. The study was relatively small, comprising 200 participants; COVID-19 diagnosis was not confirmed by a laboratory test for all included participants (RT-PCR confirmed COVID-19 diagnosis for 91% of the sample). Univariate analysis showed a significant association between treatment with chemotherapy and an increased risk of death (adjusted HR 2.54, 95% CI 1.09-6.11); this association did not remain following adjustment for confounding factors (covariates not reported).[56] Kuderer et al.[53] also utilised data from a cancer registry, the COVID-19 and Cancer Consortium (CCC19) registry database.[68] The study included n=928 cancer patients. The authors did not report a difference between the type of cancer (haematological or solid tumour) and 30-day (since COVID-19 diagnosis) all-cause mortality (adjusted OR 1.40, 95% CI 0.83 - 2.37); adjusted for age, sex, smoking status and obesity.[53] Moreover, multivariate analysis showed no association between cytotoxic, non-cytotoxic or unknown cancer therapy and an increased risk of 30-day all-cause mortality.[53] Using hospital data, Gottlieb et al. reported that those with blood borne cancer (compared to those without) had a significantly increased risk of ICU admission, (adjusted OR 3.53 95% CI 1.26-9.86); the covariates included were unclear;[51] see Appendix 3.

People with severe respiratory conditions

Alberta Health Services[7] and the CDC[8] include COPD within their list of at risk conditions, though no further detail is provided, and the Belgian public health authority includes lung disease (no definition) and type 2 diabetes in combination with 'problems of the lung'.[10] The recommendation by Alberta is based on evidence

from the rapid review (referred to above).[15] It states that pulmonary disease is poorly defined in the literature and that COPD appears to have a low strength association with severe COVID-19 outcomes whilst asthma appears to have no significant risk of severe COVID-19. They also noted that large studies and meta-analyses showed a stronger association with severe COVID-19 outcomes than small hospital-based studies and that more research is needed to clearly determine the risk posed by different pulmonary conditions and their severity.[15] The inclusion of COPD in the CDC guidance is based upon two meta-analyses, one case series and one cohort study.[39] Belgium's recommendation regarding the inclusion of lung disease in their highest risk category is based on evidence from a retrospective study conducted in China[72] and a systematic review (published in March 2020) that included 10 studies.[75]

Public Health England[12] and Health Protection Scotland[13] include people with severe respiratory conditions and list cystic fibrosis, severe asthma and severe COPD. As described above, the recommendation from Public Health England is based on available evidence and expert opinion.[73] Health Protection Scotland also includes people on home oxygen for a lung condition and provides definitions for severe asthma and severe COPD.[13] This was based upon a rapid review conducted by SIGN and informed by an unpublished meta-analysis that reported a significant association between COPD and severe illness due to COVID-19 in six out of 19 studies.[40]

The Norwegian Institute of Public Health includes chronic lung disease other than well-regulated asthma. It also includes neurological or muscular disease with impaired coughing strength or lung function and gives the example of amyotrophic lateral sclerosis;[11] this recommendation was based on the rapid review which included 11 studies.[18] Based on the findings of the non-systematic literature review described above,[16] the Danish Health Authority includes a broad risk group which could relate to severe respiratory conditions; this group includes people with certain chronic diseases and people with weakened immune systems, if these chronic conditions are not well-regulated,[9] and is said also to apply to certain children with chronic diseases. France include those with a chronic respiratory condition likely to deteriorate during a viral infection, for example obstructive pulmonary disease, severe asthma, pulmonary fibrosis, sleep apnoea syndrome and cystic fibrosis;[14] see Appendix 1.

None of the reviews and only two primary studies identified evidence relating to those with severe respiratory conditions. Clift et al. (described above) reported results of survival analyses separately for women and for men with rare lung conditions (for example, bronchiectasis, cystic fibrosis or alveolitis), relative to those without these conditions; no statistically significant associations were found.[23] The

same study reported that women with pulmonary hypertension or pulmonary fibrosis had a significantly increased risk of death, compared to those who did not (adjusted HR 1.55, 95% CI 1.00-2.40). Men with pulmonary hypertension or pulmonary fibrosis also had an increased risk of death but this was not statistically significant (adjusted HR 1.47, 95% CI 0.93-2.32); hazard ratios were adjusted for age, BMI, deprivation, ethnicity, permanent abode and a range of conditions including learning disability, kidney failure, diabetes and dementia.[23] Additionally, Williamson et al. reported on the association between severe asthma (defined as recent corticosteroid use) and mortality. Multivariate analysis showed that those with severe asthma (compared to those without asthma) had a significantly increased risk of death (adjusted HR 1.13, 95% CI 1.01-1.26), following adjustment for age, BMI, smoking, deprivation index, and comorbidities;[24] see Appendix 3.

People with rare diseases and inborn errors of metabolism

Based on expert opinion,[73] Public Health England[12] and Health Protection Scotland[13] include people with rare diseases that significantly increase the risk of infections, such as severe combined immunodeficiency or homozygous sickle cell disease, although Health Protection Scotland differs slightly by specifying that not everyone with a rare disease is at the highest risk.[13] This organisation also includes people with all forms of interstitial lung disease or sarcoidosis in this group as well as people with inborn errors of metabolism.[13]

The Norwegian Public Health Institute includes 'congenital immunodeficiency in an unstable phase that carries the risk of severe respiratory tract infections', this is reportedly based on a precautionary principle and not on evidence.[11] France include those with a rare disease,[14] while Health Services Alberta, the Belgian and Danish health authorities, and the CDC do not include people with rare diseases and inborn errors of metabolism in their highest risk category; see Appendix 1.

None of the reviews or primary studies included in this evidence summary provided evidence relating to those with rare diseases and inborn errors of metabolism.

People on immunosuppression therapies sufficient to significantly increase risk of infection

Based on the rapid reviews,[15, 16] non-systematic literature review,[18] factsheet[17] and expert opinions[19, 73] already described above, Health Services Alberta,[7] and the national public health organisations in Denmark,[9] Norway,[11] Belgium,[10] England,[12] and Scotland[13] include people with weakened immune system as a result of a disease or receiving treatment. Health Protection Scotland also includes people who have had their spleens removed and details a number of immune compromising conditions (for example autoimmune diseases and allergies) and treatments (for example, corticosteroids and cyclophosphamide).[13] France specify

congenital or acquired immunosuppression as a result of anticancer chemotherapy, immunosuppressive treatment, biotherapy, corticosteroid therapy at an immunosuppressive dose, uncontrolled HIV infection, solid organ transplant or stem cell transplant.[14] The Norwegian Institute of Public Health also provides examples such as chemotherapy, radiation therapy, and immunosuppressive therapy used to treat autoimmune diseases.[11] The CDC includes immunocompromised state (weakened immune system) from solid organ transplant only;[8] see Appendix 1.

None of the reviews included in this evidence summary provided evidence for a higher risk of severe COVID-19 occurring in those receiving immunotherapy significant to increase risk of infection. A number of the primary studies included provided an analysis of patients receiving immunotherapy which have been described above under *'People with specific cancers'*. Only one study included a specific analysis of those who had severe immunosuppression. Clift et al. reported that men and women who have sickle cell disease or severe immunodeficiency (compared to those who do not) have significantly increased risk of death from COVID-19, adjusted HR 5.94, 95% CI 1.89-18.67 and adjusted HR 4.41 95% CI 1.41-13.81, respectively;[23] see Appendix 3.

Women who are pregnant and have significant heart disease

Women who are pregnant and have significant heart disease, either congenital or acquired are identified as being at increased risk of serious disease by Public Health England[12] and Health Improvement Scotland.[13] Of note, however the Scottish categorisation only applies to those women who have conditions that require them to be followed by a specialist heart clinic during their pregnancy.[13] Both sets of guidance appear to be based on expert opinion as no evidence is provided. While the Danish Health Authority includes pregnant women and their unborn children, it does not specify women with significant heart disease;[9] they cite reports from the European Centre for Disease Prevention and Control (ECDC),[76] WHO[77] and Royal College of Obstetricians and Gynaecologists.[78] In advice dated 6 October, France noted an increased risk of severe disease in pregnant women with comorbidities (not limited to those with significant heart disease) irrespective of the term of the pregnancy, but that there were insufficient data to inform a decision with respect to women without comorbidities. However, they specified that based on analogies with other respiratory infections, there is a theoretical increased risk for all women in the third trimester and for the foetus. Of note, in the most recent advice, the continued lack of data to support a recommendation is noted, with pregnancy not specifically identified in the group at risk of serious disease.[14] The US CDC include pregnant women in the group considered to be at risk of severe illness from COVID-19; they cite two systematic reviews,[79, 80] one case control study,[81] four case series[82-85] and four cohort studies[86-89] to support this recommendation. It must be noted however that the CDC categories are based on the certainty of the underpinning

evidence (at increased risk, may be at increased risk) rather than differences in the relative risk per se. The absolute risk of severe disease in pregnancy was noted to be low in the most recent cohort study[89] that informed the update to the CDC guidance on 2 November 2020. Health Services Alberta, the Belgian and Norwegian public health authorities do not include women who are pregnant and have significant heart disease in their high risk category; see Appendix 1.

None of the reviews or primary studies included in this evidence summary provided evidence relating to women who are pregnant and have significant heart disease.

People with end-stage renal failure or on dialysis

Health Services Alberta,[7] the Belgian public health authority,[10] France[14] and Public Health England[12] and Scotland[13] include those with renal or kidney disease as being in the highest risk group; Alberta, France, England and Scotland specify end-stage chronic kidney disease, while Belgium lists chronic kidney disease generally. The Danish and Norwegian health authorities, and the CDC do not include this group. The rapid review by the Alberta SAG concludes that kidney disease is poorly defined in the literature and the risk of death from COVID-19 associated with chronic kidney disease (CKD) appears to be low, whilst the risk associated with hospital admission (including admission to ICU) is moderate;[15] See Appendix 1.

None of the reviews and three primary studies included in this evidence summary provided evidence relating to end-stage renal failure or dialysis patients. Clift et al. reported on the risk of death from COVID-19 in those with end-stage renal failure and those on dialysis. In women, compared to those with no kidney failure, there was an increased risk of death in those with end-stage renal disease (adjusted HR 3.00, 95% CI 2.19-4.12) and a hazard ratio suggestive of an increased risk in those on dialysis, though this was not statistically significant (adjusted HR 2.68 95% CI 0.86-8.36); adjusted for age, BMI, deprivation, ethnic group, permanent abode, and a range of conditions and treatments.[23] In men, when compared to those with no kidney failure, there was a significantly increased risk of death in those with end-stage renal disease, adjusted HR 2.40, 95% CI 1.83-3.15, and in those on dialysis adjusted HR 3.67, 95% CI 2.02-6.66; also adjusted for the same variables as the analysis for women.[23] Similarly, Gottlieb et al. reported that those with end-stage kidney failure and on dialysis had an increased risk of an admission to hospital, (adjusted OR 1.14, 95% 0.67-1.97); this was not significant and the covariates were not reported.[51] Using data from OpenSAFELY, Williamson et al. reported an increased risk of death in those with a history of dialysis or end-stage renal failure, (adjusted HR 3.69, 95% CI 3.09-4.39), though the covariates included in the analysis were unclear;[24] see Appendix 3.

Summary of findings from public health guidance, reviews and primary studies

Table 1 provides a summary matrix of the public health guidance, reviews and primary studies identified in this current evidence summary. These documents were selected for the present review as they included citation of sources to evidence their categorisation of particular groups as at risk of severe illness from COVID-19.

Table 1. Summary matrix of the public health guidance, reviews and primary studies identified for each extremely medically vulnerable group*

Extremely medically vulnerable groups*	Organisations issuing guidance for this group	Reviews that provide evidence of increased risk of severe COVID-19 for this group‡	Primary studies that provide evidence of increased risk of severe COVID-19 for this group^
Aged 70 years and older	▪ Alberta ▪ France	▪ Bonanad ▪ Figliozzi ▪ Villalobos ▪ Wingert	▪ Albiges ▪ García-Suárez ▪ Gottlieb ▪ Ioannou ▪ Petrilli ▪ Reilev ▪ Rentsch ▪ Rossi ▪ Williamson
Solid organ transplant recipients	▪ England ▪ France ▪ Norway ▪ Scotland ▪ US	▪ None	▪ Clift ▪ Reilev ▪ Webb ▪ Williamson
People with specific cancers	▪ Alberta ▪ England ▪ France ▪ Norway ▪ Scotland ▪ US	▪ Wang	▪ Albiges ▪ Clift ▪ Dai ▪ Garassino ▪ García-Suárez ▪ Gottlieb ▪ Gotzinger ▪ Kuderer ▪ Lee ▪ Lievre ▪ Luo ▪ Martínez-López ▪ Passamonti ▪ Pinato ▪ Robilotti ▪ Shah ▪ Williamson ▪ Yang
People with severe respiratory conditions	▪ Alberta ▪ Belgium ▪ Denmark ▪ England ▪ France ▪ Norway ▪ Scotland ▪ US	▪ None	▪ Clift ▪ Williamson

Extremely medically vulnerable groups*	Organisations issuing guidance for this group	Reviews that provide evidence of increased risk of severe COVID-19 for this group‡	Primary studies that provide evidence of increased risk of severe COVID-19 for this group^
People with rare diseases and inborn errors of metabolism	▪ England ▪ France ▪ Norway ▪ Scotland	▪ None	▪ None
People on immunosuppression therapies sufficient to significantly increase risk of infection	▪ Alberta ▪ Belgium ▪ Denmark ▪ England ▪ France ▪ Norway ▪ Scotland ▪ US	▪ None	▪ Clift
Women who are pregnant with significant heart disease	▪ England ▪ Scotland	▪ None	▪ None
End-stage renal failure or dialysis patients	▪ Alberta ▪ Belgium ▪ France	▪ None	▪ Clift ▪ Gottlieb ▪ Williamson

*As defined by guidance in Ireland.
‡To be eligible for inclusion, reviews had to have a defined search strategy, include studies from community- or population-based settings (for pregnancy and cancer, studies from hospital settings are also included), specify confirmation of SARS-CoV-2 by a positive molecular test (for example, RT-PCR test), include at least one risk factor (prior to diagnosis) for 'extremely medically vulnerable' as defined by guidance in Ireland, include the outcome of interest, that is, severe illness from COVID-19 (defined as admission to intensive care unit, ventilation or death).
^To be eligible for inclusion, primary research studies had to fulfil the study design criteria listed for reviews above (except for criterion relating to defined search strategy).

Methodological quality of included studies

Public health guidance and policy documents included in this review were included only if they presented evidence to underpin their decisions. However, as this evidence was combined with expert opinions they were considered to represent expert opinion evidence. Quality appraisal was not conducted on these documents. However, given their selection under the inclusion criteria for this review, they represent authoritative sources of expert opinion.

All five evidence synthesis studies included in this review were deemed to be of low quality.[41-45] Only one[43] of the five studies reported that study selection and data extraction were conducted in duplicate by independent reviewers. Additionally only a single study provided a list of excluded studies.[45] Other concerns include an inadequate search strategy [44] and lack of protocol or indication that methods had been established prior to conducting the review.[43, 44]

While it is acknowledged that adherence to the traditional systematic review process may be challenging in an environment where decision-making needs to be expedited, just one of the evidence synthesis reviews was specifically classified by its authors as a 'rapid review'.[45] Deviations from standard practice may result in failure to capture, and or exclude, relevant studies in an evidence synthesis. Two of the evidence synthesis studies included in this review are published as pre-prints, dating to 1 August 2020[41] and 1 September 2020[45] and have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.

A number of issues were identified relating to the methodological quality of the 24 primary studies included in this review. Firstly, all primary studies are observational studies meaning they are particularly vulnerable to biases and may not incorporate important confounding factors. In six of the studies it was deemed that the follow-up period was not necessarily long enough for the outcome of interest to occur.[23, 52, 54, 56, 63, 65] In one study, 72% of subjects had developed complications by the cut-off date with 64% still hospitalised by this time[56] and in another study the follow-up period was unclear.[47] There was also concern about the lack of adjustment for confounding variables or lack of clarity regarding which variables were adjusted for in a number of studies,[48, 49, 51, 54, 56, 63, 65] potentially leading to bias in reported findings.

The overall reporting in a number of studies was identified as poor or limited[47, 52, 54, 58] with lack of detail in the methodology[49, 59] and limited data analysis[47, 52, 56] also identified as issues. Finally, one of the primary studies included in this review is a published pre-print dating to 18 May 2020[50] and has not been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.

Discussion

For those risk groups currently listed by the HPSC[4] and HSE[5] as extremely medically vulnerable, it was identified that only eight of the 22 organisations reviewed had published public health and policy guidance documents citing evidence underpinning the categorisation of these groups as being at the highest risk of severe illness from COVID-19. It should be noted that the definition of risk varies across different organisations and thus are not directly comparable. For example, Norway, like Ireland, includes two distinct high risk groupings, with the guidance from Alberta, Belgium, Denmark and the US CDC referring to only one overall high risk group. Moreover, as previously noted, the US CDC categories are based on the certainty of the underpinning evidence (at increased risk, may be at increased risk)

rather than differences in the relative risk per se. In its most recent advice, the HCSP in France supplemented their advice on groups at increased risk of severe disease, to specify three risk categories involving an excess risk (defined as a HR greater than one).[19] This change was informed by the most recent epidemiological and published data. The risk categories were based on situations or pathologies associated with increased risk (1<HR≤3), significantly increased risk (3<HR≤5) and pathologies associated with very high significant additional risk (HR>5). Rare diseases which may expose patients to a severe form of COVID-19 were noted to be included on the basis of a precautionary principle.[19] Furthermore, the HCSP highlight the potential for multiple possible associations of these comorbidities, or between comorbidities and genetic background, that can lead to a high risk of severe disease, that may be even greater, than that of the isolated comorbidities identified to be most at risk.[19] While each of the groups categorised in Irish guidance as 'extremely medically vulnerable' are also reflected in guidance published by organisations internationally, the rationale for this classification is largely influenced by expert opinion. Two organisations (England[12] and Scotland)[13] described their advice as being underpinned by evidence available on COVID-19, knowledge of other infectious respiratory diseases and taking a precautionary approach. Whilst specific citations or details for the evidence used were somewhat lacking, SIGN have published a rapid review on this topic.[40]

The lack of evidence identified from public health guidance was reinforced by the lack of evidence identified in systematic or rapid reviews and primary studies. Overall, five systematic or rapid reviews were included in this evidence summary;[41-45] all were deemed to be of low quality. Four included reviews provided evidence on people aged 70 years or older.[41, 42, 44, 45] All concluded that increased age was associated with an increased risk of severe illness from COVID-19; of the nine primary studies that provided evidence for this group, all but one concluded the same.[24, 46, 48, 50, 61, 63, 65, 67] However, it should be noted that while studies adjusted for confounding factors, for example certain comorbidities, there may be residual confounding due to multiple unmeasured confounders or specific chronic conditions that may be particularly associated with severe illness due to COVID-19.

There is a lack of evidence relating to paediatric populations. While paediatric populations were typically eligible for inclusion in the systematic or rapid reviews and primary studies identified in this evidence summary, children were underrepresented and disaggregated data were not presented. Only one study was identified that specifically assessed risk of severe outcomes in a paediatric population.[52] This multicentre cohort study by Gotzinger et al. included 585 children and adolescents with laboratory-confirmed SARS-COV-2 infection from 21 European countries; data were collected from 1 April 2020 to 24 April 2020. Univariate analysis showed no significant increase in the odds of admission to ICU for children on

immunosuppressive therapy or in those receiving chemotherapy in the preceding six months. The authors noted that severe disease was uncommon in children and adolescents.[52] This is echoed in the included public health guidance documents. For example, the US CDC highlight that while children have been less affected by COVID-19 than adults, children with underlying medical conditions are at an increased risk for severe illness compared with children with no underlying conditions, but that the data to support this is limited.[39]

At the time of writing, published data that reflects the Irish setting is lacking. However, Hospital In-Patient Enquiry (HIPE) data from 29 February 2020 and 31 July 2020 has been used to profile the risk factors associated with ICU admission and in-hospital mortality among hospitalised COVID-19 patients in Ireland.[90] The findings agree with the conclusions drawn from this review, showing that those aged 65-84 years have a significantly increased risk of in-hospital mortality; this risk is even more pronounced for those aged 85 years and older. Additionally, obesity, diabetes and hypertension were determined to be significantly associated with an increased risk of ICU admission, while obesity, COPD and chronic renal disease significantly increased the risk of in-hospital mortality. Other comorbidities that were considered were asthma and influenza; no significant associations were reported between these comorbidities and ICU admission or in-hospital mortality.[90] It should be noted that a limitation of the HIPE data is that comorbidities may not always be recorded. Certain comorbidities such as obesity may also be poorly defined; where captured it was assumed that the obesity was considered to be clinically significant and or sufficient to be documented in the patient records. However, it is not possible to estimate the excess risk associated with different levels (BMI category) of obesity. Furthermore, this analysis focused on the first wave of COVID-19 in Ireland. Over the course of the pandemic, management has evolved and care has improved.[90]

One included review focused on people with specific cancers and reported that cancer patients (with COVID-19) receiving anti-cancer treatment (surgery, chemotherapy, targeted therapy or radiotherapy within preceding 40 days, or immunotherapy within the previous six months) did not have an increased risk of mortality. However, when stratifying by treatment type and timing, an increase risk of mortality was observed in patients receiving chemotherapy within the preceding 28 days.[43] The authors concluded that given the limitations of the data, further evaluation of the risks associated with cancer treatment, especially chemotherapy and immunotherapy in cancer patients with COVID-19 was required.[43] Similar to the systematic review on people with specific cancers and COVID-19, the primary studies relevant to this group were inconclusive. The most consistent finding was that patients receiving chemotherapy (compared to those who are not) are at a significantly increased risk of severe illness due to COVID-19.[23, 56, 58, 59, 63, 64] However, outcomes for other types of therapy were less consistent. Lee et al.[57]

utilised data from a UK cancer registry[91] and concluded that mortality from COVID-19 in cancer patients seemed to be primarily driven by age, gender and comorbidities; evidence of an increased risk of mortality for cancer patients on cytotoxic chemotherapy or other anticancer treatment (compared with those not on active treatment) was lacking.[57]

Three of the four primary studies on organ transplantation reported a significantly increased risk of mortality in transplant patients with COVID-19.[23, 24, 67] The one study that did not report an association was small (sample size n=151) and the authors noted several limitations such as short follow-up period and data on changes to immunosuppression regimens following COVID-19 diagnosis.[55] Moreover, the authors noted that the comparison cohort was limited to one region in the UK and therefore, may not be representative of COVID-19 in other geographical areas.[55]

Primary studies on people with severe respiratory conditions,[23, 24] people on immunosuppression therapies sufficient to significantly increase risk of infection[23] and patients with end-stage renal failure or dialysis patients[23, 24, 51] were consistent in their finding that these conditions were associated with a significantly increased risk of severe illness from COVID-19. However, it should be noted that this finding is from a small number of primary studies and therefore should be interpreted with caution.

Of the extremely medically vulnerable groups included in this evidence summary, no evidence (from guidance documents, systematic or rapid reviews or primary studies) was identified for people with rare diseases and inborn errors of metabolism or women who are pregnant with significant heart disease; these groups are included in guidance from England[12] and Scotland[13] which is based upon modified influenza vaccination risk groups and expert advice. As noted, France includes people with rare disease which may expose patients to a severe form of COVID-19,[14] on the basis of a precautionary principle, but highlight that it was not possible to obtain data on each of the rare diseases.[19]

The review of international guidance highlighted a number of groups, considered to be at highest risk of severe illness from COVID-19, that are not included in the current Irish guidance for the extremely medically vulnerable group. The following groups were included in guidance from Alberta, Belgium, Denmark, Norway, England and Scotland, with underpinning evidence also reported: Cardiovascular disease (CVD) and type 2 diabetes (included in guidance from Alberta,[15] Belgium,[17] France[14] and the US);[8] chronic liver disease, dementia and type 1 diabetes (included in guidance from Alberta);[15] COPD (included in guidance from Alberta,[15] and the US);[8] obesity (included in guidance from France[14] the US[8] and Denmark);[16] chronic kidney disease, severe obesity, smoking and pregnant women (included in guidance from the US);[8] pregnant women and their unborn children

(included in guidance from Denmark);[16] HIV infection with low CD4 counts (included in guidance from Norway[11] and France);[14] people with heart, lung or kidney disease and people with weakened immune systems (included in guidance from Belgium);[17] adults with Down syndrome (included in guidance from England[12] and Scotland; at the time of writing this report, the Scottish Government website has not been updated to reflect this change). France also include those who have at least stage B Child Pugh score cirrhosis, motor neuron disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia or hemiplegia, primary cerebral malignancy, progressive cerebellar disease or of a rare disease.[14] The underpinning evidence cited by these organisations included systematic reviews and meta-analyses, primary research studies and rapid reviews conducted by the organisations themselves. However, all groups apart from those with dementia, those who smoke, pregnant women (and their unborn children), HIV infection with low CD4 counts and those with Down syndrome are included in the groups considered at 'high risk' in the HSE guidance.

The advice issued by the HCSP in France,[19] notes that, within the French population, it is not possible to distinguish between those at risk and very high risk of severe illness from COVID-19 simply by an exhaustive of pathologies. As noted, they highlight that co-morbidities, demographic factors (age, sex), socio-economic factors and genetic factors must also be taken into account; thus, an individual's risk is highly variable and dependent on numerous co-existing factors.[19] However, the group have identified a number of factors that place an individual at most risk (which they define as a HR greater than 5) of severe illness from COVID-19. These factors are, age ≥70 years, Down syndrome (Trisomy 21), stem cell transplant, grade B and C chemotherapy, renal failure stage 5, transplant patient, dementia syndromes and cerebral palsy.[19]

The focus of this evidence summary was on the evidence underpinning the categorisation of extremely medically vulnerable groups as defined by the HPSC and HSE. However, it is important to note that consideration should to be given to other groups that may be at an increased risk of severe illness from COVID-19, namely those from socioeconomically deprived areas, ethnic minorities and those with mental health conditions. An interrogation of these groups was beyond the scope of this evidence summary. Internationally, those in essential services (for example, cleaning services, security, care workers, factory workers and transport services) have continued to work throughout the pandemic. Individuals working in these services tend to be impacted by increased levels of deprivation and higher rates of mortality have been reported for those working in these occupations.[92] In Ireland, a survey and statistical report by the Economic and Social Research Institute highlighted that similar patterns are evident across Ireland.[92] Whilst the evidence of this is less clear from the Irish data, the authors conclude that increased deprivation

should be treated as a risk factor for severe illness due to the strong correlation found in other countries.[92]

Evidence from the US has highlighted the disproportional impact of COVID-19 on ethnic minority and underserved groups. The literature highlights many reasons for this. Firstly, these groups are more likely to have chronic conditions and reduced access to healthcare which may compound COVID-19 outcomes. In addition, these groups are more likely to experience living and working conditions that predispose them to poorer health outcomes.[93] Similar patterns have been observed in the UK.[94] Whilst these disparities are the result of long-standing structural and societal factors, it is still important to highlight them to reduce the short-term impact of COVID-19 disparities.[93] Finally, those with mental health conditions are another group that warrant further consideration. In a study that analysed a nation-wide database of electronic health records of 61 million adult patients from 360 hospitals and 317,000 providers across 50 states in the US (up to 29 July 2020), patients with a recent diagnosis of a mental health disorder had a significantly increased risk for COVID-19 infection.[95] Moreover, those with both a recent diagnosis of a mental disorder and COVID-19 had a significantly increased risk of death and hospitalisation. These findings were further exacerbated among African Americans and women; which may have been related to higher risk of multimorbidity and metabolic risk factors in this group.[95]

This review is subject to a number of important limitations. These relate to the type of review conducted ('scoping review'), which was limited by the time constraints associated with the review, and the biases considered likely to be present in the systematic reviews and primary research studies included in this review.

This review aimed to explore evidence for the risk of severe COVID-19 among each of the eight risk groups listed by the HSE (and seven listed by the HPSC) as 'extremely medically vulnerable'. In order to comprehensively evaluate the risk associated with each of these groups, a systematic review of the evidence would be required for each of the eight individual situations. However, due to time constraints, this was not possible and a scoping review was performed. This aimed to identify key evidence through reviewing evidence cited by international organisations when classifying groups at risk of severe COVID-19, and through identifying existing systematic reviews which reported risks associated with the groups of interest. As this review did not systematically search for primary research studies other than those cited in public health guidance or policy documents or those cited in systematic reviews, more recent primary research studies that may be of relevance, and were not featured in systematic reviews, will not have been included.

Among the systematic reviews included in this review, methodological quality and quality of reporting was found to be low. Due to time limitations, the quality of

primary research studies contributing to the systematic reviews, or contributing to public health guidance or policy, were not assessed. However, it is notable that the majority of these studies were conducted early in the pandemic, and appeared to involve suboptimal methodology for assessment of risk factors, including inappropriate, or poor reporting of, adjustment for potential confounding factors.

Among primary research studies included within this review, regardless of study quality, it is likely that the data are biased both by the measures taken by individuals with these conditions, and by measures taken by public health authorities, to mitigate perceived risk. This is particularly the case where conditions have been listed in international guidance as associated with high risk of severe COVID-19, as it is likely that a large proportion of individuals with such conditions will have elected to 'cocoon' or 'shield' where possible during the pandemic to date. As such, the number of patients within these groups who have been infected with SARS-CoV-2, and thereby contributed data to estimates of risk of severe COVID-19, is likely to be artificially lowered. It is plausible that lowering the numbers infected would both lower the statistical power of studies to detect risks and bias the type of patients exposed to SARS-CoV-2 within these groups. For example, those patients considered to be of lower risk may have been less likely to shield, and consequently may be more likely to be represented in the current data on risk of severe COVID-19, alternatively, those who cannot shield due to socioeconomic factors may be overrepresented. Therefore, it is plausible that the 'true' risk of severe COVID-19 within groups may be different to that empirically estimated thus far.

In addition to the above limitations, it is difficult to discern the risk of severe COVID-19 among the included groups of interest given the large degree of heterogeneity that exists within some of these categories,[96] and the likely interaction between the categories in some cases. For example, increasing age is a strong predictor of severe illness due to COVID-19 and even where adjustment for the effect of age is performed in studies, the confounding effect of this variable may remain. Williamson et al.,[24] who used OpenSAFELY data to examine factors associated with COVID-19 death, provided a supplement to their original report, highlighting strong evidence for the interaction of age and associations of other covariates with COVID-19 death; effect sizes for the risk of severe COVID-19 associated with cancer generally, or haematological malignancy, for example, were substantially higher (of a magnitude of ten times the risk) in younger age-groups than in older age-groups. Also while increasing age is associated with an increased risk of severe illness from COVID-19, it is plausible that this may be confounded by co-morbidities which typically increase with increasing age, leading to a plausible expectation that those under 70 years with multiple chronic conditions are at an increased risk of severe illness due to COVID-19.[97]

Conclusion

Overall, among the eight groups listed by the HPSC and HSE as being 'extremely medically vulnerable' the strongest evidence supporting this classification was for those aged 70 years and older.

While evidence was available for five of the remaining seven groups, firm conclusions regarding the level of risk of severe COVID-19 associated with these groups could not be made due to inconsistency in reported results and poor quality of included studies. Evidence was unavailable for two groups, namely people with rare diseases and inborn errors of metabolism and women who are pregnant and have significant heart disease. These two groups were, however, included within the guidance of England, Scotland, France and Norway on the basis of expert opinion and or the precautionary principle. Heterogeneity of condition severity, and of the characteristics of patients within these groups, is likely to contribute to the observed inconsistency of findings in groups where evidence was available. Given the rarity of certain conditions and the likely ongoing shielding of certain patient groups resulting in reduction of their exposure to SARS-CoV-2, an absence of evidence of severe COVID-19 in certain conditions should not be interpreted as an absence of a true association.

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Appendix 1: Data extraction table for public health guidance and policy documents

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
Alberta Health Services, Canada[7] People who are most likely to experience severe outcomes https://www.alberta.ca/protecting-at-risk-albertans-from-covid-19.aspx 25 July 2020	▪ Are over the age of 70 ▪ Have underlying medical conditions, such as: ○ cardio-vascular disease (congestive heart failure, ischemic heart disease, atrial fibrillation) ○ chronic liver disease ○ chronic obstructive pulmonary disease (COPD) ○ dementia ○ diabetes (type 1 and type 2) ○ immunodeficiency disease ○ malignant cancer (excluding non-melanoma skin cancer) ○ renal disease (chronic renal failure and end-stage renal disease).	▪ Rapid review (21 August 2020) conducted by Alberta's Scientific Advisory Group (SAG).[15] ○ Topic: What risk factors (such as age, medical conditions, or lifestyle factors) are associated with the development of severe outcomes in COVID-19? ○ 12 systematic reviews, 11 prospective cohort studies, 37 retrospective studies, and 6 case series. ▪ Rapid review (15 September 2020) conducted by Alberta's Scientific Advisory Group (SAG).[98] ○ Topic: Is being immunosuppressed (in its various forms) associated with increased likelihood of recognised COVID-19 and/or increased disease severity? ○ 51 articles; 39 primary studies and the remainder from recommended articles on PubMed, reference lists of included articles, and on recommendation from reviewers involved with this report. 8 articles describing grey literature were included *ad hoc*. ▪ See SAG website for full list of guidance documents and recommendations: https://www.albertahealthservices.ca/topics/Page17074.aspx

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
Belgian Federal Ministry of Public Health[10] People who are more at risk https://www.info-coronavirus.be/en/about-the-coronavirus/ Not reported	▪ People over 65[71, 72] ▪ Diabetics (type 2), in combination with obesity and/or problems with heart, lungs or kidneys[72, 75] ▪ People with heart, lung or kidney disease[72, 75] ▪ People with weakened immune system.	▪ Scientists from the Epidemiology of Infectious Disease Unit of Sciensano summarise and interpret key information based on a comprehensive review of the literature and publish their findings in a fact sheet.[17] ○ 'Risk groups and risk factors' section was last updated on 14 June 2020. This includes summaries on: ▪ older age (2 retrospective cohort studies), ▪ co-morbidities (1 meta-analysis; 2 retrospective cohort studies), gender (2 retrospective cohort studies), ▪ smoking (1 retrospective cohort study), ▪ ethnicity (insufficiently studied and reported) ▪ health-care workers (ECDC report) ▪ genetics (genome-wide association study). ○ 'Pregnant women' section was last updated on 4 September 2020. This includes reference to nation-wide data in Sweden and US. ○ 'Other special populations' section was last updated on 4 September 2020. This includes summaries on: ▪ HIV patients (2 case reports; 2 matched case-control studies, 2 cohort studies) ▪ cancer patients (4 systematic review and meta-analysis of published reports until the end of April; 4 case series; 3 cohort studies; Belgian population-based analysis) ▪ haematolological malignancies (1 cohort study; 1 national database study) ▪ anti-cancer therapy (3 cohort studies; 4 case series).

Country/Organisation **Description of the highest risk group in the relevant guidance document** **URL** **Date updated**	**Highest risk groups**	**Evidence sources**
Danish Health Authority[9] People at higher risk of severe illness from COVID-19 https://www.sst.dk/en/English/Corona-eng/Prevent-infection/People-at-higher-risk 12 October 2020 (this is reported for the webpage with the groups and advice for these groups, however the groups may have been not have been updated on this date)	▪ Age[99, 100] ○ 80 years or older. It is well documented that you are at higher risk, regardless of whether you are healthy and fit or suffer from diseases and other conditions. ○ 65-79 years old. Many fit and healthy people in this age group are not at higher risk. However, chronic diseases or mental and physical illnesses may cause you to be at higher risk. ○ Under 65 years old. Very few are at higher risk. You are, for example, not at higher risk if you are only slightly overweight, has well-treated high blood pressure, arthritis, or mild asthma. ▪ Overweight[101] It is well documented that the following are at higher risk: ○ People with a BMI over 35. ○ People with a BMI over 30 and one or more chronic diseases. ▪ Residents in nursing homes/assisted living facilities[76, 102] ○ It is well documented that residents in nursing homes are at higher risk of severe illness from COVID-19 as they are often elderly and have chronic diseases, functional decline and fragile health. ▪ People with certain chronic diseases and people with weakened immune systems[103-105]	▪ In August 2020 the Danish Health Authority reviewed the latest knowledge and evidence in relation to which persons may be at increased risk of becoming seriously ill with COVID-19 and updated their recommendations. ▪ A non-systematic literature review (published on 23 September 2020)* was conducted focusing on hospitalisation, including admission to the intensive care unit, and death as a result of COVID-19, as well as on what factors are associated with hospitalization or death.[16] ▪ Evidence was sought in the following order of priority: 1. Cochrane reviews 2. Recommendations from (inter-) national health authorities (WHO, ECDC, CDC, health professional recommendations of comparable countries, primarily from The Norwegian Institute of Public Health and the National Health Services in England, as well as professional associations recommendations) 3. Recommendations of professional companies 4. Review articles and meta-analyses 5. Cohort studies 6. Case studies The quality of the evidence was not systematically assessed. ▪ The following diseases and conditions were reviewed in the updated evidence search: ○ high age ○ residents in nursing homes ○ overweight ○ impaired immune system

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
	○ Based on the available knowledge about other diseases, particularly influenza, people with certain chronic diseases are assumed to be at increased risk of severe illness from COVID-19 – at least if these chronic conditions are not well-regulated. This also applies to certain children with chronic diseases. ▪ People with no fixed abode ○ People without a permanent residence are presumed to be at higher risk as they often have fragile health and chronic diseases, and are often not able or willing to take advantage of the health services. ▪ Pregnant women[76-78, 106] ○ Based on a precautionary principle, pregnant women and their unborn children are considered to be at higher risk.	○ heart disease ○ lung disease ○ cancer ○ kidney disease ○ diabetes ○ gastrointestinal or liver disease ○ neurological disease ○ rheumatological disease ○ children with chronic illness ○ pregnant ○ male biological sex ○ smoking ○ socially and economically disadvantaged ○ work in the health care system. *Note: This document was translated from Danish using google translate.
Public Health England[12] Patients who are at the highest risk of severe morbidity and mortality from coronavirus (COVID-19) https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-	▪ Solid organ transplant recipients ▪ People with specific cancers: ○ people with cancer who are undergoing active chemotherapy ○ people with lung cancer who are undergoing radical radiotherapy ○ people with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment ○ people having immunotherapy or other continuing antibody treatments for cancer	▪ "The government's guidance for those considered clinically extremely vulnerable is led by the scientific evidence and clinical advice of the Chief Medical Officers. To avoid public confusion, local organisations should not issue guidance to people considered clinically extremely vulnerable that differs from the government advice in place at any given point in time, unless this is part of a response to a local outbreak agreed with government".[73] ▪ Also note from the letter (pg. 3): Now that more evidence regarding the COVID-19 risk factors is available, the government has commissioned work to develop and evaluate a clinical risk prediction model to estimate short

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#Clinically 26 November 2020	○ people having other targeted cancer treatments that can affect the immune system, such as protein kinase inhibitors or PARP inhibitors ○ people who have had bone marrow or stem cell transplants in the last 6 months or who are still taking immunosuppression drugs ▪ People with severe respiratory conditions including all cystic fibrosis, severe asthma and severe COPD. ▪ People with rare diseases that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell disease). ▪ People on immunosuppression therapies sufficient to significantly increase risk of infection. ▪ Adults with Down syndrome.(23) ▪ Adults on dialysis or with chronic kidney disease (stage 5).(23) ▪ Women who are pregnant with significant heart disease, congenital or acquired. ▪ Other people who have also been classed as clinically extremely vulnerable, based on clinical judgement and an assessment of their needs. GPs and hospital clinicians have been provided with guidance to support these decisions. The group is reported to be a subset of a wider more generally vulnerable group which was broadly any adult eligible for an annual flu vaccine. Developed by Chief Medical Officer in collaboration with expert doctors in England, to identify relevant specific medical condition at highest risk of	term risks of catching and experiencing adverse outcomes from COVID-19 in adults. ▪ Also see report on work done on review of disparities in risks and outcomes.(107) ▪ The inclusion of adults with Down syndrome and chronic kidney disease stage 5 is based on evidence from the QCOVID prediction tool, validated by Clift et al. using the QResearch database.(23, 108)

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
	severe morbidity and mortality from coronavirus. Currently reviewing the high risk groups.	

Government of France[14]
 	
Notice on updating the list of risk factors for severe Covid-19[19]
 	
https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=942
	▪ Be 65 years of age and over.
	▪ Have a cardiovascular history (ATCD): complicated arterial hypertension (with cardiac, renal and cerebral complications), ATCD of cerebrovascular accident or coronary artery disease, of cardiac surgery, NYHA stage III or IV heart failure.
	▪ Have unbalanced diabetes or have complications.
	▪ Have a chronic respiratory pathology liable to decompensate during a viral infection: obstructive pulmonary disease, severe asthma, pulmonary fibrosis, sleep apnoea syndrome, cystic fibrosis.
	▪ Have chronic renal failure on dialysis.
	▪ Have an active cancer under treatment (excluding hormone therapy).
	▪ Be obese (BMI>30 kg/m^2).
	▪ Have at least stage B Child Pugh score cirrhosis.
	▪ Have a major sickle cell syndrome or have a history of splenectomy.
	▪ Be in the third trimester of pregnancy.
	▪ Have a congenital or acquired immunosuppression:
	  ○ anticancer chemotherapy, immunosuppressive treatment, biotherapy and or corticosteroid therapy at an immunosuppressive dose.
	  ○ uncontrolled HIV infection or with CD4<200/mm^3.
	  ○ following a solid organ transplant or hematopoietic stem cell transplant.
	  ○ linked to a malignant hemopathy during treatment.
		Expert opinion from the High Council of Public Health, France in response to a request from the General Directorate of Health. The report includes epidemiological data from:
		▪ Three systematic reviews.[20-22]
		▪ Two population studies.[23, 24]
		▪ Seven observational studies.[25-31]
		▪ One cross-sectional study.[32]
		▪ Three CDC Morbidity and Mortality Weekly Reports.[33-35]

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
	▪ Have motor neuron disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia or hemiplegia, primary cerebral malignancy, progressive cerebellar disease or a rare disease. It is not possible to distinguish, within the French population of working age, among people at risk of severe form of Covid-19, the population groups identified as "at very high risk of life" by listing a list unambiguous exhaustive of pathologies. Indeed, this approach must take into account co-morbidities, demographic factors (age, sex) as well as socio-economic factors, even genetic factors and can therefore only be individual. However, this updating work has made it possible to identify the situations or pathologies most at risk of severe form of Covid-19 according to data from recent literature (HR>5): ▪ age ≥70 years ▪ Down syndrome (Trisomy 21) ▪ stem cell transplant ▪ grade B and C chemotherapy ▪ renal failure stage 5, transplant patient ▪ dementia syndromes ▪ cerebral palsy.	
Norwegian Institute of Public Health[11] Groups with moderate / high risk	▪ Residents of nursing homes ▪ Over 80 years of age[48, 109] ▪ Age 66–80 years with one of the following chronic diseases, OR age 50–65 years with two or more of the following chronic diseases: ○ cardiovascular disease (other than well-regulated high blood pressure)	▪ Rapid review conducted by The Norwegian Institute of Public Health (15 November).[18] ▪ Title: COVID-19 and risk factors for severe disease. ▪ Only studies that were peer-reviewed, population-based with a sample size of at least 5000 laboratory test positive cases and reported multivariate analysis were included.

Country/Organisation **Description of the highest risk group in the relevant guidance document** **URL** **Date updated**	**Highest risk groups**	**Evidence sources**
https://www.fhi.no/en/op/novel-coronavirus-facts-advice/facts-and-general-advice/risk-groups---advice-and-information/?term=&h=1#groups-with-moderate-high-risk 15 November 2020	○ morbid obesity (BMI ≥ 30 kg/m^2 in combination with weight-related diseases or BMI ≥ 40 kg/m^2)[48, 110-112] ○ diabetes[48] ○ chronic kidney disease and kidney failure ○ chronic lung disease (other than well-regulated asthma)[109, 111, 113] ○ chronic liver disease ○ immunosuppressive therapy such as chemotherapy, radiation therapy and immunosuppressive therapy in autoimmune diseases. ▪ Severe health condition, regardless of age*: ○ people with active cancer, ongoing or recently discontinued treatment for cancer (especially immunosuppressive therapy, radiation therapy to the lungs or chemotherapy)[109] ○ neurological or muscular disease with impaired coughing strength or lung function (e.g. ALS) ○ congenital immunodeficiency in an unstable phase that carries the risk of severe respiratory tract infections ○ blood diseases that impair the immune system ○ organ transplant ○ HIV infection with low CD4 counts ○ significant renal impairment or significantly impaired liver function ○ other, assessed by a doctor *We have included some serious health conditions in this list of a precautionary principle, although at present there are no studies indicating a higher risk of severe progression for the diseases.	▪ Update of previously published versions, 12 May and 14 April 2020. ▪ A search was conducted in EndNote database of the Norwegian Institute of Public Health's systematic and living map on COVID-19 evidence which includes COVID-19 related search results from a wide range of databases; Cochrane Library, PubMed, Embase, Scopus, ClinicalTrials, bioRxiv, medRxiv among others, with the aim to be as "comprehensive, exhaustive, and systematic as possible". ▪ The factors that were examined were age, sex, gender, race/ethnicity, deprivation, body mass index (BMI), underlying comorbidities, smoking habits, and medicine use. ▪ Five studies included: two studies were from England,[24, 114] one from the UK,[23] one from the USA[48] and one study was from Denmark.[67] Three out of five studies reported only data on the adult population. ▪ The median number of participants in the included studies was 6,083,102 (range: 11,544 to 61,414,470). ▪ 5 studies explored risk factors associated with the development of more severe/critical COVID-19.* ▪ 5 studies explored risk factors associated with death due to COVID-19.* ▪ A formal quality assessment was conducted. ▪ The certainty of evidence was not graded.

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
	High risk groups are informed by rapid reviews by NIPH utilising a regular updated database of COVID-19 evidence. Drafts of the reports are peer reviewed by two Chief Medical Officers and a member of NIPH.	
Health Protection Scotland[13] Highest risk group https://www.gov.scot/publications/covid-shielding/pages/highest-risk-classification/ 16 October 2020	▪ Solid organ transplant recipients - includes people who have had a transplant of heart, lung, stomach or other part of intestine, liver and kidney. This is because of the medication taken to stop rejection of the transplanted organ. ▪ People with specific cancers: ○ People with cancer who are undergoing active chemotherapy or have had radical radiotherapy for lung cancer. ○ People with cancers of the blood or bone marrow who are at any stage of treatment. This includes cancers such as leukaemia, lymphoma or myeloma. ○ People with cancer who are having immunotherapy or other continuing antibody treatments. ○ People having specialised, cancer treatments that can affect the immune system, such as protein kinase inhibitors or PARP inhibitors. ○ People who have had bone marrow or stem cell transplants in the last six months, or who are still taking immunosuppression drugs. ▪ People with severe respiratory conditions including all cystic fibrosis, severe asthma and severe COPD, severe bronchiectasis and pulmonary hypertension. People in this group include: ○ People with cystic fibrosis ○ People on home oxygen for a lung condition	▪ Four Chief Medical Officers decided on the shielding group based on the evidence available on Covid-19, knowledge of other infectious respiratory diseases and taking a precautionary approach.[74] ▪ A rapid review was also conducted by Health Improvement Scotland SIGN for NHS Scotland (21 July 2020). This updates a previous version published in May 2020. Title: 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. ▪ The purpose of this rapid review was to provide NHS Scotland with advice on assessment of patients with COVID-19 in primary care. ▪ 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, McMaster forum, 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

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
	○ People with severe asthma, having severe asthma and on regular inhalers and long-term oral steroid tablets. For example Prednisolone or regular injections to control their asthma ○ People with severe COPD. This usually means being on several different inhaler medications in the last year. As well as a steroid inhaler, this must include two long acting preventers. For example, Long Acting Beta Agonists and Long Acting Anti-Muscarinic Antagonists. Severe COPD means that: ▪ you are too breathless to walk 100 yards ▪ you have 2 or more lung infections a year or ▪ you need oxygen to help with your breathing. People with rare diseases including all forms of interstitial lung disease/sarcoidosis. This includes inborn errors of metabolism that significantly increase the risk of infections. For example, SCID, homozygous sickle cell disease. ○ there are many conditions classed as a rare disease ○ not everyone with a rare disease will be at a higher risk of severe illness from COVID-19 ▪ People on immunosuppression therapies that significantly increase risk of infection. Or who have had their spleens removed. ○ Immunosuppressive therapy helps to stop rejection of a bone marrow or organ transplant. It can also be used to treat conditions in which the immune system is overactive. For example, autoimmune diseases and allergies ○ In some cases these treatments may put people into a shielding group:	searched for preprints added up to and including 24 April 2020. No quality assessment was carried out. ▪ 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. ▪ The initial rapid review identified a mixture of published studies and preprints or preliminary reports, mostly retrospective observational studies, that included data on signs and symptoms from mixed healthcare settings, primarily in the US and Italy. ▪ The update was primarily based on published studies and some of the preprint papers from the initial review that have since been published. ▪ All evidence reported should be considered low quality and needs to be interpreted with caution. ▪ Scoping searches for new evidence will be conducted every 2 months. The review will be updated if new evidence emerges that changes the current conclusions.

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
	▪ people on high dose corticosteroid treatment (equal to Prednisolone 20mg or more) for 4 weeks or more ▪ people on specific single therapies, for example Cyclophosphamide. These medications are usually prescribed by specialists in hospitals ▪ people on lower dose of corticosteroids in combination with other disease modifying medication ▪ people on disease modifying medications who also have other chronic medical conditions. People who take some medication and are otherwise healthy may not need to be in the shielding groups. This includes single Disease Modifying medications (DMARD). It also includes Biologic medications such as methotrexate, azathioprine, cyclosporin, leflunomide plus others. This is to be discussed with a specialist or GP if unsure. ▪ People who are pregnant with significant heart disease, congenital or acquired ○ If you are being followed up by a specialist heart clinic during your pregnancy then you fall within this group ▪ People who are receiving renal dialysis treatment ▪ People receiving and those starting renal dialysis. Adults with Down syndrome (Note: This addition is effective from 4 November 2020. However at time of writing the Scottish Government website has not been updated to reflect this change.)	
Centers for Disease Control and Prevention[8]	▪ Cancer[49, 115-117] ▪ Chronic kidney disease[118-123] ▪ COPD[120, 124-126]	▪ Updates to the CDC list of underlying medical conditions that put adults of any age at increased risk for severe illness are currently based on published reports, articles in

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
Adults of any age with the following conditions are at increased risk of severe illness from the virus that causes COVID-19 https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html 02 November 2020	▪ Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies[2, 109, 110, 126, 127] ▪ Immunocompromised state (weakened immune system) from solid organ transplant[118, 128-134] ▪ Obesity (body mass index [BMI] of 30 kg/m2 or higher but < 40 kg/m2)[48, 101, 135-138] ▪ Severe Obesity (BMI ≥ 40 kg/m2)[25, 139-141] ▪ Pregnancy[79-89] ▪ Sickle cell disease[142-146] ▪ Smoking[2, 125, 147] ▪ Type 2 diabetes mellitus[114, 123, 148-151]	press, un-reviewed pre-prints, and internal data available between December 1, 2019 and September 1, 2020. ▪ This list is a living document that will be periodically updated by CDC. ▪ The level of evidence for each condition was determined by CDC reviewers based on available information about COVID-19. Conditions were added to the list (if not already on the previous underlying medical conditions list [originally released in March 2020]) if evidence for an association with severe illness from COVID-19 met any of the following criteria: ○ Strongest and most consistent evidence: Defined as consistent evidence from multiple small studies or a strong association from a large study ▪ Cancer (1 systematic review; 2 cohort studies; 1 case series) ▪ CKD (3 case series; 3 cohort studies) ▪ COPD (2 meta-analyses; 1 case series; 1 cohort study) ▪ Specified heart conditions (2 cohort studies; 2 meta-analyses; 1 case series) ▪ Obesity (5 cohort studies; 1 cross-sectional study) ▪ Severe obesity (2 cohort studies; 1 cross-sectional study; 1 meta-analysis) ▪ Pregnancy (2 systematic reviews; 1 case control study; 4 case series; 4 cohort studies) ▪ Sickle cell disease (5 case series) ▪ Smoking (10 meta analyses) ▪ Solid organ transplantation (7 case series; 1 meta-analysis)

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
		▪ Type 2 diabetes (1 case series; 1 longitudinal study; 2 cohort studies; 1 meta-analysis; 1 cross sectional study) ○ Mixed evidence: Defined as multiple studies that reached different conclusions about risk associated with a condition, or ○ Limited evidence: Defined as consistent evidence from a small number of studies. ▪ A full list of conditions and available evidence is available at the following link: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html ▪ CDC is also conducting ongoing disease surveillance and field investigations to better understand why some people are more likely to develop severe COVID-19 illness. ▪ CDC is working to identify risk factors for severe COVID-19 illness through a variety of investigations. These investigations include adults and children and examine: ○ severe illness resulting in hospitalizations ○ severe illness resulting in intensive care unit admissions. ▪ Surveillance networks and investigations used include: COVID-NET; The U.S. Flu Vaccine Effectiveness (VE) network, New Vaccine Surveillance Network (NVSN); Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN); Influenza Vaccine effectiveness in critically ill patients (IVY); and ongoing field investigations

Country/Organisation Description of the highest risk group in the relevant guidance document URL Date updated	Highest risk groups	Evidence sources
		▪ As investigations of risk factors for severe illness continue, the CDC will update the webpage below with new findings and new investigations: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/assessing-risk-factors.html

Appendix 2: Data extraction table for systematic and rapid reviews

First author Review type Publication date DOI	Groups considered Number of included studies	Outcomes Author conclusions
Bonanad[44] Meta-analysis 25 May 2020 10.1016/j.jamda.2020.05.045	*Groups considered:* ≥70 years old *Number of included studies*: 5 (611,583 subjects) 4 national reports from: China (44,672 subjects), Italy (214,103 subjects), Spain (220,375 subjects), and United Kingdom (129,799 subjects) 1 publication from: Northwell Health, the largest academic health system in New York State (2,634 subjects).	*Outcomes:* Mortality Odds of death greater for those aged 70-79 years compared to subjects aged 60-69 years: ▪ China (OR 2.32, 95% CI 1.97 – 2.72) ▪ US (OR 2.53, 95% CI 1.87 – 3.44) ▪ UK (OR 2.17, 95% CI 2.06 – 2.28) ▪ Spain (OR 3.24, 95% CI 3.05 – 3.44) ▪ Italy (OR 2.91, 95% CI 2.78 – 3.05) ▪ Overall (OR 2.62, 95% CI 2.18 – 3.15) Odds of death greater for those aged >80 years compared to subjects aged 70-79 years: ▪ China (OR 2.00, 95% CI 1.66 – 2.42) ▪ US (OR 2.45, 95% CI 1.87 – 3.22) ▪ UK (OR 1.30, 95% CI 1.26 – 1.35) ▪ Spain (OR 1.66, 95% CI 1.60 – 1.73) ▪ Italy (OR 1.22, 95% CI 1.19 – 1.26) ▪ Overall (OR 1.60, 95% CI 1.36 – 1.88) *Author conclusions:* The analysis of 611,583 patients shows a mortality increase related to age; this is evident in patients aged ≥60 years, increasing significantly in each decade of life.
Figliozzi[42] Systematic review and meta-analysis 29 July 2020 10.1111/eci.13362	*Groups considered:* ≥70 years old *Number of included studies:* 49 in systematic review. For estimates of age classification an expanded database was used (unknown settings) with 587,790 cases from the following 8 countries: ▪ China (n = 44,672 as of 11 February 2020),	*Outcomes:* Mortality Odds of death greater for those aged ≥70 years: ▪ compared to younger subjects (OR 13.19, 95% CI 7.72 - 22.55) ▪ compared to patients <60 years: (OR 23.46, 95% CI 13.58 - 40.52) (After excluding cases from France or Germany due to non-compatible data tabulation; n = 558,069)

First author Review type Publication date DOI	Groups considered Number of included studies	Outcomes Author conclusions
	▪ US (n = 2,449 as of 16 March 2020), ▪ South Korea (n = 10,450 as of 12 April 2020), ▪ Italy (n = 177,173 as of 24 April 2020), ▪ France (n = 29,721 as of 17 April 2020), ▪ Germany (n = 150,383 as of 24 April 2020), ▪ the Netherlands (n = 30,164 as of 24 April 2020) ▪ Spain (n = 142,278 as of 24 April 2020) Note: the total number of cases per the individual country data total 587,290 compared to a total of 587,790 reported in the paper.	▪ compared to patients <50 years: (OR 33.75, 95% CI 16.17 - 70.46) (After excluding cases from France or Germany due to non-compatible data tabulation; n = 407,686) *Author conclusions:* Advanced age conferred an increased risk of in-hospital death.
Villalobos[41] Systematic review and meta-analysis Pre-print 1 August 2020 10.1101/2020.07.30.20165050	*Groups considered:* ≥70 years old *Number of included studies:* 75 in the systematic review. Publicly available data from six country-level reports were used to calculate relative risk of death by age and focused on countries with the highest officially reported absolute number of deaths due to COVID-19 by 28 April 2020 according to Johns Hopkins University.	*Outcomes:* Mortality (status reported as: infection to death) Risk of death for those aged >70 years greater than those aged <50 years: ▪ US (RR 53.1, 95% CI 51.3 – 54.9) ▪ Italy (RR 53.8, 95% CI 48.5 – 59.8) ▪ Spain (RR 47.3, 95% CI 42.3 – 52.8) ▪ England (RR 26.6, 95% CI 24.8 – 28.6) ▪ Belgium (RR 32.0, 95% CI 27.2 – 37.7) ▪ Germany (RR 195.1, 95% CI 159.6 – 238.5) *Author conclusions:* We identified and confirmed population groups that are vulnerable and that require targeted prevention approaches.
Wang[43] Systematic review and meta-analysis 22 September 2020 10.1080/2162402X.2020.1824646	*Groups considered:* Cancer *Number of included studies:* 17 (comprising 3,581 cancer patients). 9 studies included in meta-analysis for risk of death.	*Outcomes:* Mortality No significant correlation between anti-cancer therapy and the risk of mortality in cancer patients with COVID-19. Cancer patients who received any anti-cancer therapy: OR 1.33, 95% CI 0.84–2.10, p=0.23. No statistically significant correlation was shown between anti-cancer therapy (including surgery, chemotherapy, targeted therapy, immunotherapy, and radiotherapy) and the risk of death events in cancer patients with COVID-19.

First author Review type Publication date DOI	Groups considered Number of included studies	Outcomes Author conclusions
		Subgroup analysis (stratifying by treatment time) Cancer patients who received chemotherapy within the previous: - 28 days had an increased risk of death (OR 1.45, 95% CI 1.10–1.91, p=0.008). - 40 days did not have an increased risk of death (OR 0.56, 95% CI 0.27-1.13, p=.11) *Author conclusions:* Cancer patients recently under anti-cancer treatment before diagnosed with COVID-19, including surgery, targeted therapy, immunotherapy, and radiotherapy, were not associated with increased risk of exacerbation and mortality. Chemotherapy within 28 days increased the risk of mortality. The role of anti-cancer therapy in cancer patients with COVID-19 still needs further exploration, especially chemotherapy and immunotherapy.
Wingert[45] Rapid review Pre-print 1 September 2020 10.1101/2020.08.27.20183434	*Groups considered:* ≥70 years old *Number of included studies:* 34 in rapid review. A COVID-19 positive population (n=3 studies, n=87,819 subjects) (not necessarily hospitalised) was used to calculate relative risk of death by age. A community sample of COVID-19 positive population (n=11 studies, n=6,877 subjects) (not necessarily hospitalised) was used to calculate risk of mortality with increased age.	*Outcomes:* Mortality Risk of mortality for those aged >70 years or >75 years greater than those aged ≤45 years: RR ≥5.00 (moderate confidence in association*) Risk of mortality for those aged >80 years greater than those aged ≤45 years: RR ≥5.00 (low confidence in association*) Risk of mortality with increased age - approximately 5-10% relative increase in risk of mortality per year (moderate confidence in association*). *Note: low means that the evidence indicates that there ***may*** be an association; moderate means that the evidence indicates that there ***probably*** is an association.

First author Review type Publication date DOI	Groups considered Number of included studies	Outcomes Author conclusions
		Author conclusions: Among the factors identified as increasing risk of severe outcomes, age seemed to be the most influential but there are likely to be multiple unmeasured confounders that have not been accounted for.

Appendix 3: Data extraction table for primary studies

First author Country Design Publication date DOI	Setting/Data source Sample size Demographics Groups considered	Outcomes Author conclusions
Albiges[63] France Prospective cohort study 22 September 2020 10.1038/s43018-020-00120-5	*Setting:* Gustave Roussy Cancer Centre. Data collected from 24 March 2020 to 29 April 2020. *Sample size:* n=178 cancer patients (total sample) *Median age:* 61 years (IQR 52.0-71.0 years) *Male:* n=76 (42.7%) *Groups considered:* Aged ≥70 years; Haematological malignancy; Chemotherapy in previous 3 months; Immune checkpoint inhibitors in previous 3 months.	*Outcomes:* Univariate analysis for overall survival. ▪ Aged ≥70 years compared to <70 years. HR 2.13, 95% CI 1.04 - 4.36 p=0.04 ▪ Haematological malignancy vs solid tumour. HR 0.67, 95% CI 0.23 - 1.90 p=0.45 ▪ Chemotherapy in previous 3 months vs none. HR 2.20, 95% CI 1.08 - 4.49 p=0.03 ▪ Immune checkpoint inhibitors in previous 3 months vs none. HR 1.05, 95% CI 0.32 - 3.45 p=0.94
Clift[23] UK Population based cohort study 23 September 2020 10.1136/bmj.m3731	*Setting:* QResearch database, comprising 1,205 general practices in England with linkage to COVID-19 test results, Hospital Episode Statistics and death registry data. ▪ Derivation and first validation cohort data collected from 24 January 2020 to 30 April 2020. ▪ Second temporal validation cohort data were collected from 1 May 2020 to 30 June 2020. *Sample size:* ▪ Derivation and first validation cohort n=6,083,102 adults aged 19-100 years. N=4384 deaths (derivation cohort) and n=1722 deaths (first validation cohort). ▪ Second temporal validation cohort n=2,173,056. N=621 deaths. *Mean age (±SD):* Derivation and first validation cohort: 48.21 years (18.57 years)	*Outcomes:* Mortality *Adjusted* hazard ratio of death from COVID-19 in women* End-stage renal failure: ▪ End-stage renal disease compared to no kidney failure: HR 3.00, 95% CI 2.19 - 4.12 ▪ Dialysis compared to no kidney failure: HR 2.68, 95% CI 0.86 - 8.36 ▪ Transplant patients compared to no kidney failure: HR 7.84, 95% CI 3.38 - 18.17 Chemotherapy: ▪ Chemotherapy grade A compared to no chemotherapy in previous 12 months: HR 2.30, 95% CI 1.35 - 3.94

First author Country Design Publication date DOI	Setting/Data source Sample size Demographics Groups considered	Outcomes Author conclusions
	Male: Derivation and first validation cohort n=3,035,409 (49.9%) *Groups considered:* End-stage renal disease; dialysis; transplant patients; cancer patients; immunosuppressed patients; pulmonary fibrosis, rare lung conditions.	▪ Chemotherapy grade B compared to no chemotherapy in previous 12 months: HR 3.52, 95% CI 2.29 - 5.42 ▪ Chemotherapy grade C compared to no chemotherapy in previous 12 months: HR 17.31, 95% CI 6.52 - 45.98 ▪ Blood cancer: HR 1.50, 95% CI 1.06 - 2.12 ▪ Bone marrow or stem cell transplant in past 6 months: HR 2.78, 95% CI 0.22 - 34.55 ▪ Respiratory tract cancer: HR 1.70, 95% CI 1.16-2.49 ▪ Radiotherapy in past 6 months: HR 2.11, 95% CI 1.30 - 3.41 ▪ Solid organ transplant (excluding kidney and bone marrow): HR 1.46, 95% CI 0.36 - 5.92 ▪ Immunosuppressant medication from GP 4+ scripts in past 6 months: HR 1.09, 95% CI 0.56 - 2.10 ▪ Leukotriene or long acting β agonist 4+ scripts in past 6 months: HR 1.23, 95% CI 0.78 - 1.94 ▪ Oral steroids 4+ scripts in past 6 months: HR 1.83, 95% CI 1.52 - 2.19 ▪ Sickle cell disease or severe immunodeficiency HR 5.94 95% CI (1.89-18.67) ▪ Rare lung conditions (bronchiectasis, cystic fibrosis, or alveolitis), HR 0.85 95% CI 0.60 - 1.19

First author Country Design Publication date DOI	Setting/Data source Sample size Demographics Groups considered	Outcomes Author conclusions
		▪ Pulmonary hypertension or pulmonary fibrosis: HR 1.55, 95% CI 1.00 - 2.40 *Adjusted* hazard ratio of death from COVID-19 in men* End-stage renal failure: • End-stage renal disease compared to no kidney failure: HR 2.40, 95% CI 1.83 - 3.15 ▪ Dialysis compared to no kidney failure: HR 3.67, 95% CI 2.02 - 6.66 ▪ Transplant patients compared to no kidney failure: HR 3.20 95% CI 1.62 - 6.33 Chemotherapy: ▪ Chemotherapy grade A compared to no chemotherapy in previous 12 months: HR 1.74, 95% CI 1.10 - 2.75 ▪ Chemotherapy grade B compared to no chemotherapy in previous 12 months: HR 3.50, 95% CI 2.54 - 4.82 ▪ Chemotherapy grade C compared to no chemotherapy in previous 12 months: HR 3.37, 95% CI 1.17 - 9.64 ▪ Blood cancer: HR 1.29, 95% CI 0.97 - 1.71 ▪ Bone marrow or stem cell transplant in past 6 months: HR 6.10, 95% CI 1.11 - 33.54 ▪ Respiratory tract cancer: HR 1.27, 95% CI 0.89 - 1.81 ▪ Radiotherapy in past 6 months: HR 2.09, 95% CI 1.48 - 2.96

First author **Country** **Design** **Publication date** **DOI**	**Setting/Data source** **Sample size** **Demographics** **Groups considered**	**Outcomes** **Author conclusions**
		▪ Solid organ transplant (excluding kidney and bone marrow): HR 1.72, 95% CI 0.71 - 4.21 ▪ Immunosuppressant medication from GP 4+ scripts in past 6 months: HR 1.58, 95% CI 0.95 - 2.62 ▪ Leukotriene or long acting β agonist 4+ scripts in past 6 months: HR 1.04, 95% CI 0.64 - 1.70 ▪ Oral steroids 4+ scripts in past 6 months: HR 1.44, 95% CI 1.19 - 1.73 ▪ Sickle cell disease or severe immunodeficiency: HR 4.41, 95% CI 1.41 - 13.81 ▪ Rare lung conditions (bronchiectasis, cystic fibrosis, or alveolitis): HR 1.20, 95% CI 0.93 - 1.56 ▪ Pulmonary hypertension or pulmonary fibrosis: HR 1.47, 95% CI 0.93 - 2.32 * Adjusted for age and body mass index, deprivation (Townsend score (linear)), ethnic group, domicile (residential care, homeless, neither), and a range of conditions and treatments.
Dai[59] China (Hubei province) Case series 28 April 2020 10.1158/2159-8290.CD-20-0422	*Setting:* Multicentre (14 centres) hospital-based study (data collected 01/01/2020 to 24/02/2020) *Sample size*: COVID-19 patients without cancer: n=536 COVID-19 patients with cancer n=105 Chemotherapy n=17 (16.2%) Targeted therapy n=4 (3.8%)	*Outcomes:* Multivariate logistic regression analysis (adjusted for age, sex, diabetes, hypertension, smoking, and COPD at admission) ▪ Cancer vs No cancer ○ (i) death OR 2.34, 95% CI 1.15 - 4.77 ○ (ii) ICU OR 2.84, 95% CI 1.59 - 5.08 ○ (iii) IMV* OR 14, 95% CI 4.30 - 45.56

First author Country Design Publication date DOI	Setting/Data source Sample size Demographics Groups considered	Outcomes Author conclusions
	Immunotherapy n=6 (5.7%) Blood cancers n=9 (8.6%) *Median age (with cancer):* 64.0 years (IQR 14.0 years) *Median age (without cancer):* 63.5 years (IQR 14.0 years) *Groups considered:* ▪ Haematological cancers vs no cancer ▪ Cancer with immunotherapy vs no cancer ▪ Cancer with chemotherapy vs no cancer ▪ Cancer with targeted therapy vs no cancer ▪ Cancer with active treatment vs no cancer ▪ Cancer with active treatment vs cancer without active treatment	▪ Haematological cancer vs no cancer (i) death OR 9.07, 95% CI 2.16 - 38.18, (ii) ICU OR 9.66, 95% CI 2.49 - 37.36, (iii) IMV* OR 38, 95% CI 5.95 – 242.63 ▪ Cancer chemotherapy vs no cancer (i) death OR 4.54, 95% CI 1.21 - 16.99; (ii) ICU OR 4.39, 95% CI 1.34 - 14.40; (iii) IMV* OR 20.46, 95% CI 3.44 - 121.86 ▪ Cancer targeted therapy vs no cancer (i) death OR 0, 95% CI 0.12 - 16.99; (ii) ICU OR 0, 95% CI 0.08 - 29.04; (iii) IMV* OR 0, 95% CI 0.75 - 369.09 ▪ Cancer immunotherapy vs no cancer (i) death OR 9.07, 95% CI 1.59 - 51.66; (ii) ICU OR 2.41, 95% CI 0.28 - 21.16; (iii) IMV* OR 0, 95% CI 0.53 - 33.58 ▪ Cancer with active treatment vs cancer without active treatment (i) death OR 1.16, 95% CI 0.32 - 4.17; (ii) ICU OR 0.97, 95% CI 0.34 - 2.81; (iii) IMV* OR 1.59, 95% CI 0.42 - 6.09 ▪ Cancer with active treatment vs no cancer (i) death OR 2.23, 95% CI 0.98 - 5.11; (ii) ICU OR 2.87, 95% CI 1.47 - 5.56; (iii) IMV* OR 11.91, 95% CI 3.28 - 43.29 *IMV = invasive mechanical ventilation *Author conclusion:* Patients with hematologic cancer, lung cancer, or with metastatic cancer (stage IV) had the highest frequency of severe events. Patients with non-metastatic cancer experienced similar frequencies of severe

First author Country Design Publication date DOI	Setting/Data source Sample size Demographics Groups considered	Outcomes Author conclusions
		conditions to those observed in patients without cancer. Patients who received surgery had higher risks of having severe events, whereas patients who underwent only radiotherapy did not demonstrate significant differences in severe events when compared with patients without cancer. *Notes:* Only cancer treatments within 40 days before the onset of COVID 19 symptoms were considered.
Garassino[56] Multinational Mixed study with cross-sectional and longitudinal components 21 July 2020 10.1016/S1470-2045(20)30314-4	*Data source:* The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT), a global registry aimed at understanding the effect of SARS-CoV-2 infection on patients with thoracic malignancies. Data were collected between 26 March 2020 and 12 April 2020. *Sample size:* n=200 patients from 42 institutions across eight countries (Italy, Spain, France, Switzerland, Netherlands, US, UK and China). 91% were diagnosed based on RT-PCR, 3% based on clinical symptoms and 7% based on radiological findings. *Median age:* 68.0 years (IQR 61.8–75.0 years) *Male:* n=141 (70.0%) Groups considered: People with specific cancers	*Outcomes:* Univariate analysis showed that those receiving chemotherapy, compared to those who were not, had an increased risk of death HR 2.54, 95% CI 1.09-6.11.
García-Suárez[61] Spain Prospective cohort study using population-based registry	*Setting:* 22 regional health service hospitals and 5 private healthcare centres in Madrid including outpatient centres covering a population of 6.6 million inhabitants. Data collected from 28 February 2020 to 25 May 2020.	*Outcomes:* ▪ Death in those aged 70-79 years vs 18-49 years. Adjusted* HR 5.20, 95% CI 2.12 - 12.8, p<0.001

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8 October 2020 10.1186/s13045-020-00970-7	*Sample size:* n=697 (all patients with hematologic malignancies and COVID-19 PCR) *Median age:* 72 years (IQR 60–79 years) *Male:* n=413 (60%) *Groups considered:* ▪ People aged ≥70 years ▪ People with cancer who are undergoing active chemotherapy or radical radiotherapy for lung cancer. ▪ People having immunotherapy or other continuing antibody treatments for cancer. ▪ People having other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors.	▪ Death in those aged ≥80 years vs 18-49 years. Adjusted* HR 10.1, 95% CI 4.03 - 25.4, p<0.001 ▪ Acute myeloid leukaemia vs Non-Hodgkin lymphoma. Adjusted* HR 2.22, 95% CI 1.31 - 3.74, p=0.003 ▪ Ph-negative myeloproliferative neoplasms vs Non-Hodgkin lymphoma. Adjusted* HR 0.33, 95% CI 0.14 - 0.81, p=0.015 ▪ Conventional chemotherapy vs no active therapy. Adjusted* HR 1.50, 95% CI 0.99 - 2.29, p=0.056 ▪ Monoclonal antibodies vs no active therapy. Adjusted* HR 0.47, 95% CI 0.23 - 0.94, p=0.032 *Adjusted for age, sex, comorbidities, haematological malignancy and recent active cancer therapy. *Author conclusion:* Our findings support the vulnerability of patients with hematologic malignancies in the COVID-19 pandemic and provide several important considerations for clinical care. The higher mortality in patients with hematologic malignancies and severe/critical COVID-19 who did not receive antiviral therapy provides the rationale for including these patients in investigational strategies. Further studies and long-term follow-up are required to validate these criteria for risk-stratifying patients with hematologic malignancies in a future healthcare

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		crisis and for defining appropriate timing and types of antineoplastic treatments.
Gottlieb[51] US Retrospective cohort study 6 August 2020 10.1111/acem.14104	*Setting:* Rush University Medical Center in Chicago, Illinois. Data collected from 4 March to 21 June. *Sample size:* n=8,673 COVID-19 patients. Compares outcomes of patients admitted to ICU with hospitalised and non-hospitalised COVID-19 patient admitted with COVID-19 during the same time (n=1,115). *Median age:* 41 y (IQR 29–54) *Male:* 46.6% *Groups considered:* ▪ People who are over 70 years of age ▪ People with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment. ▪ People who are at end-stage renal disease and on dialysis	*Outcomes:* ICU admission Age ▪ 65–74 vs 19–44: aOR* 1.01, 95% CI 0.67-1.52 ▪ 75 or older vs 19–44: aOR* 0.81 95% CI 0.51-1.28 *End-stage renal disease (currently on dialysis)* ▪ aOR* 1.14, 95% 0.67-1.97 Blood-borne cancer ▪ aOR 3.53 95% CI 1.26-9.86 *Covariates unclear *Author conclusion:* Male sex, congestive heart failure, obstructive sleep apnea, bloodborne cancer, leukocytosis, an elevated absolute neutrophil count/absolute lymphocyte count, hypoalbuminemia, an elevated aspartate aminotransferase, an elevated lactate, and elevated D-dimer and an elevated troponin were associated with critical illness.
Gotzinger[52] Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Norway, Portugal, Slovakia, Slovenia,	*Setting:* Children and adolescents admitted to hospital or identified during community screening in 77 health-care institutions located in 21 European countries. Data collected from 1 April 2020 to 24 April 2020. *Sample size:* n=585.	*Outcomes:* Admission to ICU – either neonatal or paediatric intensive care. Multivariable logistic regression analysis: ▪ Immunosuppressive therapy

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Spain, Sweden, Switzerland, Turkey, and the UK. Multicentre cohort study 1 September 2020 10.1016/S2352-4642(20)30177-2	*Median age:* 5.0 years (IQR 0.5–12.0 years) *Male:* n=311 (57.5%) *Groups considered:* Malignancy	OR 1.3, 95% CI 0.30 - 4.40 ▪ Chemotherapy in past 6 months OR 0.9, 95% CI 0.2 - 4.2 *Author conclusion:* Our data show that severe COVID-19 is uncommon in young children, including infants, despite their immune maturation being incomplete, with only few requiring mechanical ventilation. It was striking that all children who died in our cohort were older than 10 years. The number of children receiving antiviral or immunomodulatory treatment was too small to draw meaningful conclusions regarding their effectiveness. *Notes:* The study population is likely to primarily represent individuals at the more severe end of the disease spectrum.
Ioannou[46] US Longitudinal cohort study 23 September 2020 10.1001/jamanetworkopen.2020.22310	*Setting:* The Department of Veterans Affairs (VA) national health care system. Patients who tested positive for SARS-CoV-2 between 28 February and 14 May 2020 were followed up through 22 June 2020. *Sample size:* n=10,131 patients who tested positive for SARS-CoV-2. *Mean age (±SD):* 63.6 years (±16.2 years) *Male:* n=9,221 (91%) *Groups considered:* ≥70yrs	*Outcomes:* ▪ Mechanical ventilation Older age significantly associated with increased risk of mechanical ventilation. In comparison to those aged 18-49 years: 65-79 years aHR* 4.32, 95% CI 2.88 - 6.47 ≥80 years aHR* 3.98, 95% CI 2.54 - 6.24 ▪ Mortality Older age significantly associated with increased risk of mortality. In comparison to those aged 18-49 years: 65-79 years aHR* 27.47, 95% CI 13.48 - 55.99

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		≥80 years aHR* 60.80, 95% CI 29.67 - 124.61 *Adjusted for a large range of sociodemographic characteristics, comorbid conditions, and symptoms. *Author conclusion:* In this national cohort of VA patients, increasing age was the characteristic most strongly associated with mechanical ventilation and death.
Kuderer[53] US, Canada and Spain Multicentre cohort study 28 May 2020 10.1016/s0140-6736(20)31187-9	*Data source:* COVID-19 and Cancer Consortium (CCC19) database. Data collected from 17 March 2020 to 16 April 2020, with a follow-up through to 7 May 2020. *Sample size:* n=928 cancer patients *Median age:* 66 years (IQR 57–76) <65yrs 412 (44%); 65-74yrs 237 (26%); ≥75yrs 279 (30%). *Male:* n=468 (50.0%) *Groups considered:* Cancer	*Outcomes:* Mortality (all-cause within 30 days of COVID-19 diagnosis) ▪ Compared to those with solid tumours, those with haematological cancer - OR 1.40, 95% CI 0.83 - 2.37.* ▪ Compared to those receiving no treatment in the previous 4 weeks, those receiving: ○ cytotoxic treatment - aOR 1.47, 95% CI 0.84 – 2.56* ○ non-cytotoxic therapy - aOR 1.04, 95% CI 0.62-1.76* ○ unknown therapy - aOR 1.60, 95% CI 0.18-14.14* *Adjusted for age, sex, smoking status, and obesity. *Author conclusion:* This study of patients with cancer and COVID-19 reinforces several important considerations for clinical care, and emphasises the urgent need for more data. Longer-term follow-up and larger sample sizes

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		are needed to more completely understand the effect of SARS-CoV-2 on outcomes in patients with cancer.
Lee[57] UK Prospective observational study 20 June 2020 10.1016/ S0140-6736(20)31173-9	*Setting:* UKCCMP database of UK patients with COVID-19 and Cancer from 55 cancer centres. Data collected from 18 March 2020 to 26 April 2020. *Sample size*: n=800 Patients who died n=226 Lymphoma n=60 Other haematological n=109 Chemotherapy n=281 Immunotherapy n=44 Hormonal therapy n=64 Targeted therapies n=72 *Median age*: All patients = 69 years (IQR 59-76) Patients who died = 73 years (IQR 66-80) Patients who survived = 66 years (IQR 57-74) *Male:* All patients n=449 (56%) Patients who died n=146 (65%) Patients who survived n=303 (53%) *Groups considered:* ▪ Lymphoma ▪ Other haemotological cancers ▪ Chemotherapy vs no chemotherapy ▪ Hormone therapy vs no hormone therapy ▪ Immunotherapy vs no immunotherapy ▪ Targeted treatment vs no targeted treatment	*Outcomes:* *Mortality* Univariate regression analysis: ▪ Lymphoma OR 1.30, 95% CI 0.71 - 2.30 ▪ Other haematological cancers: OR 1.57, 95% CI 1.01 - 2.42 Therapy within 4 weeks of COVID-19 diagnosis ▪ Chemotherapy vs no chemotherapy: Univariate OR 0.78, 95% CI 0.55 - 1.11 Multivariate analysis* OR 1.18, 95% CI 0.81 - 1.72, p=0.380 ▪ Hormone therapy vs no hormone therapy: Univariate OR 1.16, 95% CI 0.63 - 2.06 Multivariate analysis* OR 0.90, 95% CI 0.49 - 1.68, p=0.744 ▪ Immunotherapy vs no immunotherapy: Univariate OR 0.60, 95% CI 0.27 - 1.24 Multivariate analysis* OR 0.59, 95% CI 0.27 - 1.27, p=0.177 ▪ Targeted treatment vs no targeted treatment Univariate OR 0.56, 95% CI 0.30 - 1.01 Multivariate analysis* OR 0.83, 95% CI 0.45 - 1.54, p=0.559 *Adjusted for age, sex and comorbidities at admission. *Author conclusion:* Mortality from COVID-19 in cancer patients appears to be principally driven

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		by age, gender, and comorbidities. We are not able to identify evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment are at an increased risk of mortality from COVID-19 disease compared with those not on active treatment. *Notes:* Patients were deemed to have COVID-19 if positive based on RT-PCR test. For inclusion in study patients had to present with symptomatic COVID-19.
Lievre[64] France Cohort study (mixed prospective and retrospective design) 8 October 2020 10.1016/j.ejca.2020.09.035	*Setting*: Multicentre hospital/cancer centre based study. Data collected from 4 April 2020 to 11 June 2020). *Sample size:* n=1,289; patients who died=370 (29%) *Median age:* 67 years *Male:* n=795 (62%) *Groups considered:* ▪ Cytotoxic treatment within 3 months vs no cytotoxic treatment within 3 months ▪ Corticosteroid therapy prior to COVID 19	*Outcomes:* All-cause mortality (univariate analysis) ▪ Cytotoxic treatment within 3 months OR 1.31, 95% CI 1.02 - 1.66 All-cause mortality (multivariate analysis*) ▪ Cytotoxic treatment within 3 months OR 1.32, 95% CI 0.92 - 1.98 *Adjusted for smoking status, tumour location, tumour stage, presence of lung metastases, cytotoxic treatment, corticosteroid therapy, anticoagulant therapy, CEI/AIIA, Sex, ECOG PS, updated Charlson score and age. COVID-19 severity – defined as admission to an ICU and/or use of mechanical ventilation and/or death (univariate analysis) ▪ Cytotoxic treatment within 3 months OR 1.27, 95% CI 1.01 - 1.61 ▪ Corticosteroid prior to COVID-19 OR 1.64, 95% CI 1.18 - 2.28

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		COVID-19 severity – defined as admission to an ICU and/or use of mechanical ventilation and/or death (multivariate analysis*) ▪ Cytotoxic treatment within 3 months OR 1.27, 95% CI 0.91 - 1.78 *Smoking status, tumour location, tumour stage, presence of lung metastases, cytotoxic treatment, corticosteroid therapy, anticoagulant therapy, CEI/AIIA, sex, ECOG PAS, updated Charlson score and age. *Author conclusion:* Sex along with corticosteroids before COVID-19 diagnosis, and thoracic primary tumour site were independently associated with COVID-19 severity. None of the anticancer treatments administered within the previous 3 months had any effect on mortality or COVID-19 severity, except cytotoxic chemotherapy in the subgroup of patients with detectable SARS-CoV-2 by RT-PCR, which was associated with a slight increase of the risk of death.
Luo[47] US Retrospective cohort study 12 May 2020 10.1158/2159-8290.CD-20-0596	*Setting:* Single outpatient centre. Data collected from 12 March 2020 to 13 April 2020. *Sample size:* n=69 consecutive outpatients with lung cancers. *Median age:* 69 years (range 31- 91 years) *Male:* n=33 (48%)	*Outcomes:* Mortality (42/67) Multivariable logistic analysis comparing lung cancer patients who received PD-1 blockade therapy (41/69) to lung cancer patients who did not receive PD-1 (28/69). Adjusted* OR 1.13, 95% CI 0.25 - 5.03. *Adjusted for smoking history and gender

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	Groups considered: People having immunotherapy or other continuing antibody treatments for cancer.	*Author conclusion:* PD-1 blockade exposure was not associated with increased risk of severity of COVID-19. PD-1 blockade does not appear to impact the severity of COVID-19 in patients with lung cancers. Our analysis of patients with lung cancers supports the safety of PD-1 blockade treatment to achieve optimal cancer outcomes.
Martínez-López[62] Spain Retrospective case series Preprint 30 June 2020 10.1101/2020.06.29.20142455	*Setting:* 73 hospitals within the Spanish Myeloma Collaborative Group network in Spain. Data collected from 1 March 2020 to 30 April 2020. *Sample size:* n=51 multiple myeloma patients who have had stem cell transplantation (total population n=167) *Median age (for total population):* 71 years (IQR 62-78 years); <65yrs n=55 (33%), 65-74yrs n=55 (33%), ≥75yrs n=57 (34%). *Male (for total population):* n=95 (57.0%) *Groups considered:* Multiple myeloma patients who have had stem cell transplantation.	*Outcomes:* Mortality in multiple myeloma patients who have had stem transplantation vs those who have not. aOR 0.6, 95% CI 0.2 - 1.7, p=0.4* *adjusted for age, sex, myeloma status, comorbidities at diagnosis of COVID19.
Passamonti[66] Italy Multicentre, retrospective, cohort study 13 August 2020 10.1016/S2352-3026(20)30251-9	*Setting:* 66 Italian hospitals. Data collected between 25 February 2020 and 18 May 2020. *Sample size:* n=536 patients with a WHO-defined haematological malignancy *Mean age (±SD):* 66.3 years (±13.8); <50yrs n=62 (12%), 50-59yrs n=86 (16%), 60-69yrs n=137 (26%), 70-79yrs n=158 (29%), ≥80yrs n=93 (17%)	*Outcomes:* Risk of death in different types of haematological malignancy compared to myeloproliferative neoplasms. ▪ Myelodysplastic syndromes HR 1.58, 95% CI 0.69 - 3.62 ▪ Acute myeloid leukaemias HR 3.49, 95% CI 1.56 - 7.81 ▪ Acute lymphoblastic leukaemias

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	Male: n=340 (63.0%) *Groups considered:* Haematological malignancies	HR 1.65, 95% CI 0.46 - 5.94 ▪ Hodgkin lymphomas HR 1.30, 95% CI 0.36 - 4.66 ▪ Chronic lymphoproliferative neoplasms HR 1.64 95% CI 0.77 - 3.51 ▪ Indolent lymphomas HR 2.19 95% CI 1.07 - 4.48 ▪ Aggressive lymphomas HR 2.56 95% CI 1.34 - 4.89 ▪ Plasma cell neoplasms HR 2.48 95% CI 1.31 - 4.69 *Author conclusion:* Overall survival was independently predicted by type of malignancy. Diagnosis of acute myeloid leukaemia, non-Hodgkin lymphomas, and plasma cell neoplasms were predictive for a poor outcome.
Petrilli[48] US Prospective cohort study 14 May 2020 10.1136/bmj.m1966	*Setting:* Single academic medical centre in New York City and Long Island. Data collected between 1 March and 8 April 2020, with a follow-up through to 5 May 2020. *Sample size:* n=5,279 people who tested positive for SARS-CoV-2. *Median age:* 54 years (IQR 38-66 years) *Male:* n=2615 (49.5%) *Groups considered:* age ≥70 years	*Outcomes:* Critical illness*- older age associated with a greater risk of critical illness. In comparison to those aged 19-44yrs: ▪ 65-74yrs aOR^ 2.88, 95% CI 2.09 - 4.0, p<0.001 (excluding vital signs and laboratory results (n=2725)) ▪ 65-74yrs aOR^ 1.73, 95% CI 1.19 - 2.5, p=0.004 (including vital signs and laboratory results (n=2725)) *Critical illness defined as a composite of intensive care, mechanical ventilation, discharge to hospice or death.

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		^Covariates not reported. Mortality - older age associated with a greater risk of death. In comparison to those aged 19-44yrs: ▪ 65-74yrs aHR^ 6.99, 95% CI 4.34 - 11.27, p<0.001 (excluding vital signs and lab results (n=2,725)) ▪ 65-74yrs aHR^ 4.83, 95% CI 2.93 - 7.96, p<0.001 (including vital signs and lab results (n=2,725)) Critical illness*- older age associated with a greater risk of critical illness. In comparison to those aged 19-44yrs: ▪ ≥75yrs aOR^ 3.46, 95% CI 2.46 - 4.8, p<0.001 (excluding vital signs and lab results (n=2,725)) ▪ ≥75yrs aOR^ 2.32, 95% CI 1.57 - 3.4, p<0.001 (including vital signs and lab results (n=2,725)) *Critical illness defined as a composite of intensive care, mechanical ventilation, discharge to hospice or death. Mortality - older age associated with a greater risk of death. In comparison to those aged 19-44yrs:

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		▪ ≥75yrs aHR^ 10.34, 95% CI 6.37 - 16.79, p<0.001 (excluding vital signs and lab results (n=2,725)) ▪ ≥75yrs aHR^ 7.69, 95% CI 4.60 - 12.84, p<0.001 (including vital signs and lab results (n=2,725)) *Author conclusion:* Age and comorbidities are powerful predictors of requirement for admission to hospital rather than outpatient care; however, degree of oxygen impairment and markers of inflammation are most strongly associated with poor outcomes during hospital admission. Clinicians should consider routinely obtaining inflammatory markers during hospital stay for people with COVID-19.
Pinato[54] UK, Italy, Spain and Germany Observational study 31 July 2020 10.1158/2159-8290.CD-20-0773	*Setting:* 19 cancer centres in the UK, Italy, Spain and Germany. Data collected from 26 Feb 20 to 1 April 2020. *Sample size:* n=890 cancer patients (UK n=218, 24.5%; Italy n=343, 38.5%; Spain n=323, 36.3%; and Germany n=6, 0.7%). *Age:* Mean (SD): 68yrs (13); Range: 21-99yrs. *Male:* n=503 (56.5%) *Groups considered:* Cancer	*Outcomes:* Mortality (multivariable analysis) ▪ Treatment with anticancer therapy compared to no treatment HR 0.71, 95% CI 0.53-0.95, p=0.02 Mortality (univariate analysis) ▪ Treatment with anticancer therapy compared to no treatment HR 0.77, 95% CI 0.60-1.00, p=0.10 ▪ Treatment with ongoing immunotherapy compared to no treatment HR 0.80, 95% CI 0.46-1.40, p=0.43

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		▪ Treatment with ongoing chemotherapy compared to no treatment HR 0.78, 95% CI 0.57-1.07, p=0.12 ▪ Treatment with ongoing targeted therapy compared to no treatment HR 0.80, 95% CI 0.47-1.39, p=0.44 ▪ Treatment with ongoing endocrine therapy compared to no treatment HR 1.20, 95% CI 0.71-2.04, p=0.48 *Author conclusion:* In our study, provision of active anticancer treatment was not associated with worse mortality.
Reilev[67] Denmark Retrospective cohort study 10 July 2020	*Setting:* nationwide cohort of all individuals who tested positive for SARS-CoV-2 in Denmark based on registry data. *Sample size:* 11,122 individuals with a positive PCR test result were analysed. Data collected from 27 February 2020 to 19 May 2020 *Median age:* 48y (IQR 33-62 years) *Male:* 42% *Extremely medically vulnerable groups identified:* • People aged ≥ 70 years • Solid organ transplant recipients	*Outcomes:* All-cause mortality (defined as deaths occurring from 2 days before the index date to 30 days after) *Analysis:* Multiple logistic regression comparing positive case with the outcome with positive cases without the outcome. Middle-aged adults, 50–59 years, was the reference group. All-cause mortality (n=577): Age 70 to 79 • Adjusted* OR (95% CI): 15.2 (8.7 – 26.3 Age 80 to 89 • Adjusted* OR (95% CI): 29.9 (17.2 – 51.9) Age 90+

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		• Adjusted* OR (95% CI): 90.2 (50.2 – 162.2) *age, sex, and number of comorbidities Organ transplant • Adjusted* OR (95% CI): 3.4 (1.7 – 6.6) • Adjusted** OR (95% CI): 2.0 (0.8 – 5.1) * age and sex ** age, sex and total number of comorbidities *Authors conclusion:* In this nationwide population-based study, increasing age, sex and the number and type of co-morbidities were closely associated with hospitalization and death in SARS-CoV-2 PCR-positive cases. In the absence of co-morbidities, the mortality was, however, lowest until the age of 80 years.
Rentsch[50] US Retrospective cohort study Preprint 18 May 2020 10.1101/2020.05.12.20099135	*Setting:* United States Department of Veterans Affairs. Data collected from 8 February 2020 to 4 May 2020, with 30-day follow-up. *Sample size:* n=5,834,543 Tested for SARS-CoV-2 n=62,098 Tested positive n=5,630 *Age:* Of those tested 13,494 (21.7%) were aged under 50 years. 10,844 (17.5%) were aged 50-59, 15,579 (25.1%) were aged 60-69, 15,358 (24.7%) were aged 70-79 and 6,823 (11%) were aged 80+ years *Male (of those tested):* n=54,906 (88.4%)	*Outcomes:* 30-day mortality Of 2,420 who tested positive, 284 died within 30 days: ▪ Age adjusted OR 70-79 years compared to 60-69 years: OR 2.01, 95% CI 1.45-2.80 ▪ Age adjusted OR 80+years compared to 60-69 years: OR 5.52, 95% CI 3.79-8.02 Multivariable OR (adjusted for age and baseline comorbidity): ▪ 70-79 years compared to 60-69 years: OR 1.80, 95% CI 1.28-2.54 ▪ 80+ years compared to 60-69 years: OR 4.62, 95% CI 3.07-6.94

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	Groups considered: Age ≥ 70yrs	*Author conclusion:* Veterans tend to be older and have a higher prevalence of chronic health conditions and risk behaviours than the general population.
Robilotti[49] US Observational study 24 June 2020 10.1038/s41591-020-0979-0	*Setting:* Tertiary care cancer centre in New York city. Data collected 10 March 2020 to 7 April 2020, with a follow-up period of at least 30 days or death *Sample size:* n=423 symptomatic positive COVID-19 cases *Age:* <18yrs 7 (2%); 18-29yrs 11 (3%); 30-39yrs 19 (4%); 40-49yrs 51 (12%); 50-59yrs 101 (24%); 60-69yrs 134 (32%); ≥70yrs 100 (24%) *Male:* n=212 (50.0%) *Groups considered:* Cancer ▪ Hematologic cancer ▪ Systemic chemotherapy (within 30 days) ▪ Chronic lymphopenia or corticosteroids ▪ Immunotherapy checkpoint inhibitors	*Outcomes:* Severe respiratory illness* - the following are associated with a greater risk of severe respiratory illness in comparison with other cancer patients with COVID-19: ▪ Hematologic cancer: aHR 1.79, 95% CI 0.97 - 3.32, p=0.06 ▪ Systemic chemotherapy (within 30 days): HR 1.19, 95% CI 0.78 - 1.82, p=0.41 ▪ Chronic lymphopenia or corticosteroids: aHR 1.42, 95%CI 0.86 - 2.34, p=0.16 ▪ Immunotherapy checkpoint inhibitors: aHR 2.74, 95% CI 1.37 - 5.46, p=0.004 *Severe respiratory illness defined as the requirement for high-flow oxygen supplementation or mechanical ventilation. *Author conclusion:* This group of 423 patients with cancer had substantial rates of severe respiratory outcomes (20%) and death (12%) with COVID-19. The ongoing risk of contracting the illness and indirect consequences of treatment disruptions are expected to have a lasting effect on the health and safety of patients undergoing treatment for cancer. Continuous preparedness is paramount as routine cancer care is resumed in the coming weeks and months amidst the unpredictable threat posed by COVID-19. Informed approaches with universal

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		screening, aggressive testing and rigorous control measures will be essential for the safe ongoing delivery of oncologic care.
Rossi[65] Italy Population-based prospective cohort study 27 August 2020 10.1371/journal.pone.0238281	*Data source:* Patients with confirmed SARS-CoV-2 in the Reggio Emilia province of Northern Italy. Data registered in a database which is linked with routinely available administrative databases of the Local Health Authority. Analysis based on symptomatic patients in the region who tested positive for SARS-CoV-2. Data collected from 27 February 2020 to 3 April 2020. *Sample size:* Symptomatic cases n=2,653 Male: n=1,328 (50.1%) *Age:* <51 years 26.2%; 51-60 years 19.9%; 61-70 years 15.6%; 71-80 years 15.8%; ≥81 years 22.5%. *Groups considered:* ≥70yrs	*Outcomes:* Older age associated with increased risk of death. In comparison to those aged <51yrs: ▪ 71-80 years HR 9.1, 95% CI 4.0 - 20.6 ▪ ≥81 years HR 27.8, 95% CI 12.5 - 61.7 *Author conclusion:* The effect of age is particularly strong for increased risk of death.
Shah[58] UK Retrospective cohort study 11 June 2020 10.1111/bjh.16935	*Setting:* Single hospital setting. *Sample size:* n=68 hospitalised haematological malignancy. Compares outcomes to general medical patients admitted with COVID-19 during the same time (n=1,115). *Median age:* 69.4 years (range 30-95 years) *Male:* n=52 (65%) *Groups considered:*	*Outcomes:* Cox proportional hazards model comparing haematology (n=80) to non-haematology COVID-19 patients (n=1,115) and risk of death. Intensive^ ▪ aHR* 4.66, 95% CI 2.29 - 9.47, p=<0.001 Non-intensive ▪ aHR* 1.90, 95% CI 1.05 - 3.48, p=0.04 Watch and wait (never treated) ▪ aHR* 1.30, 95% CI 0.65 - 2.64, p=0.46 *Adjusted for age and gender.

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	▪ People with cancer who are undergoing active chemotherapy or radical radiotherapy for lung cancer. ▪ People with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment. ▪ People who have had bone marrow or stem cell transplants in the last 6 months, or who are still taking immunosuppression drugs.	^Patients were categorised into 3 groups based on treatments received; intensive (chemotherapy which causes profound cytopenia and requires at least a level 2 inpatient facility), non-intensive (any other chemotherapy or immunomodulatory therapy, mainly outpatient based) and active surveillance ('watch and wait'). *Author conclusion:* We found no correlation between age or male gender between survivors and non-survivors with COVID-19 and haematological cancer, compared to a general, non-haematology cohort, and contrary to previous publications.
Webb[55] UK and US Multicentre cohort study 28 August 2020 10.1016/S2468-1253(20)30271-5	*Data source:* 2 international registries (COVID-Hep and SECURE-Cirrhosis). Data collected from 25 Mar 2020 to 26 Jun 2020. *Sample size:* n=151 (liver transplant recipients from 18 countries); n=627 (non-transplant patients). *Median age (liver transplant patients):* 60 years (IQR 47-66) *Median age (non-transplant patients):* 73 years (IQR 55-84) *Male (liver transplant patients):* n=102 (68%) *Male: (non-transplant patients):* n=329 (52%) *Groups considered:* Solid organ transplant patients.	*Outcomes:* ▪ Liver transplantation did not significantly increase the risk of death in patients with SARS-CoV-2 infection (absolute risk difference 1.4%, 95% CI −7.7 - 10.4).* *Adjusted for age, sex, creatinine concentration, obesity, hypertension, diabetes and ethnicity. *Author conclusion:* Liver transplantation was not independently associated with death.
Williamson[24] UK Clinical register	*Setting:* National primary care health records in UK – OpenSAFELY. Data were collected from 1 February 2020 to 5 May 2020.	*Outcome: Mortality* Age Adjusted for sex:

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(Note: includes clinically suspected COVID-19 cases). 20 August 2020 10.1038/s41586-020-2521-4	*Sample size:* n= 17,278,392 adults COVID 19 related deaths N=10,926 *Age:* Included adults over 18 years only. 18–39years 5,914,384 (34.2%) 40–49 years 2,849,984 (16.5%) 50–59 years 3,051,110 (17.7%) 70–79 years 1,938,842 (11.2%) 80+ years 1,131,680 (6.5%) *Male:* n=8,647,989 (50.1%) Haematological malignancy diagnosed <1 year ago = 8,704 Haematological malignancy diagnosed 1-4.9 years ago = 27,742 Haematological malignancy diagnosed ≥5 years ago = 63,460 Organ transplant = 20,001 Severe asthma (defined as with recent oral corticosteroid use) = 291,670 Kidney dialysis = 23,978 *Groups considered:* ▪ Age ▪ Haematological malignancy vs no haematological malignancy ▪ Organ transplant vs no organ transplant ▪ Severe asthma ▪ Dialysis or end-stage renal failure	▪ 70-79 vs 50-59: HR 8.62, 95% CI 7.84 - 9.46 ▪ 80+ vs 50-59: HR 38.29, 95% CI 35.02 - 41.87 Adjusted for BMI, smoking, index of multiple deprivation quintile, and comorbidities: ▪ 70-79 vs 50-59: HR 6.07, 95% CI 5.61 - 6.69 ▪ 80+ vs 50-59: HR 20.60, 95% CI 19.70 - 22.68 Haematological malignancy Adjusted for age and sex: ▪ Diagnosed <1 year ago: HR 3.02, 95% CI 2.24 -4.08 ▪ Diagnosed 1–4.9 years ago: HR 2.56, 95% CI 2.14 – 3.06 ▪ Diagnosed ≥5 years ago: HR 1.70, 95% CI 1.46 -1.98 Adjusted for age, BMI, smoking, index of multiple deprivation quintile, and comorbidities: ▪ Diagnosed < 1 year ago: HR 2.80, 95% CI 2.08 - 3.78 ▪ Diagnosed 1–4.9 years ago: HR 2.46, 95% CI 2.06–2.95 ▪ Diagnosed ≥5 years ago: HR 1.61, 95% CI 1.39 - 1.87 Organ transplant Adjusted for age and sex: ▪ HR 6.00, 95% CI 4.73 -7.61 Adjusted for age, BMI, smoking, index of multiple deprivation quintile, and comorbidities: ▪ HR 3.53, 95% CI 2.77 - 4.49

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		Asthma Adjusted for age and sex: ▪ Asthma (not severe – defined as no recent oral corticosteroid use): HR 1.13, 95% CI 1.07 - 1.20 ▪ Asthma (severe – defined as recent oral corticosteroid use): HR 1.55, 95% CI 1.39 - 1.73 Adjusted for age, BMI, smoking, index of multiple deprivation quintile, and comorbidities: Asthma (not severe): HR 0.99, 95% CI 0.93 -1.05 Asthma (severe): HR 1.13, 95% CI 1.01 - 1.26 History of dialysis or end-stage renal failure Covariates unclear ▪ HR 3.69, 95% CI 3.09 - 4.39 *Authors conclusion* Most comorbidities were associated with increased risk, including cardiovascular disease, diabetes, respiratory disease (including severe asthma), obesity, a history of haematological malignancy or recent other cancer, kidney, liver and neurological diseases, and autoimmune conditions. South Asian and Black people had a substantially higher risk of COVID-19-related death than white people, and this was only partly attributable to comorbidities, deprivation or other factors.

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Yang[60] Hubei, China Retrospective cohort study 1 July 2020 10.1016/S1470-2045(20)30310-7	*Setting:* 9 hospitals including some designated COVID-19 hospitals. Data collected from 13 January 2020 to 18 March 2020. *Sample size:* n=205 cancer patients with solid tumours (except for brain cancer). N=180 included in final model. *Median age:* 63 years (IQR 56-70 years; range 14-96 years). *Male:* n=96 (47%) *Groups considered:* ▪ People with cancer who are undergoing active chemotherapy or radical radiotherapy for lung cancer. ▪ People with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment.	*Outcomes:* Death Haematological malignancy vs solid tumour (multivariable logistic regression): ▪ aOR* 2.07 95% CI 0.68 – 6.35, p=0.20 ▪ aOR^ 2.04, 95% CI 0.64 - 6.53, p=0.23 Receiving chemotherapy within four weeks vs not receiving ▪ aOR* OR 3.51, 95% CI 1.16 – 10.59, p=0.03 ▪ aOR^ 3.50, 95% CI 1.15 - 10.71, p=0.03 *Adjusted for sex, cancer type, receipt of chemotherapy within the previous 4 weeks and time since cancer diagnosis ^Adjusted for sex, cancer type, receipt of chemotherapy within the previous 4 weeks, time since cancer diagnosis and study centre Time since cancer diagnosis analysed, <1 year (p=0.11), 1-5 years (p=0.26) compared to >5 years, all were statistically insignificant. *Author conclusion:* In particular, male sex and receiving chemotherapy within 4 weeks before symptom onset were identified as risk factors for death in patients with cancer who were diagnosed with COVID-19.

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		Although older age and underlying diseases have been found to be risk factors for severe events in a previous study, this was not observed in our study. This difference might be due to the fact that our study already comprised an elderly population (median age 63 years) with underlying diseases.

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