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memo

COVID-19-EPIDEMIC :

COVID-19 and risk factors for hospital admission, severe disease and death – a rapid review, 3rd update

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Key messages

This rapid review is an update of a version published on May 12th, 2020. In this review, only peer-reviewed population-based studies with more than 5000 laboratory test positive cases are included.

The findings are based on searches in MEDLINE and Embase on October 27th, 2020. One researcher screened the search results, and two researchers selected studies for inclusion and synthesised the results. Experts in the field assisted with study inclusion and provided helpful input during the review process. In the current situation, there remains an urgent need for identifying the most important evidence quickly. Hence, we opted for this rapid approach despite an inherent risk of overlooking key evidence or making misguided judgements.

We included five studies that reported results from multivariate analyses of demographic and medical risk factors. We excluded risk factors that constituted laboratory findings, vital signs or symptoms of COVID-19. Two studies were from England, one from the UK, one from the USA and one study was from Denmark. Three out of five studies reported only data on the adult population.

Meta-analysis was not feasible, and the main results of this rapid review are therefore presented in tabular and narratively. Risk factors associated with (i) hospitalisation, (ii) severe/critical disease, and (iii) death due to COVID-19 are reported separately below. Only two large studies included populations under 18 years, but for this age group the results are not representative as the total number of registered incidents is small. Other population groups, which may not have been captured by the included studies will also require further research.

Risk factors for hospitalisation due to COVID-19

Three studies assessed risk factors for hospitalisation due to COVID-19. Overall, age, comorbidities and severity of disease were found to be strong predictors of hospital admission. All three studies provided a granular overview of adjusted hazard ratios (HRs)/odds ratios (ORs) for a broad selection of comorbidities, conditions and ongoing treatments. Most of these were associated with a greater risk for admission, with apparent increases in risk based on severity of condition. Two studies showed a clear dose response relationship between increasing age and hospital admission. Two studies reported an increased risk for hospital admission in adult males. Two studies reported an increased risk of hospital admission with increasing body mass index (BMI) and the majority of assessed ethnicities compared to whites. One study reported increasing risk by number of co-existing comorbidities and severe kidney disease, diabetes type I, ongoing chemotherapy, severe immunodeficiency, heart failure and Down syndrome stand out with a greater associated risk of admission (OR/HR >=3).

Risk factors for developing more severe or critical COVID-19 (ICU treatment)

Two studies assessed risk factors for ICU admissions due to COVID-19, but information on ICU admission alone was only provided by a single study with descriptive information. We therefore

included severe illness in this outcome group, as another study defined this as a composite measure including ICU admissions. Overall, age was found to be the strongest predictor of severe COVID-19, with a dose response relationship between increasing age and increased risk. Furthermore, male sex, morbid obesity (BMI>40), heart failure and diabetes was associated with increased risk for severe COVID-19. Being of African American decent was associated with decreased risk.

Risk factors for death due to COVID-19

Four studies assessed risk factors for death due to COVID-19. All studies provided a granular overview of predicting factors. Overall, increasing age was found to be the strongest predictor of death due to COVID-19. Furthermore, male sex, number of and severity of most comorbidities were found to be significant predictors of COVID-19-related death. Ethnicity other than white was consistently associated with modest but increased risk of death, with Blacks having the highest risk of death. Two studies found increasing risk of death with increasing degree of deprivation. Kidney disease, diabetes mellitus type I and II, dementia, ongoing chemotherapy, organ transplant patients, severe immunodeficiency, major psychiatric disorder with antipsychotics, cerebral palsy and Down syndrome (one study) were reported as the strongest predictors of COVID-19 related death (OR/HR >=3). Most singular comorbidities were associated with an increased risk of death.

Conclusion

Based on the data at hand, the elderly are clearly the main group at risk of hospital admission, severe illness, and death if infected by COVID-19. Most comorbidities appear to increase risk. An increasing number and severity of comorbidities contribute to a further increase in the overall risk. Male sex, obesity, non-white ethnicity and deprivation are also associated with increased risk.

Hovedbudskap

Denne hurtigoppsummeringen er en oppdatering av en tidligere versjon, publisert 12. mai, 2020 (1). I denne oppdaterte versjonen inkluderte vi kun fagfellevurderte populasjonsbaserte studier med over 5000 deltagere med påvist covid-19.

Resultatene som presenteres i denne oppsummeringen er basert på litteratursøk i MEDLINE og Embase den 27. oktober 2020. En forsker gjennomgikk søkeresultatene og to forskere valgte ut studier for inklusjon, uthenting av data og sammenstilling av resultater. Eksperter i relevante fagfelt bidro i vurderingen av studier for inklusjon samt bisto med faglig input fortløpende igjennom reviewprosessen.

Sett i lys av dagens situasjon er det et stort behov for å raskt kunne innhente evidensbasert kunnskap om populasjonsgrupper som er sårbare for alvorlige utfall knyttet til covid-19. Derfor valgte vi en hurtigoppsummeringstilnærming for denne rapporten på tross av den potensielle risikoen for å overse viktig informasjon eller å foreta forhastede vurderinger.

Vi inkluderte fem studier som rapporterte resultater fra multivariate analyser av demografiske og medisinske risikofaktorer. Vi ekskluderte risikofaktorer rapportert som biologiske markører, fysiologiske funksjoner og symptomer på covid-19. De inkluderte studiene var fra følgende land; to fra England, én fra Storbritannia, én fra USA og én fra Danmark. Tre av fem studier rapporterte kun data om den voksne befolkningen.

Sammenstilling av resultatene med metaanalytiske metoder ble vurdert som ikke gjennomførbart, så hovedresultatene i denne hurtigoppsummeringen blir presentert narrativt og i tabellformat. Risikofaktorer assosiert med (i) sykehusinnleggelse, (ii) alvorlig sykdomsforløp og (iii) død knyttet til covid-19 rapporteres separat nedenfor. Kun to store studier inkluderte populasjoner under 18 år, men for denne aldersgruppen er ikke resultatene representative da det totale antall registrerte hendelser er lite. Andre befolkningsgrupper, som kanskje ikke er fanget av de inkluderte studiene, vil også kreve videre forskning.

Risikofaktorer for sykehusinnleggelse på grunn av covid-19

Tre studier undersøkte risikofaktorer for sykehusinnleggelse på grunn av covid-19. Samlet sett så var høy alder, komorbiditet og alvorlighetsgrad av lidelser assosiert med økt risiko for sykehusinnleggelse. Alle studiene rapporterte resultater fra multivariate analyser med HRs eller ORs som effektestimater for et stort antall demografiske og medisinske risikofaktorer. De fleste medisinske tilstandene var assosiert med forhøyet risiko for sykehusinnleggelse, hvor tilstandens alvorlighetsgrad kombinert med antall komorbide lidelser i stor grad påvirket risikoen. To studier viste en sterk positiv sammenheng mellom økt alder og økt risiko for sykehusinnleggelse. Videre rapporterte to studier forhøyet risiko for sykehusinnleggelse for menn, de med overvekt og fedme, og de fleste ikke-hvite etniske grupper. Videre ble alvorlig nyresykdom, type 1-diabetes, pågående cellegiftkur, hjertesvikt, alvorlig immunsvikt og Downs syndrom assosiert med en betydelig forhøyet risiko for sykehusinnleggelse (OR/HR >=3).

Risikofaktorer for alvorlig eller kritisk covid-19 forløp og innleggelse ved akuttmottak

To studier undersøkte risikofaktorer for innleggelse ved akuttmottak på grunn av covid-19, men kun én studie så på dette utfallet separat og det ble kun beskrevet deskriptivt i løpende tekst. Derfor inkluderte vi alvorlig sykdomsforløp i denne utfallsgruppen, da en annen studie definerte dette som et kompositttmål hvor innleggelse ved akuttmottak var inkludert. I denne studien var økt alder den sterkeste prediktoren for alvorlig sykdomsforløp, med en klar dose-respons sammenheng. Videre ble menn, fedme grad III (BMI>40), hjertesvikt, diabetes assosiert med en forhøyet risiko for alvorlig sykdomsforløp. Afroamerikansk etnisitet var assosiert med en lavere risiko for alvorlig sykdomsforløp.

Risikofaktorer for covid-19 relatert død

Fire studier undersøkte risikofaktorer for covid-19 relatert død. Samlet sett så ble det funnet at økende alder var den sterkeste prediktoren for covid-19 relatert død. Videre ble ikke-hvit etnisitet, menn, de fleste medisinske tilstander, komorbiditet og sykdommenes alvorlighetsgrad identifisert som risikofaktorer for covid-19 relatert død. To studier fant også en økt risiko for covid-19 relatert død ved økt grad av fattigdom. Alvorlig nyresykdom, diabetes, demens, pågående cellegiftkur, organtransplantasjonspasienter, alvorlig immunsvikt, psykiske lidelser behandlet med antipsykotika, cerebral parese og Downs syndrom ble rapportert som de sterkeste medisinske prediktorene for covid-19 relatert død (OR/HR >=3).

Konklusjon

Basert på resultatene fra de inkluderte studiene er det tydelig at eldre mennesker er den populasjonen med høyest risiko for sykehusinnleggelse, alvorlig sykdomsforløp og død relatert til covid-19. De fleste kroniske sykdommer er assosiert med forhøyet risiko, hvor komorbiditet og sykdomsalvorlighet har stor betydning for den overordnede risikoen for de ulike covid-19 utfallene. Menn, ikke-hvit etnisitet, fattige og de med fedme har også en sannsynlig forhøyet risiko for covid-19 utfallene inkludert i denne hurtigoversikten.

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Problem statement

In relation to the ongoing COVID-19 outbreak, it is important to gather information about which patient groups are most at risk of severe outcomes. The outbreak team at the Norwegian Institute of Public Health has asked us to update a rapid review of the existing research on risk factors for hospitalisation, serious/critical COVID-19, or death, published May 20th 2020 (1).

Methods

Literature search

To investigate which demographic and medical risk factors are associated with hospitalisation, severity of disease, and death due to COVID-19, we searched for studies with more than 5000 participants that had laboratory confirmed COVID-19 and reported risk factors for the three main outcomes. Research librarian Elisabet Hafstad conducted a search on October 27th, 2020 in the MEDLINE and Embase database for studies published in the period 01.08.2020 -26.10.2020.

Inclusion criteria:

Population: More than 5000 confirmed COVID-19 participants from the general population. COVID-19 cases should be defined by PCR/ antigen testing.
Outcome: Hospital admission, ICU admission, ICU with ventilation, severe illness, death
Study types: Cohort studies, prospective studies, retrospective studies

Study selection

We included publications assessing the importance of various demographic and medical risk factors for the risk of COVID-19-related hospitalisation, severe disease/ICU admission and death. The factors examined were age, sex, ethnicity, deprivation, body mass index (BMI), underlying comorbidities, as well as substance and medicine use. Clinical and laboratory-based risk factors were not included in this report. In this third report update we excluded studies with less than 5000 participants due to power considerations. Only studies where the relative importance of various risk factors was assessed using multivariate statistical models were included. We excluded systematic reviews and studies only assessing risk factors in univariate analyses.

Review process

One researcher (JH) performed title and abstract screening. Two researchers (TB, JH) reviewed the studies in full text, selected studies for inclusion, and extracted and summarised data/results from included studies in tables. A group of experts in the field assisted during the study inclusion process (KG, SF, JB). This rapid review includes a formal quality assessment with the Newcastle-Ottawa quality assessment scale of included papers (2), but does not include a grading of the certainty of evidence. Therefore, the results should be interpreted with caution.

Peer review

Kirsten Gravningen, Siri Feruglio (both senior medical officers, Norwegian Institute of Public Health), and Jacob Berild (medical officer, Norwegian Institute of Public Health) specified the review criteria, assisted in final article selection, formatting of tables and critically reviewed the draft before publication. External feedback was received after publication, leading to minor amendments in this text.

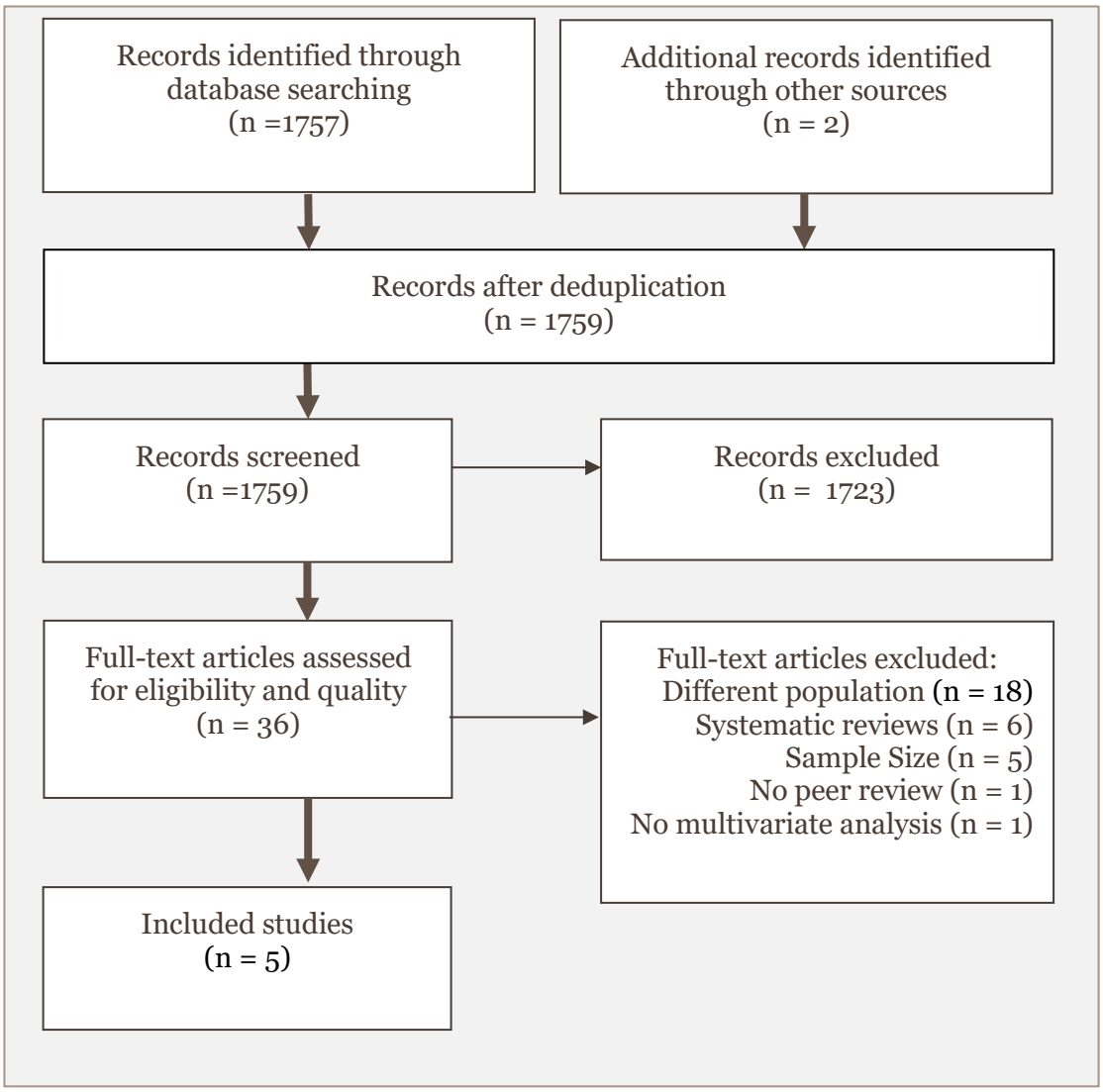
Results

Description of studies

Results of the literature search

We identified 1757 references through the systematic literature searches in MEDLINE and Embase. JH screened all titles and abstracts. We considered 36 references possibly relevant and read these in full text.

Figure 1. PRISMA flow diagram of study inclusion



Following full text screening, 11 studies were discussed with a group of experts determining final inclusion. We included five studies that reported results from multivariate analyses of demographic (e.g. sex, ethnicity, smoking) and medical risk factors (3-7). Two studies were from England (3, 4) , one from the UK (7), one from the USA (5), and one from Denmark (6). Three out of five studies reported only data on the adult population. All studies were published in international peer reviewed journals.

Included studies

We included five studies (Table 1.) and excluded 31 studies (Appendix 2).

Table 1. Included reviews

First author	Study type	Study population	Outcomes reported	Sample size					Covariates included in multivariate model
				Total	COVID - 19 positive*	Severe illness	Hospitalised	Died	
Barron (3) England	Retrospective study	Individuals registered with a general practice (age group: 0-80+ (lowest age group 0-39)	Death (Death in hospital with COVID-19 in the overall population)	61,414,470 individuals in general practice	Unclear	.	.	23,698	Model 1: Age, sex, ethnicity, deprivation, geographic region, coronary heart disease, cerebrovascular disease and heart failure. Model 2: Age, sex, ethnicity, deprivation, geographic region, and diabetes status
Clift (4) England	Population based cohort study	Adults in general practice (age group 19-100)	1. Death (Death in from COVID-19 either in hospital or outside hospital) 2. Hospitalisation	6,083,102	Unclear		10,776	4,384	Age, BMI, deprivation score, residency, ethnicity, kidney disease, cancer, diabetes, lung disease, heart disease, neurologic disease, mental illness, and more. All models were stratified by sex.
Petrilli (5) USA	Prospective cohort study	Adult patients in an academic medical centre in New York/Long Island (age group 19-75+)	Hospitalization, severe illness	11,544	5,279	990	2,741		Age at time of testing, sex, ethnicity, hypertension, hyperlipidemia, coronary artery disease, heart failure, pulmonary disease, malignancy, diabetes, obesity
Reilev (6) Denmark	Cohort study	Nationwide cohort tested for COVID-19 (age group 0-90+ (0-19 (2.7%))	Severe illness, hospitalization death	410,697	11,122	314	2,254	577	Age, sex, chronic lung disease, hypertension, ischaemic heart disease, heart failure, atrial fibrillation, stroke, diabetes, dementia, cancer, chronic liver disease, kidney disease, alcohol abuse, substance abuse, major psychiatric disorders, organ transplantation, overweight/ obesity, and/or rheumatoid arthritis/connective-tissue disease. (Only provided descriptive information for ICU outcome)
Williamson (7) UK	Cohort registry study	Adult primary care patients (age group 18-80+)	Death	17,278,392				10,926	Age, sex, BMI, smoking, IMD, hypertension/high blood pressure, asthma, chronic heart disease, diabetes, non-haematological cancer, haematological malignancy, reduced kidney function, liver disease, stroke or dementia, other neurological disease, organ transplant, asplenia, rheumatoid arthritis, lupus or psoriasis,other immunosuppressive condition.

We distinguish between studies that explore risk factors associated with

(i) hospitalisation due to COVID-19 (N=3)(4-6),

(ii) development of more severe /critical COVID-19 (N=2) (5, 6), and

(iii) death due to COVID-19 (N=5) (3-7)

Quality assessment

We performed quality assessment of included studies with the Newcastle–Ottawa Scale (NOS) for cohort studies (4-7) and case-control studies (3) (Table 2.) The NOS assesses methodological quality relating to three aspects of a study (Selection, Comparability and Outcome) and categorises studies as being of good, fair or poor methodological quality, based on level of fulfilment for each of the three criteria (maximum score is 9 points). We set no cut-off for included studies by total quality score.

Table 2. Newcastle–Ottawa Scale quality assessment

First author	Selection				Comparability	Outcome			Total score
	1	2	3	4	5	6	7	8	
Barron	1(a)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Clift	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Petrilli	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Reilev	1(b)	1(a)	1(a)	1(a)	2(a,b)/0[i]	1(b)	1(a)	1(a)	9/7[i]
Williamson	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(b)	9

[i] For ICU admission outcome, only descriptive information was provided in text

Risk factors for hospitalisation due to COVID-19

Brief summary: Three studies (4-6) assessed risk factors for hospitalisation due to COVID-19. All studies provided a granular overview of predicting factors. Results are listed side by side in Table 3. Overall, age, comorbidities and severity of disease were found to be strong predictors of hospital admission. Heart failure, kidney disease, diabetes, Down syndrome and ongoing chemotherapy is reported to have an especially high risk. Some evidence suggests that sex and ethnicity is associated with increased risk of hospital admission (4, 5).

Clift et al (4) reported characteristics of hospitalisation in a nationwide cohort comprising 1205 general practices in England with linkage to COVID-19 test results, Hospital Episode Statistics, and death registry data. The results in detail, based on 10776 admitted COVID-19 cases in the study period January 24th to April 30th, 2020 are presented in Table 3 stratified by sex. Hospital admission was defined as an ICD-10 code for either confirmed or suspected COVID-19, or new hospital admission associated with a confirmed SARS-CoV-2 infection in the study period. The authors report increased risk for all ethnicities compared to non-Hispanic whites, and most of the assessed comorbidities. Interestingly, the adjusted hazard ratios for body mass index, age, and the interaction between age and type 2 diabetes for hospital admissions due to COVID-19 showed higher risks associated with younger ages (Figure A, B in supplementary table of original study). The authors found the highest risk for populations undergoing chemotherapy, followed by individuals suffering from severe kidney disease.

The authors point out that no systematic community testing was performed and that only those unwell enough to attend hospital were tested. This, they conclude would overestimate risks of severe outcomes in those who tested positive.

Petrilli et al (5) investigated risk factors associated with admission to hospital based on a prospective cohort study with 5279 confirmed COVID-19 cases in New York City, USA, between March 1st, 2020 and April 8th, 2020, with complete follow-up through May 5th. 2741 participants were admitted to hospital, of whom 1904 were discharged alive without hospice care and 665 were discharged to hospice care or died. The strongest risk factor for hospital admission was age, with an OR of >2 for all age groups older than 44 years and OR 37.9 (95% confidence interval 26.1 to 56.0) for ages 75 years and older. Other risk factors were heart failure (OR 4.4, 2.6 to 8.0), male sex (OR 2.8, 2.4 to 3.2), chronic kidney disease (OR 2.6, 1.9 to 3.6), and BMI above normal weight range (e.g., for BMI >40: OR 2.5, 1.8 to 3.4). Petrilli et al also found a reduced OR for current and former smokers but increased OR for those with unknown smoking status (15% of participants). Detailed findings are listed in table 3, side by side with other relevant studies.

The authors point out that data on patients not admitted to hospital were more limited and might not have had reported a less detailed medical history. In addition, this limitation may have been further exacerbated by that patients treated and discharged from the emergency department were not commonly tested and thus omitted from analysis unless later admitted to the hospital. As this was a single centre study, some not admitted patients might have been admitted to other institutions, and some discharged patients might have been readmitted elsewhere with critical illness or could have died post-discharge.

Reilev et al (6) reports characteristics of hospital admissions in a nationwide cohort comprising 11 122 confirmed COVID-19 cases in Denmark starting February 7th, 2020 until May 19th, 2020. In general, the authors observed only minor differences in age, sex, medical history and prior drug use between PCR positive cases and test-negative individuals. Among all PCR-positive

cases, the median age was 48 years. Eighty percent of the PCR positive cases were community-managed and 20% were hospitalised, with more than 60% among cases hospitalised being older than 70 years. Twenty-two percent of those who died were managed in the community. Fifteen percent of community-managed cases had two or more comorbidities, whereas the corresponding proportion was 56% for hospitalised cases. The majority of hospitalised cases were admitted on the date of the positive PCR test (57%). The strongest predictors for hospital admission were age and number of comorbidities. Most major chronic diseases were associated with hospitalisation, with ORs ranging from 1.3–1.4 (e.g. stroke, ischaemic heart disease) to 2.6–3.4 (e.g. heart failure, hospital-diagnosed kidney disease, organ transplantation). Detailed findings are listed in table 3, side by side with other relevant studies.

The authors point out that test strategy in Denmark was initially directed at those who were most sick and potentially in need of medical care. This test strategy may have contributed to an overestimation of the case fatality and the proportion of hospitalised cases. They also report a strict, early lockdown with hospital capacity never being overwhelmed. The communicated seriousness and ease of healthcare access might also have influenced patients to present early, and a low threshold for admittance.

Across the studies, trends are apparent. However, due to the heterogeneity between studies in relation to study designs, risk factor definitions, data analysis and –reporting, we stress that there are uncertainties in direct comparisons of results between included studies.

Two studies showed a clear dose response relationship between increasing age and risk of hospital admission (5, 6). Two studies reported an increased adjusted HR/OR for hospital admission in men and for people overweight and obese (5, 6). Based on two studies, the majority of non-whites were at increased risk of admission. Three studies (4-6) provided a granular overview of adjusted HRs/ORs for a broad selection of comorbidities, conditions and ongoing treatments. Most of these were associated with a greater risk for admission, with apparent increases in risk based on severity of condition. One study (6) reported increasing risk by number of co-existing comorbidities. Severe kidney disease, diabetes type I, ongoing chemotherapy, severe immunodeficiency, heart failure, and Down syndrome stand out with a greater associated risk of hospital admission (OR/HR >=3).

Table 3. Studies assessing risk factors predicting hospitalisation due to COVID-19; overview of reported findings by author, significant values greater-than-or-equal 3 are marked red, values greater-than-or-equal 2 are marked orange, all significant findings below 2 are bold black. Non-significant findings are one font size smaller.

Author	**Clift**		**Petrilli**	**Reilev**
Country	England		US	Denmark
Participants	6,083,102		11,544	410,697
COVID-19 admitted	10,776		2,741	11,122
Testing method	PCR		PCR	PCR
Statistic	Adjusted hazard ratio (95 % CI)		Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Participants sex	men	women	mixed	mixed
Age				
19- 44			reference	
20-39				**OR 0.4 (0.3–0.5)[1]**
40-49				**OR 0.6 (0.5–0.8)[1]**
50-59				reference
45-54			**OR 2.14 (1.76 to 2.59)*** **	
60-69				**OR 1.6 (1.3–1.9)[1]**
55-64			**OR 3.67 (3.01 to 4.48)*** **	
70-79				**OR 4.7 (3.9–5.7)[1]**
65-74			**OR 8.7 (8.77 to 11.22)*** **	
> 75			**OR 37.87 (26.1 to 56.03)*** **	
80-89				**OR 4.8 (3.9–5.8)[1]**
> 90				**OR 3.5 (2.6–4.7)[1]**
Sex				
male			**OR 2.76 (2.39 to 3.2)*** **	**OR 1.8 (1.6–2.0)[1]**
Race/ ethnicity				
non-Hispanic white	reference		reference	
non-Hispanic African American			OR 0.81 (0.65 to 1.01)	
Asian			OR 1.29 (0.97 to 1.72)	
Blacks	**HR 2.59 (2.27 to 2.97)**	**HR 2.30 (1.97 to 2.68)**		
Indian	**HR 2.15 (1.89 to 2.44)**	**HR 1.89 (1.60 to 2.24)**		
Chinese	**HR 1.51 (1.03 to 2.20)**	HR 1.15 (0.71 to 1.85)		
Pakistani	**HR 2.01 (1.72 to 2.36)**	**HR 1.52 (1.21 to 1.89)**		
Bangladeshi:	**HR 1.71 (1.41 to 2.08)**	**HR 1.41 (1.11 to 1.79)**		
Asian (other)	**HR 2.29 (1.91 to 2.74)**	**HR 2.14 (1.74 to 2.64)**		
Hispanic			**OR 1.63 (1.35 to 1.97)*** **	
other/multiracial	**HR: 2.12 (1.83 to 2.46)**	**HR 1.90 (1.64 to 2.21)**	**OR 1.6 (1.21 to 2.11)*** **	
unknown			OR 0.89 (0.65 to 1.23)	
Comorbidities				
0 comorbidity				reference
1 comorbidity				**OR 1.7 (1.5–2.0)[2]**
2 comorbidities				**OR 2.1 (1.8–2.5)[2]**
3 comorbidities				**OR 3.1 (2.5–3.8)[2]**
4+ comorbidities				**OR 3.9 (3.2–4.8)[2]**
Cardiovascular				
Heart failure	**HR 1.33 (1.21 to 1.46)**	**HR 1.38 (1.23 to 1.55)**	**OR 4.43 (2.59 to 8.04)*** **	**OR 2.6 (2.0–3.4)[2]**
CAD /CHD /IHD	HR 1.06 (0.99 to 1.14)	**HR 1.11 (1.02 to 1.22)**	OR 1.08 (0.81 to 1.44) .	**OR 1.4 (1.2–1.7)[2]**
Atrial fibrillation	**HR 1.19 (1.10 to 1.29)**	**HR 1.34 (1.22 to 1.47)**		**OR 1.4 (1.2–1.7)[2]**
Thrombo-embolism	**HR 1.30 (1.17 to 1.44)**	**HR 1.34 (1.21 to 1.50)**		
Peripheral vascular disease	**HR 1.27 (1.13 to 1.42)**	**HR 1.21 (1.03 to 1.44)**		
Congenital heart disease	HR 0.97 (0.75 to 1.25)	HR 0.97 (0.75 to 1.25)		
Hypertension			**OR 1.78 (1.49 to 2.12)*** **	**OR 1.7 (1.5–1.9)[2]**
Stroke	**HR 1.31 (1.20 to 1.42)**	**HR 1.39 (1.27 to 1.53)**		**OR 1.3 (1.1–1.6)[2]**
Hyperlipidaemia			**OR 0.62 (0.52 to 0.74)**	
Kidney				
chronic kidney disease/ Hospital-diagnosed kidney disease			**OR 2.6 (1.89 to 3.61)*** **	**OR 2.9 (2.2–3.9)[2]**
Chronic kidney disease stage 3	**HR 1.28 (1.19 to 1.38)**	**HR 1.35 (1.25 to 1.46)**		
Chronic kidney disease stage 4	**HR 2.00 (1.67 to 2.39)**	**HR 1.79 (1.48 to 2.17)**		
Chronic kidney disease stage 5	**HR 3.86 (3.25 to 4.58)**	**HR 4.17 (3.39 to 5.12)**		
Chronic kidney disease stage 5 with dialysis	**HR 5.90 (4.22 to 8.25)**	**HR 3.72 (2.06 to 6.75)**		
Chronic kidney disease stage 5 with transplant	**HR 7.09 (5.30 to 9.47)**	**HR 5.54 (3.55 to 8.67)**		
Liver				
Chronic liver disease				**OR 2.3 (1.6–3.3)[2]**
Cirrhosis of the liver	**HR: 1.88 (1.46 to 2.41)**	**HR 1.83 (1.35 to 2.49)**		
Pulmonary				
Pulmonary disease (chronic obstructive pulmonary disease or asthma)			OR 1.08 (0.88 to 1.33)	**OR 1.8 (1.5–2.1)[2]**
COPD	**HR: 1.36 (1.25 to 1.49)**	**HR 1.34 (1.21 to 1.49)**		
Asthma	**HR: 1.10 (1.02 to 1.19)**	**HR 1.12 (1.04 to 1.21)**		
Rare lung conditions (bronchiectasis, cystic fibrosis, or alveolitis)	**HR 1.28 (1.06 to 1.55)**	**HR 1.28 (1.06 to 1.55)**		
Pulmonary hypertension or pulmonary fibrosis	**HR 1.56 (1.12 to 2.17)**	**HR 1.56 (1.12 to 2.17)**		
Endocrine				
Diabetes			**OR 2.24 (1.84 to 2.73)*** **	**OR 1.8 (1.6–2.2)[2]**
DM1	**HR: 3.66 (2.90 to 4.62)**	**HR 4.03 (3.12 to 5.22)**		
DM2	**HR: 2.57 (2.27 to 2.91)**	**HR 2.64 (2.27 to 3.07)**		
Any insulin use				**OR 2.3 (1.7–3.0)[2]**
Non-insulin glucose-lowering-drug use				**OR 1.7 (1.4–2.1)[2]**
Insulin monotherapy use				**OR 2.4 (1.5–3.6)[2]**

Neurological, mental				
Dementia	**HR: 2.12 (1.92 to 2.34)**	**HR 1.73 (1.56 to 1.92)**		OR 0.5 (0.4–0.7)[2]
Severe mental illness	**HR: 1.28 (1.19 to 1.38)**	**HR 1.37 (1.28 to 1.47)**		
Major psychiatric disorder				**OR 2.1 (1.2–3.7)[2]**
Major psychiatric disorder, Benzodiazepines and derivate use				**OR 1.7 (1.4–2.1)[2]**
Major psychiatric disorder, Antipsychotic use				**OR 1.5 (1.1–1.9)[2]**
Major psychiatric disorder, Antidepressant use				**OR 1.3 (1.1–1.5)[2]**
Motor neurone disease, multiple sclerosis, myasthenia gravis, or Huntington's	**HR 2.47 (1.90 to 3.22)**	**HR 2.47 (1.90 to 3.22)**		
Cerebral palsy	**HR 2.66 (1.42 to 4.98)**	**HR 2.66 (1.42 to 4.98)**		
Epilepsy	**HR 1.57 (1.33 to 1.86)**	**HR 1.57 (1.33 to 1.86)**		
Parkinson	**HR 1.70 (1.32 to 2.18)**	**HR 1.70 (1.32 to 2.18)**		
No learning disability	**ref**			
Learning disability apart from Down's Syndrome	**HR 1.38 (1.22 to 1.56)**	**HR 1.53 (1.34 to 1.76)**		
Down's syndrome	**HR 4.36 (2.39 to 7.94)**	**HR 4.36 (2.39 to 7.94)**		
Other				
Organ transplantation				**OR 3.4 (1.7–6.6)[2]**
Solid organ transplant (excluding kidney and bone marrow)	**HR: 2.02 (1.27 to 3.21)**	HR 1.57 (0.80 to 3.05)		
Rheumatoid arthritis				**OR 1.5 (1.1–1.9)[2]**
Rheumatoid arthritis or SLE (Lupus)	**HR: 1.30 (1.07 to 1.57)**	**HR 1.35 (1.17 to 1.56)**		
Malignancy			OR 0.88 (0.65 to 1.19)	**OR 1.4 (1.2–1.6)[2]**
Blood cancer	**HR: 1.29 (1.05 to 1.57)**	**HR 1.40 (1.10 to 1.78)**		
Respiratory tract cancer	**HR: 1.44 (1.14 to 1.83)**	**HR 1.65 (1.25 to 2.17)**		
Not on chemotherapy in last 12 months	reference	reference		
Chemotherapy grade A	**HR 1.72 (1.24 to 2.37)**	**HR 2.11 (1.48 to 3.01)**		
Chemotherapy grade B	**HR 3.64 (2.95 to 4.49)**	**HR 4.19 (3.28 to 5.37)**		
Chemotherapy grade C	**HR 4.11 (2.20 to 7.68)**	**HR 15.53 (8.36 to 28.85)**		
Sickle cell disease or severe immunodeficiency	**HR: 4.87 (2.67 to 8.87)**	**HR 6.68 (4.06 to 10.97)**		
Oral steroids 4+ scripts in past 6 months	**HR 1.42 (1.25 to 1.62)**	**HR 1.92 (1.71 to 2.17)**		
BMI				
< 25			reference	
> 25 / 25 - 29.9 (Overweight)			**OR 1.3 (1.07 to 1.57)****	
> 30			**OR 1.8 (1.47 to 2.2)*****	**OR 2.1 (1.8–2.5)[2]** (Based on ICD code for overweight)
>40 / ≥40 (Obese class III)			**OR 2.45 (1.78 to 3.36)*****	
unknown			**OR 0.47 (0.31 to 0.69)*****	
Smoking/ Substance abuse				
Never smoker			reference	
Current smoker			**OR 0.59 (0.43 to 0.81)****	
Former smoker			**OR 0.69 (0.56 to 0.85)*****	
Unknown smoking status			**OR 1.43 (1.16 to 1.75)*****	
Alcohol abuse				**OR 1.7 (1.3–2.3)[2]**
Substance abuse				OR 1.3 (0.9–1.9)[2]
Explanatory information	Adjusted for variables shown, deprivation, and fractional polynomial terms for body mass index (BMI) and age. Model includes fractional polynomial terms for age (3 3) and BMI (0.5 0.5 ln (bmi)) and interaction terms between age terms and type 2 diabetes.		Pvalue: *** = p<0.001; ** = p<0.01,* = p<0.05	[1] = Age-, sex- and number of comorbidities adjusted OR (95% CI), table 4 in supplementary files of original study; [2] = Age and sex-adjusted OR (95% CI);

Risk factors for severe illness, including ICU admission, due to COVID-19

Brief summary: Two studies (5, 6) assessed risk factors in relation to ICU admissions, but information on ICU admission alone was provided by just one study and only with descriptive information (6). Therefore, we included severe illness in this outcome group, as Petrilli et al defined this as a composite measure including ICU admissions. Overall, increasing age, male sex, morbid obesity, heart failure, diabetes and unknown smoking status was associated with increased risk for severe illness. Being of non-Hispanic African American decent was associated with decreased risk of severe illness. A dose response relationship between increasing age and increasing risk of severe illness was observed.

Reilev et al (6) report on characteristics of ICU admissions in a nationwide cohort comprising 11,122 confirmed COVID-19 cases in Denmark in the period February 7th, 2020 until May 19th, 2020. Compared to non-ICU participants, ICU admitted participants (2.8%) were comprised of a higher ratio of men (73%) to women (27%) (non-ICU: men (51%), women (49%)) and were slightly younger (median 68 (interquartile range(IQR) 58–75)) (non-ICU: median 72 (IQR 55–81)). Compared to fatal cases (5.2%), non-fatal cases admitted to the ICU were younger and presented with fewer comorbidities. The authors argue this might be due to ICU prioritisation of patients with better outcome prospects if provided with intensive care treatment, for example ventilation.

Petrilli et al (5) investigated risk factors associated with critical illness based on a prospective cohort study with 5279 confirmed COVID-19 cases in New York City, USA, between March 1st, 2020 and April 8th, 2020. They defined critical illness as a composite measure incorporating ICU admission, use of mechanical ventilation, discharge to hospice or death. In their fully adjusted models, they report increased risk of severe illness for age, with a 2-fold increase in risk for age groups 55-64 years, 3-fold increase for ages 65-74, and almost 3.5-fold increase for those aged ≥75. For morbid obesity and unknown smoking status they report about a 50% increase in risk, and almost a 1-fold increased risk associated with heart failure. The authors state that overall, risk of severe illness decreased across the study period. For details on reported risk factors, see Table 4.

Table 4. Studies assessing risk factors predicting development of severe illness[i] due to COVID-19; overview of reported findings by author, significant values greater-than-or-equal 3 are marked red, values greater-than-or-equal 2 are marked orange, all significant findings below 2 are bold black. Non-significant findings are one font size smaller.

Author	***Petrilli***
Country	US
Participants	11,544
Testing method	PCR
COVID-19 admitted	2,741
Statistic	Adjusted odds ratio (95% CI)
Participants sex	Mixed
Age	
19-44	reference
45-54	OR 1.12 (0.80 to 1.6)
55-64	**OR 2.04 (1.50 to 2.8)*** **
65-74	**OR 2.88 (2.09 to 4.0)*** **
≥75	**OR 3.46 (2.46 to 4.8)*** **
Male sex	**OR 1.54 (1.29 to 1.8)*** **
Ethnicity	
non-Hispanic white	reference
non-Hispanic African American	**OR 0.67 (0.51 to 0.9)** **
Asian	OR 1.30 (0.92 to 1.8)
Hispanic	OR 0.93 (0.74 to 1.2)
Other/multiracial	OR 1.15 (0.84 to 1.6)
Unknown	OR 1.23 (0.80 to 1.9)
BMI	
18.5-24.9 (Normal weight)	reference
30 -34.9 (Obese class I)	OR 0.86 (0.69 to 1.1)
35–39.9 (Obese class II)	OR 0.98 (0.77 to 1.2)
≥40 (Obese class III)	**OR 1.52 (1.04 to 2.2)***
Unknown	OR 0.80 (0.46 to 1.4)
Coronary artery disease	OR 0.96 (0.77 to 1.2)
Heart failure	**OR 1.88 (1.43 to 2.5)*** **
Hyperlipidaemia	OR 0.94 (0.77 to 1.1)
Hypertension	OR 0.96 (0.77 to 1.2)
Diabetes	**OR 1.24 (1.03 to 1.5)***
Asthma or COPD	OR 0.89 (0.70 to 1.1)
Chronic kidney disease	OR 1.07 (0.85 to 1.3)
Cancer	OR 1.23 (0.95 to 1.6)
Smoking	
Never	reference
Former	OR 1.06 (0.85 to 1.3)
Current	OR 0.77 (0.52 to 1.2)
Unknown	**OR 1.52 (1.19 to 1.9)** **

[i] Definition of severe illness: care in the intensive care unit, use of mechanical ventilation, discharge to hospice, or death

[ii] P-value: *** = p<0.001; ** = p<0.01; * = p<0.05

Risk factors for death due to COVID-19

Brief summary: Four studies assessed risk factors for death due to COVID-19 (3, 4, 6, 7). All studies provided a granular overview of predicting factors. Results are summarised side by side in Table 5. Overall, increasing age was found to be the strongest predictor of death due to COVID-19. Furthermore, male sex, ethnicity, most comorbidities, increasing severity and number of comorbidities were found to be significant predictors of COVID-19-related death.

Barron et al (3) performed a whole-population study assessing risks of COVID-19 related in-hospital death between March 1st and May 11th, 2020. The authors included 61,414,470 individuals registered with a general practice in England who were alive on Feb 16, 2020. They used multivariable logistic regression to examine the effect of diabetes status, by type, on in-hospital COVID-19 related death, adjusting for demographic factors and cardiovascular comorbidities. 0.4% had a recorded diagnosis of type 1 diabetes, 4.7% type 2 diabetes and 0.1% another types of diabetes. 23 698 COVID-19 related in-hospital deaths occurred during the study period, where 7434 deaths, about one third, occurred in people with type 2 diabetes, 364 with type 1 diabetes, and 69 in people with other types of diabetes. Adjusted for age, sex, index of multiple deprivation, ethnicity and region, the OR for death in people with type 1 diabetes was 3.51 (95% CI 3.16–3.90) and for people with type 2 diabetes 2.03 (1.97–2.09) compared with the population without known diabetes. A limitation with this study is that the registration of death was limited to in-hospital occurrences. The authors were also limited in their ability to adjust for other comorbidities because of limitations in the datasets used and available.

Clift et al (4) report on characteristics related to death due to COVID-19 in a nationwide cohort comprising 1205 general practices in England with linkage to COVID-19 test results, Hospital Episode Statistics, and death registry data. The practices were randomly assigned to a derivation dataset and to a validation cohort. The validation cohort provided a basis for two calibrations of the risk models over different periods. The results in detail, based on 4384 deaths of the derivation cohort, are presented by sex in Table 5. Their primary outcome was time to death from COVID-19 (either in hospital or outside hospital), defined as confirmed or suspected death from COVID-19 as per the death certification or death occurring in an individual with confirmed SARS-CoV-2 infection at any time in the period 24 January to 30 April 2020. Their findings show increased hazard ratios for all non-white males, and most of the investigated comorbidities. Interestingly, the adjusted hazard ratios for body mass index, age, and the interaction between age and type 2 diabetes for deaths due to COVID-19 showed higher risks associated with younger ages. The highest risk was identified in individuals with Down syndrome, with a HR of 2.55 (18.13-58.42) in women and HR 9.80 (4.62-20.78) in men.

The authors point out that no systematic community testing was performed and that only those unwell enough to attend hospital were tested. This, they conclude would overestimate risks of severe outcomes in those who tested positive.

Reilev et al (6) investigated risk factors for death due to COVID-19 in a nationwide cohort comprising 11 122 confirmed COVID-19 cases in Denmark in the period February 7th, 2020 until May 19th, 2020. During this period there were 577 COVID-19-related deaths registered. They report a mortality rate of below 5% for persons under 80 years of age without any comorbidities, while almost 4 out of 5 fatal cases had two or more co-morbidities. The strongest predictor for death was age, with a clear dose response relationship, with odds of death being 4.4 times greater for age group 60-69 compared to the reference group (50-59), and the odds of death for those 90 years old and above being 90 times greater than the reference group. Weaker,

but still significant, findings were reported for male sex (OR 1.94 (1.89–1.99)), dementia (OR 1.7 (1.3-2.2)) and major psychiatric disorders (OR 1.5-3)).

Williamson et al (7) investigated risk factors for COVID-19-related death in a retrospective registry study of 17 278 392 adults in the UK. 10 926 COVID-19-related deaths where included, Highest risks were found for high age (70-79: HR 6.07 (5.51–6.69), >80: HR 20.60 (18.70–22.68)), organ transplantation (HR 3.53 (2.77–4.49)), blood cancer diagnosed less than one year ago (HR 2.80 (2.08–3.78), neurological disorders (HR 2.58 (2.38–2.79) and kidney disease (HR 2.52 (2.33–2.72)). Increased risk was also seen for male sex (HR 1.59 (1.53–1.65)), ethnicities other than white (HR 1.3-1.5), diabetes (HR 1.90 (1.72–2.09)), chronic liver disease (HR 1.75 (1.51–2.03)), obesity (BMI 35-39.9 HR 1.40 (1.30-1.52), BMI $\geq$40 HR 1.92 (1.72–2.13)) and deprivation score (HR 1.79 (1.68–1.91) for most deprived). The authors found a lower risk associated with current smoking status (HR: 0.89 (0.82–0.97)), but the association was found to be largely driven by chronic respiratory disease, of which smoking is a key risk factor. The authors highlight that these findings need to be evaluated with caution. For more details on reported results, see Table 5.

Across the studies, trends are apparent. These trends need to be interpreted with caution due to heterogeneity in study designs, selected predicting factors, data analysis and data reporting. All studies assessing age as a predictor found it to be a consistent and strong risk factor for death with a steep and continuous increase in risk with increasing age. Ethnicity other than white was also consistently, but more modestly, associated with increased risk of death, with Blacks having the highest risk of death. Two studies (3, 7) found increasing risk of death with increasing degree of deprivation (measure by Indices of multiple deprivation (IMD)). Most medical risk factors investigated are associated with higher risk of death, with increasing numbers and severity of comorbidities increasing the risk for death further. Of the medical risk factors, severe kidney disease, diabetes mellitus type I and II, dementia, ongoing chemotherapy, organ transplant patients, severe immunodeficiency, major psychiatric disorder with antipsychotic treatment, cerebral palsy and Down syndrome is associated with the highest risk of death (OR/HR >=3). Williamson et al found increasing risk with increasing BMI above normal weight, this was not found by Reilev et al for patients with medical overweight.

Table 5. Studies assessing risk factors predicting death due to COVID-19; overview of reported findings by author, significant values greater-than-or-equal 3 are marked red, values greater-than-or-equal 2 are marked orange, all significant findings below 2 are bold black. Non-significant findings are one font size smaller.

Author	Williamson	Clift		Barron	Reilev
Country	UK	England		England	Denmark
Participants	17,278,392	6,083102		61,414,470	410,697
Testing method	ICD U071 or U072	PCR		Positive test or COVID-19 registered as cause of death	PCR
COVID-19 admitted		10776			11122
COVID-19 deaths	10,926	4,384		23698 in-hospital	577 (5.2%)
Statistic	Adjusted hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)		Adjusted odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)
Participants sex	mixed	men	women	mixed	mixed
Age					
0-39				**OR 0.01 (0.01–0.01)**	
18-39	**HR 0.06 (0.04–0.08)**				
40-49	**HR 0.30 (0.25–0.36)**			**OR 0.11 (0.10–0.12)**	
50-59	reference			**OR 0.36 (0.34–0.39)**	reference
60-69	**HR 2.40 (2.16–2.66)**			reference	**OR 4.4 (2.5–7.9)**[2]
70-79	**HR 6.07 (5.51–6.69)**			**OR 2.64 (2.53–2.76)**	**OR 15.2 (8.7–26.3)**[2]
>80	**HR 20.60 (18.70–22.68)**			**OR 9.20 (8.83–9.58)**	
80-89					**OR 29.9 (17.2–51.9)**[2]
> 90					**OR 90.2 (50.2–162.2)**[2]
Sex					
male	**HR 1.59 (1.53–1.65)**			**OR 1.94 (1.89–1.99)**	**OR 2.1 (1.7–2.6)**[2]
Number of comorbidities					
0					reference
1					**2.6 (1.6–4.0)**[2]
2					**2.6 (1.7–4.1)**[2]
3					**3.5 (2.2–5.4)**[2]
+4					**5.2 (3.4–8.0)**[2]
Index of multiple deprivation quintile					
1	**HR 1.79 (1.68–1.91)**			**OR 1.88 (1.80–1.96)**	
2	**HR 1.51 (1.42–1.61)**			**OR 1.53 (1.47–1.60)**	
3	**HR 1.22 (1.15–1.30)**			**OR 1.25 (1.20–1.31)**	
4	**HR 1.12 (1.05–1.19)**			**OR 1.14 (1.09–1.19)**	
5 (least deprived)	reference			reference	
Race/ ethnicity					
non-Hispanic white	reference	reference	reference	reference	
Black	**HR 1.48 (1.29–1.69)**	**HR 3.03 (2.42-3.80)**	**HR 1.98 (1.39-2.83)**	**OR 1.71 (1.61–1.82)**	
Asian	**HR 1.45 (1.32–1.58)**			**OR 1.35 (1.28–1.42)**	
Indian		**HR 1.59 (1.25-2.01)**	**HR 1.89 (1.43-2.51)**		
Chinese		**HR 2.47 (1.49-4.09)**	HR 1.21 (0.51-2.90)		
Pakistani		**HR 1.84 (1.39-2.44)**	HR 1.40 (0.91-2.14)		
Bangladeshi		**HR 2.27 (1.65-3.12)**	HR 1.41 (0.88-2.26)		
Asian (other)		**HR 2.02 (1.49-2.74)**	HR 1.19 (0.72-1.97)		
other/multiracial	**HR 1.43 (1.11–1.84)**	**HR 2.04 (1.60-2.58)**	**HR 1.73 (1.28-2.35)**	**OR 1.43 (1.23–1.67)**	
other	**HR 1.33 (1.10–1.61)**				
unknown				**OR 0.33 (0.31–0.35)**	
Cardiovascular					
Heart failure		**HR 1.40 (1.24-1.59)**	**HR 1.37 (1.18-1.60)**		OR 1.1 (0.8-1.5)[1]
CAD /CHD /IHD	**HR 1.17 (1.12–1.22)**	**HR 1.13 (1.02-1.24)**	**HR 1.24 (1.10-1.40)**		OR 0.7 (0.5-0.9)[1]
Atrial firbrillation		HR 1.11 (1.00-1.24)	**HR 1.18 (1.04-1.34)**		OR 1.1 (0.8-1.4)[1]
Thrombo-embolism		**HR 1.18 (1.01-1.38)**	**HR 1.18 (1.01-1.38)**		
Peripheral vascular disease		**HR 1.42 (1.15-1.76)**	**HR 1.42 (1.15-1.76)**		
Congenital heart disease		**HR 1.23 (0.75-2.03)**	**HR 1.23 (0.75-2.03)**		
Hypertension	**HR 0.89 (0.85–0.93)**				OR 0.6 (0.5-0.8)[1]
Stroke		**HR 1.24 (1.11-1.38)**	**HR 1.34 (1.19-1.51)**		OR 1.0 (0.8-1.3)[1]
Stroke or dementia	**HR 2.16 (2.06–2.27)**				
Kidney					
Chronic kidney disease					OR 1.3 (0.9-1.8)[1]
Kidney disease, eGFR 30–60	**HR 1.33 (1.28–1.40)**				
Kidney disease, eGFR < 30	**HR 2.52 (2.33–2.72)**				
Chronic kidney disease stage 3		**HR 1.18 (1.06-1.30)**	**HR 1.30 (1.17-1.45)**		
Chronic kidney disease stage 4		**HR 1.83 (1.46-2.29)**	**HR 1.37 (1.05-1.80)**		
Chronic kidney disease stage 5		**HR 2.40 (1.83-3.15)**	**HR 3.00 (2.19-4.12)**		
Chronic kidney disease stage 5 with dialysis		HR 2.68 (0.86-8.36)	**HR 3.67 (2.02-6.66)**		
Chronic kidney disease stage 5 with transplant		**HR 3.20 (1.62-6.33)**	**HR 7.84 (3.38-18.17)**		
Spleen					
Asplenia	HR 1.34 (0.98–1.83)				
Liver					
Chronic liver disease	**HR 1.75 (1.51–2.03)**				OR 1.2 (0.7-2.3)[1]
Cirrhosis of the liver		HR 1.29 (0.83-2.02)	**HR 1.85 (1.15 to 2.99)**		
Pulmonary					
Pulmonary disease (COPD or asthma)					OR 1.1 (0.8-1.4)[1]
Respiratory disease excluding asthma	**HR 1.63 (1.55–1.71)**				
COPD		**HR 1.25 (1.11-1.42)**	**HR 1.50 (1.29-1.74)**		
Asthma		HR 1.03 (0.91-1.17)	HR 0.84 (0.73-0.97)		
Asthma with no recent OCS use	HR 0.99 (0.93–1.05)				
Asthma with recent OCS use	**HR 1.13 (1.01–1.26)**				
Rare lung conditions (bronchiectasis, cystic fibrosis, or alveolitis)		HR 0.85 (0.60-1.19)	HR 0.85 (0.60-1.19)		
Pulmonary hypertension or pulmonary fibrosis		HR 1.55 (1.00 -2.40)	HR 1.55 (1.00-2.40)		

Endocrine					
Diabetes					OR 1.1 (0.8-1.4)[1]
DM type 1		**HR 5.84 (3.97-8.60)**	**HR 4.02 (2.07-7.82)**	**OR 3.51 (3.16–3.90)**	
DM Type 2 (at mean age)		**HR 4.74 (3.34-6.71)**	**HR 6.29 (4.08-9.70)**	**OR 2.03 (1.97–2.09)**	
Other Diabetes				**OR 2.14 (1.69–2.71)**	
With HbA1c < 58 mmol mol	**HR 1.31 (1.24–1.37)**				
With HbA1c ≥ 58 mmol mol	**HR 1.95 (1.83–2.08)**				
With no recent HbA1c measure	**HR 1.90 (1.72–2.09)**				
Diabetes, Non-insulin glucose lowering drugs					OR 1.0 (0.7-1.3)[1]
Diabetes, Insulin					OR 1.3 (0.9-1.8)[1]
Diabetes, Insulin monotherapy					OR 1.0 (0.6-1.7)[1]
Neurological, mental					
No learning disability		reference	reference		
Learning disability apart from Down's syndrome		**HR 1.36 (1.14-1.60)**	**HR 1.36 (1.11-1.65)**		
Down's syndrome		**HR 9.80 (4.62-20.78)**	**HR 32.55 (18.13-58.42)**		
Parkinsons disease		HR 1.13 (0.79-1.62)	HR 1.13 (0.79-1.62)		
Dementia		**HR 3.14 (2.81-3.50)**	**HR 2.91 (2.58-3.28)**		**OR 1.7 (1.3-2.2[1])**
Epilepsy		**HR 1.58 (1.23-2.03)**	**HR 1.58 (1.23-2.03)**		
Motor neurone disease, multiple sclerosis, myaesthenia gravis, or Huntington's		**HR 1.99 (1.24-3.18)**	**HR 2.75 (1.83-4.12)**		
Cerebral Palsy		**HR 3.45 (1.10-10.78)**	**HR 3.45 (1.10-10.78)**		
Severe mental illness		**HR 1.26 (1.13-1.42)**	**HR 1.29 (1.15-1.45)**		
Major psychiatric disorder					OR 1.9 (0.9-3.9)[1]
Major psychiatric disorder, Benzodiazepines and derivates					**OR 1.8 (1.4-2.4)[1]**
Major psychiatric disorder, Antipsychotics					**OR 3.0 (2.1-4.2)[1]**
Major psychiatric disorder, Antidepressants					**OR 1.5 (1.2-1.9)[1]**
Neurological disorders often with compromised respiratory function (MND, MG;MS,Parkinsons, CP etc)	**HR: 2.58 (2.38–2.79)**				
Other neurological disease	**HR 2.58 (2.38–2.79)**				
Other					
Organ transplantation	**HR 3.53 (2.77–4.49)**				OR 2.0 (0.8-5.1)[1]
Solid organ transplant (excluding kidney and bone marrow)		HR 1.46 (0.36-5.92)	HR 1.46 (0.36- 5.92)		
Rheumatoid arthritis/		HR 1.02 (0.75-1.38)	**HR 1.32 (1.06-1.65)**		OR 0.9 (0.6-1.3)[1]
Rheumatoid arthritis, lupus or psoriasis)	**HR 1.19 (1.11–1.27)**				
Sickle cell disease or severe immunodeficiency		**HR 4.41 (1.41-13.81)**	**HR 5.94 (1.89-18.67)**		
Other immunosuppressive condition	**HR 2.21 (1.68–2.90)**				
Oral steroids 4+ scripts in past 6 months		**HR 1.44 (1.19-1.73)**	**HR 1.83 (1.52-2.19)**		
Bone marrow or stem cell transplant in past 6 months		HR 1.58 (0.95-2.62)	HR 2.78 (0.22-34.55)		
Cancer					
Malignancy					OR 1.0 (0.8-1.3)[1]
Cancer (non-haematological, versus none), Diagnosed <1 year ago	**HR 1.72 (1.50–1.96)**				
Cancer (non-haematological, versus none), Diagnosed 1–4.9 years ago	**HR 1.15 (1.05–1.27)**				
Cancer (non-haematological, versus none), Diagnosed ≥5 years ago	HR 0.96 (0.91–1.03)				
Blood cancer		HR 1.29 (0.97-1.71)	**HR 1.50 (1.06-2.12)**		
Blood cancer, Diagnosed <1 year ago	**HR 2.80 (2.08–3.78)**				
Blood cancer, Diagnosed ≥5 years ago	**HR 2.46 (2.06–2.95)**				
Blood cancer, Diagnosed 1–4.9 years ago	**HR 1.61 (1.39–1.87)**				
Respiratory tract cancer		HR 1.27 (0.89-1.81)	**HR 1.70 (1.16-2.49)**		
Radiotherapy in past 6 months		**HR 2.09 (1.48-2.96)**	**HR 2.11 (1.30-3.41)**		
Not on chemotherapy in past 12 months		reference	reference		
Chemotherapy grade A		**HR 1.74 (1.10-2.75)**	**HR 2.30 (1.35-3.94)**		
Chemotherapy grade B		**HR 3.50 (2.54-4.82)**	**HR 3.52 (2.29-5.42)**		
Chemotherapy grade C		**HR 3.37 (1.17-9.64)**	**HR 17.31 (6.52-45.98)**		
BMI					
18.5-24.9 (Normal weight)	reference				
30 -34.9 (Obese class I)	HR: 1.05 (1.00–1.11)				OR 1.0 (0.7-1.4)[1], defined as medical overweight
35–39.9 (Obese class II)	**HR: 1.40 (1.30–1.52)**				
≥40 (Obese class III)	**HR: 1.92 (1.72–2.13)**				
Smoking/ Substance abuse					
Never smoked	reference				
Current smoker	**HR: 0.89 (0.82–0.97)**				
Former smoker	**HR: 1.19 (1.14–1.24)**				
Substance abuse					OR 1.3 (0.7-2.2)[1]
Alcohol abuse					OR 1.3 (0.9-2.0)[1]
Explanatory information	Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios.	Age, BMI, deprivation score, residency, ethnicity, kidney disease, cancer, diabetes, lung disease, heart disease, neurologic disease, mental illness, and more . All models were stratified by sex.		Data are the results of a multivariable logistic regression, which included the explanatory variables shown, plus region	[1] = Age-, sex- and number of comorbidities adjusted OR (95% CI); tbl 4 in suppl. of original study; [2] = Age and sex-adjusted OR (95% CI)

Discussion and conclusion

We included five studies assessing possible risk factors for hospitalisation, ICU admission/severe or critical disease, and death due to COVID-19. We excluded studies with fewer than 5000 laboratory test positive cases, and studies that only reported results from univariate analyses, as several larger studies with multivariate analyses had become available since we published the previous version of this rapid review (May 12th, 2020). Three out of five studies reported only data on the adult population, so generalisability for younger populations is presumed low.

In this review update, older and increasing age stands out as the predominant individual risk factor for hospital admission, severe disease, and death due to COVID-19. Male sex, race/ethnicity, deprivation score and obesity are all factors that also appear to be associated with increased risk. Furthermore, most comorbidities appear to be associated with increased risk, with increased number and severity of comorbid condition(s) appearing to be of compelling importance for increased risk of hospital admission and death. Only two large studies included populations under 18 years, but for this age group the results are not representative as the total number of registered incidents is small. Other population groups, which may not have been captured by the included studies will also require further research.

Individuals with some conditions stand out as having particularly high risk, and further investigations are required to obtain more robust data, for example for individuals with Down syndrome. As there is only limited data available on the age group below 18 years of age, there remains a need for further studies of this population group. Generally, there is high agreement among study findings in relation to important risk factors. For differing results there is a need to identify and evaluate what the driving factors for these differences are. For example, there remains uncertainty on smoking as an independent risk factor. Smoking increases the risk of cardiovascular disease, cancer and chronic lung disease, all of which are risk factors for severe COVID-19. In analyses where one adjusts for both smoking and diseases caused by smoking, conflicting findings have been reported on smoking as a separate risk factor. Therefore, further studies are needed to clarify the role of smoking as an independent risk factor in relation to COVID-19 related outcomes.

Documentation for ICU admissions is less exhaustively covered compared to the other outcomes. The threshold for ICU admission might also be less clear than for hospital admission or death. Also, ICU admission might not provide an accurate image of those with the most severe illness, but rather a combination of those with severe illness that have a better prognosis. Depending on available resources and a necessity for care triage, patients might be admitted to intensive care differently at different times. This is important to consider when interpreting the reported findings. Hence, ICU admissions might not provide a good basis for decisions relating to which population groups are at most risk for severe COVID-19 outcomes.

The outcome hospitalisation might also not be completely representative, as ease of access to care might vary from one setting to another. Several factors influence seeking medical care and hospital admission, e.g., higher out of pocket payments might disincentivise individuals seeking

help, leading to only registration of more severe. This is particularly relevant to consider for studies from the USA, as there is no universal healthcare program. On the other hand, ease of access might overrepresent less severe cases, as suspected in the Danish study. In addition, organisational aspects of how care is provided vary between countries. In Norway, nursing home patients with COVID-19 are usually not admitted to hospital but managed within the nursing home setting.

Nonetheless, since our last update the evidence base regarding important risk factors for hospital admission or death is more robust. We were able to reaffirm some of our previous findings and to expand and strengthen our evidence base. We were able to increase the threshold for minimum participants tenfold, while only looking at peer reviewed publications. Inadvertently the choice to increase the threshold might have led to some populations groups not being captured equally well, as seen in the absence of data on the youngest age groups. Additionally, we performed quality assessment of included studies. We did not grade the certainty of evidence, which is why the results from this review should still be interpreted with caution. It should be noted that only associations are reported in the included studies, hence causal relationships cannot be confirmed or refuted.

The included studies were heterogeneous in terms of statistical methods and procedures applied for selection of factors to include in the multivariate model. Some studies provided odds ratios whereas other studies reported hazard ratios. As several registry studies looking at a similar population in the same country were included, there is a possibility that some study participants are included in more than one study. There was also large variability in the number of factors included in the multivariate model. One study reported all results separately for each sex. We also found large variability in the way different factors were categorised. Differences in reporting also represent differences in target population and characteristics, as for example ethnical groups in one location may not be representative for that of another location. The existing heterogeneity impairs direct comparison of risk estimates across studies, and meta-analysis was therefore not feasible.

Conclusion

The elderly are clearly the main group at risk of hospital admission, severe illness, and death if infected by COVID-19. Most comorbidities appear to increase risk, with increasing number of and severity of comorbidities contributing to a further increase in the overall risk. Male sex, obesity, non-white ethnicity and deprivation are also associated with increased risk.

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Appendix

Appendix 1; Search strategy

Search: 2020-10-27

Ovid MEDLINE(R) ALL 1946 to October 26, 2020

1	(((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sars-coronavirus2 or sars-coronavirus-2 or sars-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemic*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	68513
2	Hospitalization/ or exp Mortality/ or Critical Care/ or exp Intensive Care Units/ or exp Respiration, Artificial/ or (hospitalization* or hospitalization* or hospitalized or hospitalised or ((admit* or admission*) adj3 hospital*) or death* or mortality or ICU or ((intensive or critical) adj3 care) or ventilat* or intubat*).mp.	2535401
3	Cohort Studies/ or Prospective Studies/ or Meta-Analysis.pt. or Systematic Review.pt. or (population-based or (large adj population*) or nationwide or nation-wide).mp. or (cohort* or systematic review or meta-analys*).ti.	1225100
4	1 and 2 and 3	1765
5	(202008* or 202009* or 202010*).dt.	361781
6	4 and 5 [referanser lagt til august, september, oktober 2020]	834
7	4 not 5 [referanser lagt til fram til juli 2020]	931

.

Embase 1974 to 2020 October 26

1	(((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sars-coronavirus2 or sars-coronavirus-2 or sars-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemic*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.	69616
2	Hospitalization/ or exp Mortality/ or Intensive Care/ or exp Intensive Care Unit/ or exp Artificial Ventilation/ or (hospitalization* or hospitalization* or hospitalized or hospitalised or ((admit* or admission*) adj3 hospital*) or death* or mortality or ICU or ((intensive or critical) adj3 care) or ventilat* or intubat*).mp.	3620613
3	Cohort Analysis/ or Prospective Study/ or Systematic Review/ OR Meta Analysis/ or (population-based or (large adj population*) or nationwide or nation-wide).mp. or (cohort* or systematic review or meta-analys*).ti.	1785709
4	1 and 2 and 3	3102
5	Limit 4 to embase status	2323
6	(202008* or 202009* or 202010*).dc.	664242
7	5 and 6 [referanser lagt til august, september, oktober 2020]	1648
8	5 not 6 [referanser lagt til fram til juli 2020]	675

Appendix 2; Excluded studies

Table of excluded studies

First author	Reason for exlusion
Abate (8)	Systematic review
Akiyama (9)	Systematic reviews
Attauabi (10)	Different population
Attaway (11)	Different population
Barochiner (12)	Systematic reviews
Boulle (13)	Different population
Caraballo (14)	Different population
de Chaisemartin (15)	Different population
Derikx (16)	Different population
Du (17)	Systematic reviews
Fresan (18)	Different population
Graziani (19)	Not peer reviewed
Harrison (20)	Different population
Hippisley-Cox (21)	Different population
Hamer (22)	Sample size
Hamer (23)	Sample size
Holman (24)	Different population
Ioannou (25)	Different population
Lee (26)	Different population
Li (27)	Systematic reviews
Punjani (28)	No multivariate analysis reported
O'Reilley (29)	Sample size
Ravanan (30)	Different population
Rentsch (31)	Different population
Schultze (32)	Different population
Yang (33)	Different population
Yanover (34)	Sample size
Yonas (35)	Systematic reviews
Wang (36)	Different population
Woolford (37)	Sample size
Zhu (38)	Different population

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