NIPH
Norwegian Institute of Public Health

memo

COVID-19-EPIDEMIC :

COVID-19 and risk factors for severe disease – a rapid review, 2nd update

Title	COVID-19 and risk factors for severe disease – a rapid review, 2nd update
Institution	Folkehelseinstituttet / Norwegian Institute of Public Health
Responsible	Camilla Stoltenberg, Director-General
Authors	Flodgren GM, *Senior Researcher*, Vestrheim DF, Senior *Medical Officer*, Brurberg KG, *Head of Department*; *Norwegian Institute of Public Health*
ISBN	978-82-8406-097-2
Memo	May – 2020
Publication type	Rapid review
Number of pages	24
Commissioned by	Folkehelseinstituttet / Norwegian Institute of Public Health
Citation	Flodgren GM, Vestrheim DF, Brurberg KG. COVID-19: Risk factors associated with disease severity – a rapid review, 2nd update. [Covid-19 og risikofaktorer for alvorlig sykdom - en hurtigoversikt, andre oppdatering. Hurtigoversikt 2020] Oslo: Norwegian Institute of Public Health, 2020.

Key messages

This rapid review is an update of a version published 14th of April, 2020 (1). In this review update we excluded studies that only reported results from univariate analyses, and studies with small sample sizes (<400 participants).

The findings are based on rapid searches in EndNote database for the Norwegian Institute of Public Health's systematic and living map on COVID-19 evidence.. One researcher screened the search, selected studies for inlusion and synthesised the results. Two other researchers assisted with summarising the results in text, and provided other helpful input during the review process. In the current situation, there is 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 11 studies that reported results from multivariate analyses of age and other demographic risk factors. We excluded risk factors that constituted laboratory findings, vital sign or symptoms of COVID-19. Four studies were from the USA, three from China, two from the UK, one from Iran and one from Brazil. Four of the studies were in press or published in international peer reviewed journals, and seven studies were unpublished pre-prints not subjected to peer review. All but one study were retrospective. The median number of participants in the included studies was 1,580 (range: 442 to 17,425,445).

Meta-analysis was not feasible, and the main results of this rapid review are therefore presented narratively. Risk factors associated with (i) hospitalisation, (ii) severe/critical disease, and (iii) death due to COVID-19 are reported separately below:

Risk factors for hospitalisation due to severe COVID-19

Two unpublished studies reported increased risk of hospitalisation due to COVID-19 with older age, but mixed results for gender and co-morbidity (i.e. hypertension). One of the studies reported significant associations for South-Asian race, high BMI, and many other comorbidities, while the other, smaller study, did not include these outcomes.

Risk factors for developing more severe or critical COVID-19

Results from four studies suggest that age is an important risk factor for developing more severe or critical COVID-19. The results for gender and race/ethnicity were mixed. Most studies provided some support for comorbidity as an important risk factor for severity of disease, but the number and type of comorbidities included in the analyses varied across studies. Two studies identified BMI as an important risk factor for severity of disease, while the other three did not include BMI in their analyses.

Risk factors for death due to COVID-19

Evidence from eight studies suggest that age play a significant role in mortality due to COVID-19. The results for male gender were mixed, but in saying this, it should be noted that two of the largest included studies both reported significant associations between male sex and death. One of these studies also reported significant associations for race/ethnicity in a UK population and deprivation (IMD score), while a smaller study, also from the UK, reported no association for either. Results further indicate that comorbidity may be an important risk factor for COVID-19 mortality, but again the number and type of co-morbidities included in the analyses varied across studies. The evidence for smoking as a risk factor was inclusive.

Conclusion

In conclusion, age stands out as the predominant individual risk factor for hospitalisation, severe disease, and death due to COVID-19. Obesity (BMI>30), male gender and comorbidities are also factors that appear to be associated with increased risk. Race/ethnicity and deprivation may contribute additional risk, but results from different studies point in different directions. Results for smoking habits and use of ACE inhibitors and ARBs are also inconclusive regarding their importance for serious progress and death due to COVID-19.

We did not perform a formal quality assessment of included studies, nor did we grade the certainty of evidence, why the results from this rapid review should be interpreted with caution. In addition, it should be noted that only associations are reported in the included studies, why cause and effect relationships cannot be confirmed or refuted.

Hovedbudskap (Norwegian)

Denne hurtigoppsummeringen er en oppdatering av en tidligere versjon, publisert 14 april, 2020 (1). I denne oppdaterte versjonen ekskluderte vi studier som kun rapporterte univariate analyser, og studier med færre enn 400 deltakere på grunn av begrenset statistisk styrke.

Resultatene som presenteres i dette notatet er basert på søk i EndNotedatabasen for Folkehelseinstituttets Levende kart over covid-19-forskning. Én forsker gjennomgikk søkeresultater, selekterte studier og syntetiserte resultatene i tabeller. To andre forskere hjalp til med å oppsummere resultatene i tekst og fortolke resultater. I den nåværende situasjonen er det et presserende behov for å identifisere de viktigste bevisene raskt, så vi valgte denne raske tilnærmingen til tross for en iboende risiko for å overse viktige data eller gjøre feilvurderinger.

Vi inkluderte 11 studier med flervariabelanalyser av alder og andre demografiske risikofaktorer for covid-19. Vi oppsummerte ikke laboratoriefunn, vitale tegn eller symptomer på covid-19. Fire studier var fra USA, tre fra Kina, to fra Storbritannia, en fra Iran og en fra Brasil. Fire av studiene var til trykking eller allerede publisert i internasjonale fagfellevurderte tidsskrift. Sju studier var tidlige versjoner av artikler som ikke hadde gjennomgått fagfellevurdering. Alle unntatt én studie var retrospektive analyser. Median antall deltakere i de inkluderte studiene var 1.580, med range fra 442 til 17.425.445.

Vi vurderte det ikke som hensiktsmessig å lage metaanalyser, og hovedresultatene i denne hurtigoversikten presenteres derfor narrativt. Risikofaktorer forbundet med (i) sykehusinnleggelse, (ii) alvorlig / kritisk sykdom og (iii) død på grunn av covid-19 rapporteres separat.

Risiko for sykehusinnleggelse på grunn av covid-19

To upubliserte studier rapporterte at høyere risiko for sykehusinnleggelse var assosiert med økende alder, men resultatene var blandet for kjønn og høyt blodtrykk. Én av studien rapporterte en assosiasjon mellom sør-asiatisk opprinnelse, høy BMI og flere andre komorbiditeter, mens den andre studien ikke undersøkte disse risikofaktorene.

Risiko for alvorlige eller kritiske sykdomsforløp ved covid-19

Fire studier viser at høy alder øker risiko for alvorlige eller kritiske sykdomsforløp. Resultatene for kjønn og etnisitet/rase var inkonsistente. De fleste studiene antydet at komorbiditet øker risiko for alvorlige sykdomsforløp, men hvilke komorbiditeter som var inkludert i analysene varierte mellom studiene. De to studiene som inkluderte BMI i sine analyser, konkluderte med at høy BMI er assosiert med mer alvorlig sykdom.

Risiko for død ved covid-19

Åtte studier antyder sterk sammenheng mellom høy alder og risiko for å dø av covid-19. Studiene rapporterte ulike resultater for spørsmålet om menn har høyere risiko enn kvinner, og to av de største studiene konkluderte med at risiko for død er høyere blant menn. En av disse studiene rapporterte en tydelig sammenheng mellom risiko for død og etnisitet/rase i en britisk befolkning (svart og asiatisk rase) og fattigdom (IMD-poengsum), mens en britisk studie med færre deltakere ikke fant noen slik sammenheng. Komorbiditet ser ut til å være en viktig risikofaktor for covid-19-relatert død, men det var stor variasjon mellom hvilke komorbiditeter som ble undersøkt i de ulike studiene. Dokumentasjonen er ikke entydig med tanke på sammenhengen mellom røykevaner og risiko for å dø.

Konklusjon

Høy alder peker seg ut den dominerende risikofaktoren for sykehusinnleggelse, alvorlig sykdom og død på grunn av covid-19. Fedme (BMI >30), kjønn og komorbiditet ser også ut til å være assosiert med høyere risiko. Etnisitet og fattigdomsscore kan være assosiert med forhøyet risiko, men ulike studier peker i ulike retninger. Røykevaner samt bruk av ACE hemmer/ARB viser ingen tydelig sammenheng med risiko for alvorlig infeksjon og død grunnet covid-19.

Vi vurderte ikke kvaliteten til de inkluderte studiene, og vi vurderte heller ikke kvaliteten til dokumentasjonen. Resultatene fra denne hurtigoversikten må derfor tolkes med varsomhet. Det inkluderte studiene påviser assosiasjoner og sammenhenger, men kan ikke benyttes til å bekrefte eller avkrefte årsaks- eller virkningsforhold.

Contents

Problem statement

In connection with the ongoing COVID-19 outbreak, it is important to gather information about which patient groups are most at risk. 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 14th of April 2020 (1).

Method

Searches

To explore which risk factors that best predict severity of disease, and death due to COVID-19, we searched for studies where these relationships were analysed using multivariate analyses, i.e. where age can be controlled for to investigate the effect of other explanatory variables, and vice versa.

Research librarian Elisabet Hafstad conducted a search in the EndNote database of the Norwegian Institute of Public Health's systematic and living map on COVID-19 evidence[1], using the terms "regression" or "multivariate" or "multi-variate".

The database was last updated May 12th by searching the May 11th version of the Stephen B. Thacker CDC Library's collection of COVID-19 research articles. Information specialist Martha Knuth at the Centers for Disease Control and Prevention (CDC) search 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 methods used are detailed on their website. https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html

Study selection

We included publications assessing the importance of various demographic risk factors on the risk of COVID-19 related hospitalisation and severe disease. The factors that were examined were age, sex, gender, race/ethnicity, deprivation, body mass index (BMI), underlying comorbidities, but also, smoking habits, and medicine use were also considered. Clinical and laboratory-based risk factors were not included in this report. In this second update of the report we excluded studies with less than 400 participants due to lack of power.

[1] https://www.fhi.no/en/qk/systematic-reviews-hta/map/

Only studies where the relative importance of various risk factors was assessed using multivariate statistical models, were included. We excluded systematic reviews and other studies assessing risk factors in univariate analysis.

Review process

One researcher reviewed the search results, selected studies for inclusion, and extracted and summarised data/results from included studies in tables. Two other researchers assisted with summarising the results in text, and provided various other input on the report.

This rapid review does not include a formal quality assessment of included papers, nor does it include a grading of the certainty of evidence. The results should therefore be interpreted with caution.

We have chosen this approach as it has been imperative to obtain the research results quickly, even though it is associated with a certain risk of overlooking important documentation and that we may make errors along the way.

Peer review

Siri Laura Feruglio, Kirsten Gravningen (both Chief Medical Officers, Norwegian Institute of Public Health), and Helena Eide (MD, Norwegian Institute of Public Health) briefly reviewed the draft before publication.

Results

We included 11 studies that reported results from multivariate analyses of age and other demographic risk factors (e.g. gender, underlying comorbidities, race/ethnicity, smoking, medicine use)(2-11). Only one of the included studies were also included in the previous version of this rapid review (7). Four studies were from the USA (3, 4, 7, 12), three from China (2, 5, 11), two from the UK (8, 10), one study was from Iran (6) and one from Brazil (9). Four of the studies were in press or published in international peer reviewed journals (2, 5, 6, 12), and the remaining seven studies were unpublished pre-prints not subjected to peer review. All but one study (3) were retrospective. The median number of participants in the included studies was 1,580 (range: 442 to 17,425,445).

We distinguish between studies that explore risk factors associated with

(i) need for hospitalisation due to severe COVID-19 (N=2),
(ii) development of more severe /critical COVID-19 (N=4), and
(iii) death due to COVID-19 (N=8)

Risk factors for hospitalisation due to severe COVID-19

Brief summary: We included two unpublished preprints for this comparison (7, 9) (See Table 1). Both studies reported that older age was significantly associated with hospitalisation, but mixed results for gender and hypertension as risk factors for hospitalisation due to COVID-19. The larger of the studies (N=4,103) reported in, addition to the very strong association for older age, also significant associations for South-Asian race, BMI, and other comorbidities (7). The smaller study (N=1,464) these other factors in the analysis (9) (See Table 1). Median age was only 39 years in this study, with 25 percent of the participants being younger than 39 years (9).

Petrilli and co-workers followed a cohort consisting of 4,103 patients with COVID-19 (Median age: 52 (IQR: 36 to 65)), and explored characteristics of patients admitted to hospital using multivariable logistic regression (and factors selected based on testing for clinical significance). They found that the risk of hospitalisation increased with age: Compared to patients between 19 and 44 years old, the odds ratio (OR) was 4.17 (95% CI 3.35 to 5.2) for people between 55 and 64, 10.91 (95% CI 8.35 to 14.34) for people between 65 and 74, and 66.79 (44.73-102.62) for people aged 75 or

older. High body mass index (BMI), heart failure, chronic kidney disease, diabetes and male gender were identified as independent predictors of hospitalisation.

Souza et al used multivariate logistic regression analysis to explore associations between demographics, symptoms, and hospitalisation in a Brazilian cohort with COVID-19. The study included 1,468 patients with a median age of 39 years (IQR: 30 to 53). Twenty-five percent of the patients were younger than 39 years. Moreover, 147 of the patients were in need of hospitalisation, and 23 needed mechanical ventilation. The authors did not find a clear association between age or gender and hospitalisation, but cardiovascular disease/hypertension were associated with increased risk (Table 1). The severity of COVID-19 cases was categorised according to the WHO interim guidance.

Table 1 Studies assessing risk factors predicting hospitalisation due to COVID-19 (N=3)

Reference Country	Participants	Outcome	Factors included in multivariate model	Odds ratio (95% CI)
Petrilli 2020 (7) Retrospective USA medRxiv	N=4,103 One health system Median age, years (IQR): 52 (36 to 65) N=1,999 hospitalised; N=2,114 non-hospitalised	Hospitalisation	**Age ≥75*** **Age (65-74)*** **Male sex** African American** **Asian**** Cancer Coronary artery disease **Chronic kidney disease** **Diabetes** **Heart failure** **Hyperlipidaemia** Hypertension **BMI 30-40** **BMI>40** Pulmonary disease: **Smoke***	**66.8 (44.7 – 102.6)** **10.91 (8.35-14.34)** **2.80 (2.38-3.30)** 0.88 (0.69-1.11) **1.44 (1.04-1.98)** 1.24 (0.81-1.93) 0.88 (0.57-1.40) **3.07 (1.78-5.52)** **2.81 (2.12-3.72)** **4.29 (1.89-11.18)** **0.67 (0.51-0.87)** 1.23 (0.97-1.57) **4.26 (3.5-5.2)** **6.20 (4.21-9.25)** 1.33 (0.96-1.84) **0.71 (0.57-0.87)**
Souza 2020 (9) Retrospective Brazil medRxiv	N=1,468; Nationwide cohort Median age, years (IQR): 39 years (30 to 53) 147/1,408 hospitalised	Hospitalisation	**Age (per 1-year increase)** Male sex: **CVD/Hypertension:** Clinical symptoms	**1.04 (1.02-1.05)** 0.96 (0.63 to 1.47) **3.41 (1.97-5.87)**

*Reference category 19-44 years old; **Reference category white; ***Current or former smoker:
BMI=Body mass index, COPD= Chronic obstructive pulmonary disease

Risk factors for more severe or critical COVID-19

Brief summary: We included four studies for this comparison of which three were unpublished preprints (4, 5, 7, 11) (see Table 2). Results from all four studies indicate that age is an important risk factor for developing more severe or critical COVID-19(4, 5, 7, 11). The results for gender were mixed with one study reporting that males had significantly increased risk to develop severe COVID-19 (4), while two other studies reported no association (7, 11). The results on race/ethnicity were also mixed, with one study reporting that Black people (but not Hispanics) were more likely to suffer more severe disease than white people (4), while one study reported that people of South-Asian race were at greater risk, but not Black people (7). All studies reported significant associations between at least one comorbidity (range 1-4) and severity of COVID-19, but the number and type of comorbidities included in the analyses varied across studies. Two studies that included BMI in their analysis reported greater risk for people with high BMI to develop more severe or critical disease (4, 7). One study reported that use of ACE inhibitors and/or ARBs increased the risk for more severe disease (13), and one study reported no associations (4). One study reported no increased risk for smokers (7).

Ebinger et al. assessed possible associations between demographics, comorbidities, medicine use and severity of COVID-19 using multivariate linear regression (significant factors for this analysis were selected from an age and sex adjusted model) (4). Illness severity was defined by the level of required care: (i) severe illness=need for hospital admission; (ii) critical illness=need for intensive care; (iii) respiratory failure=need for intubation. The results of the study, which included 442 New Yorkers with confirmed COVID-19, suggest that those who required higher levels of care were more likely to be older, male, Afro-Americans, obese, with diabetes, and with a higher comorbidity index. The authors reported no associations with prior myocardial infarction or heart failure, chronic obstructive pulmonary disease (COPD) or asthma, Hispanic race, or use of ACE inhibitors or ARBs.

Li and co-workers retrospectively enrolled 548 patients admitted to a Chinese hospital due to COVID-19, of whom 269 had severe disease (5). The authors used multivariable binary logistic regression analysis to explore the association between risk factors and severity of disease. Age and hypertension were significantly associated with severe COVID-19. Comorbidities were not included in the multivariate analysis.

Petrilli and co-workers, studied predictors of critical disease, i.e. care in the intensive care unit, use of mechanical ventilation, discharge to hospice, or death, among COVID-19 cases admitted to hospital (7). Their findings suggest that some factors that seem to predict need for hospitalisation, do not seem to predict critical COVID-19 (or death). Only age and BMI remained statistically significant risk factors for critical disease or death.

Zhang et al used a multivariable risk prediction model to study the associations between age, sex, comorbidities and poor outcome (composite outcome of ICU admission or death) due to COVID-19 in a Chinese cohort (N=775)(11). The authors reported significant associations with age, male sex, hypertension, chronic pulmonary disease, heart disease, immunocompromising disease and poor outcome of COVID-19.

Table 2 Studies assessing factors predicting severe or critical COVID-19 (N=4)

Reference	Participants	Outcome	Factors included in multivariate model	Odds ratio (95% CI)
Ebinger 2020 (4) Retrospective USA medRxiv	N=442; one medical centre and one hospital Mean age, years (SD):52.7 (19.7) 228 not admitted; 157 admitted to non-ICU, 77 admitted to ICU	Severity of COVID-19	**Age (per 10 years increase)** **Male sex** **African-American** Hispanic **BMI (>30)** Hypertension **Diabetes** **Co-morbidity index (per SD)** Prior MI or heart failure COPD or asthma ACE inhibitor use ARB use	**1.49 (1.30-1.70)** **2.01 (1.34-3.04)** **2.13 (1.19-3.83)** 1.39 (0.79-2.45) **1.95 (1.11-3.42)** 1.19 (0.71-1.99) **1.77 (1.03-3.03)** **1.77 (1.37-2.28)** 0.56 (0.27-1.18) 0.76 (0.44-1.31) 0.48 (0.22-1.04) 1.05 (0.54-2.06)
Li 2020 (5) Retrospective study China In press: J Allergy Clin immunology	N=548; 1 hospital Median age, uears (IQR):69 (48 to 69) 269 severe cases at admission	Severity of COVID-19	**Age (>65 years)** **Hypertension** Laboratory findings	**2.2 (1.5-3.5)** **2.0 (1.3-3.2)**
Petrilli 2020 (7) Retrospective USA medRxiv	N=1,582; one health system 932 non-critical and discharged; 650 critical cases	Critical illness[&]	**Age (65-74)** **Age (≥75)** Male sex: **African American*** **Asian*** Cancer: Coronary artery disease **Chronic kidney disease** Diabetes Heart failure: Hyperlipidaemia: Hypertension: **BMI (30-40)** **BMI (> 40)** Pulmonary disease Smoke**	**1.88 (1.20-2.95)** **2.57 (1.62-4.11)** 0.99 (0.74-1.33) **0.58 (0.39-0.87)** **1.91 (1.09-3.37)** 1.14 (0.67-1.91) 0.89 (0.55-1.41) **0.51 (0.29-0.89)** 1.14 (0.83-1.58) 1.31 (0.73-2.34) 0.96 (0.68-1.37) 0.95 (0.68-1.33) **1.38 (1.03-1.85)** **1.73 (1.03-2.90)** 1.21 (0.79-1.86) 0.89 (0.65-1.21)
Zhang 2020 (11) Retrospective China (Scotland) medRxiv	N=775 adults; 2 hospitals Median age, years (IQR):61 (50 to 68) 75 (9.3%)had poor outcomes	Poor outcome (ICU admission or mortality):	**Age (per year increase)** Male sex **Chronic lung disease** Diabetes **Immunocompromised** Malignancy **Hypertension** **Heart disease** Chronic renal disease Laboratory & symptoms	**1.05 (1.02-1.07)** 1.23 (0.72-2.09) **3.42 (1.61-7.25)** 1.00 (0.50-2.01) **4.19 (1.05-16.75)** 1.00 (0.25-3.99) **1.94 (1.11-3.39)** **2.10 (1.08-4.08)** 2.70 (0.90-8.06)

*Reference category white; **Current or former smoker:

Risk factors predicting of COVID-19 mortality

Brief summary: We included eight studies for this comparison (2, 3, 5, 6, 8, 10-12) (See table 3). High age was in all studies identified as an independent risk factor for death due to COVID-19. Four studies, including two large studies reported that males were more likely to suffer death due to COVID-19 than women (5, 6, 10, 12) , while three studies reported no association (3, 8, 11). Seven studies reported significant associations between various co-morbidities and death, while one study did not include comorbidities in the analyses (5). One large study reported significant associations between deprivation scores and death, and that Black and Asian people were more likely to suffer death from COVID-19 than white people (10). One study reported higher risk for Asians to die of COVID-19 than white people, but did not report higher risk for Black people (8). Current smoking was reported to be associated with a higher COVID-19 mortality in one large study(12), and associated with lower mortality in another large study(10). In the latter study was being a former smoker significantly associated with COVID-19 mortality (10).

Chen and co -workers published a retrospective study of 1,590 hospitalised patients in China (2). Fifty of the 1,590 patients died. The authors analysed the predictive value of various demographic, clinical (and laboratory factors) using a Cox proportional hazard model, and concluded that age, coronary heart disease, cerebrovascular disease, (dyspnea, procalcitonin levels and aspartate aminotransferase levels) were independent risk factors for death (2).

Cummings and co-workers conducted a prospective study which included 1,150 patient hospitalised with COVID-19 in New York (3). Eighty-six patient died, and risk factors predicting deaths were analysed using Cox proportional hazard models. Age, hypertension and COPD were found to be independent factors associated with higher risk of death. No associations were found for male sex, chronic kidney disease, diabetes mellitus, or BMI. Some of the risk estimates were imprecise, i.e. associated with broad confidence intervals (3).

Li and co-workers retrospectively enrolled 548 patients who had been admitted to a Chinese hospital due to COVID-19 (5). Eighty-seven patients died, and risk factors predicting deaths were analysed using Cox proportional hazard models. Nine factors were selected for inclusion in a Cox model based on findings in the univariate analysis and clinical importance. The model included sex and age, but no co-morbidities. Both male sex and age were significant predictors (5).

Mehra and co-workers used a multivariate linear regression model to study risk factors for in-hospital mortality among 8,910 COCID-19 cases admitted to 169 hospitals in Asia, Europe, and North America, focusing on cardiovascular disease (12). Of the cases admitted, 515 died. The authors found a significant association with chronic

artery disease, heart failure, cardiac arrhythmia, while no association to use of ACE inhibitors, or ARBs. In addition, they found a significant association with COPD, current smoking and age > 65 years. Females were reported to be less likely to die of COVID-19 than males, and use of statins showed an inverse correlation with death (12).

Nikpouraghdam and colleagues studied the associations between age, gender and underlying disease with fatal outcome of COVID-19 in Iran (6). They described an increasing fatality rate by age. In a multi-variable analysis the authors found age, male gender and underlying disease to be associated with fatal outcome. The risk associated with specific underlying diseases was not assessed in the model. However, the most frequent underlying diseases were diabetes, chronic respiratory disease, hypertension and chronic vascular disease (6).

In a retrospective cohort study, Sapey et al. used the Cox proportional hazards model to study the association between ethnicity and mortality in an UK-setting (8). Among the 2,217 included cases (611 died), the majority were White, followed by South Asian ethnicity (18.5 %). In this setting, South Asian ethnicity (but not Black race, which constituted only 6.4%) was associated with a higher risk of death (aHR 1.66 [95%CI: 1.32-2.10]). Age and comorbidity was also found to be associated with mortality in this study. Male sex and deprivation scores were not found to be associated with death(8).

Williamson and colleagues studied the associations between demographic variables and death of COVID-19 in a very large UK cohort using a Cox proportional hazards model (N=17,425,445,) using linked electronic health records data from the COVID-19 patient notification system (CPNS) (10). Their findings showed significant associations between male gender, older age, deprivation scores, Black or Asian race and increased COVID-19 mortality. They studied associations with several comorbidities, including DM and asthma (and several additional comorbidities). They found a higher risk for uncontrolled DM than controlled DM, as defined by HbA1c level (aHR 2.36 and 1.50, respectively). The risk associated with asthma with recent use of oral corticosteroids was slightly higher than asthma without such use, but both risks were lower than that of other respiratory diseases (aHR 1.78). Haematological malignancy diagnosed in the previous year was associated with a higher risk than malignancy diagnosed five or more years ago (aHR 3.52 and 1.88, respectively). Hypertension was in this study not found to be associated with mortality. The authors also reported a slightly lower risk of death for current smokers, but a higher risk for former smokers (10).

Zhang et al studied the associations between age, sex, comorbidities and death due to COVID-19 in a Chinese cohort (N=775)(11). They reported significant associations

with COVID-19 mortality for age and chronic lung disease. Many of the assessed comorbidities showed no association with death after adjusting for age (11).

Table 3 Studies assessing risk factors predicting death due to COVID-19 (N=8)

Reference	No of participants	Outcome	Factors included in multivariate model	
Chen 2020 (2) Retrospective nationwide cohort. China In press; Chest	N=1,590; 575 hospitals Median age, years (IQR)fatal case):69(53 to 84) years	Mortality; N=50 died		*Hazard ratio (95% CI)*
			Age (65-75)	**3.43 (1.24-9.5)**
			Age (>75)	**7.86 (2.44-25.35)**
			CHD	**4.28 (1.14-16.13)**
			CBVD	**3.1 (1.07-8.94)**
Cummings 2020 (3) Prospective USA medRxiv	N=1,150; 2 hospitals Median age, years (IQR): 62 (51 to 72) years 257 critically ill	Mortality; N=86 died		*Hazard ratio (95% CI)*
			Age (per year increase)	**1.04 (1.02-1.06)**
			Male sex	1.35 (0.80-2.25)
			Hypertension	**2.12 (1.13-3.99)**
			COPD	**4.22 (2.02-8.84)**
			Chronic kidney disease	1.46 (0.81-2.13)
			Diabetes	1.28 (0.77-2.13)
			BMI (≥35)	0.94 (0.55-1.77)
			Laboratory factors	
Li 2020 (5) Retrospective China In press: J Allergy Clin immunology	N=548; 1 hospital Median age, years (IQR):69 (48 to 69) 269 (49.1%) severe cases at admission	Mortality N=87 died		*Hazard ratio (95% CI)*
			Age (>65)	**1.7 (1.1.-2.7)**
			Male sex	**1.7 (1.0-2.8)**
Mehra 2020 (12) Retrospective USA New England Journal of Medicine	N=8,910; 169 hospitals in Asia, Europe, and North America Mean age, years(SD):49 (16)	Mortality (in hospital) N=515 died		*Odds ratio (95% CI)*
			Age (>65)	**1.93 (1.60-2.41)**
			Female sex	**0.79 (0.65-0.98)**
			Coronary artery disease	**2.70 (2.08-3.51)**
			Heart failure	**2.48 (1.62-3.79)**
			Cardiac arrhythmia	**1.95 (1.33-2.86)**
			COPD	**2.96 (2.00-4.40)**
			Smoking (current)	**1.79 (1.29-2.47)**
			ACE inhibitor use	**0.33 (0.20-0.54)**
			ARB use	1.23 (0.87-1.74)
			Statin use	**0.35 (0.24-0.52)**

Nikpouraghdam 2020 (6) Retrospective Iran Journal pre-proof: J of Clinical Virology	N=2,968; one hospital Median age, years (IQR):56 (46 to 65)	Mortality N=239 died	**Age (per year increase)** **Male sex** **Co-morbidities***	*Odds ratio (95% CI)* **1.05 (1.04 -1.06)** **1.45 (1.08-1.96)** **1.53 (1.04-2.24)**
Sapey 2020 (8) Retrospective UK medRxiv	N=2,217; One hospital Median age, years (IQR):73 (58 to 84)	Mortality (in hospital or post-discharge); N=611 died	*HR (95% CI)* **Age** Male sex **Asian** Black race IMD (score 4) IMD (score 5) **1-2 comorbidities** **>2 comorbidities**	*Hazard ratio (95% CI)* **2.80 (1.92-4.09)** 1.16 (0.94-1.92) **1.66* (1.32-2.10)** 1.12 (0.78-1.63) 0.94 (0.71-1.23) 1.10 (0.77-1.82) **2.15 (1.50-3.09)** **3.0 (2.69-4.31)**
Williamson 2020 (10) Retrospective UK medRxiv	N=17,425,445 adults Electronic health records linked data from the COVID-19 patient notification system (CPNS) for death for hospital in-patients with confirmed COVID-19	Mortality (in hospital); N=5,683 (0.03% of the total cohort)	**Age (60-70):** **Age (70-80):** **Age (>80)** **Male sex** **Black race** **Asian race** **IMD (score 4)** **IMD (score 5)** **Uncontrolled DM** **Severe asthma** **BMI (30-35)** **BMI (35-40)** **BMI (>40)** Hypertension **Chronic heart disease** **Chronic kidney disease** **Smoke (current)** **Smoke (former)**	*Hazard ratio (95% CI)* **2.09 (1.84-2.38)** **4.77 (4.23-5.38)** **12.64 (11.19-14.28)** **1.99 (1.88-2.10)** **1.71 (1.44-2.02)** **1.62 (1.43-1.82)** **1.39 (1.37-1.63)** **1.74(1.60-1.91)** **2.36 (2.18-2.56)** **1.25 (1.08-1.44)** **1.27 (1.18-1.36)** **1.56 (1.41-1.73)** **2.27(1.99-2.58)** 0.95 (0.89-1.01) **1.27 (1.20-1.35)** **1.72 (1.62-1.83)** **0.88 (0.79-0.99)** **1.25 (1.18-1.33)**
Zhang 2020 (11) Retrospective China medRxiv	N=775 adults, 2 hospitals Median age, years (IQR):61 (50 to 68)	Mortality N= 33 died (4.3%)	Age (per year increase) Male sex Chronic lung disease Diabetes Immunocompromised Malignancy Hypertension Heart disease Chronic renal disease Symptoms & laboratory	*Odds Ratio (95% CI)* **1.05 (1.01-1.08)** 1.37 (0.62-3.03) **3.00 (1.07-8.37)** 1.56 (0.60-4.09) 3.97 (0.64-24.65) 1.02 (0.15-7.05) 1.41 (0.62-3.23) 1.97 (0.77-5.02) 3.75 (0.92-15.30)

[&]Care in the intensive care unit, use of mechanical ventilation, discharge to hospice, or death

* Diabetes, hypertension, COPD etc.

BMI=Body mass index, CI=confidence interval, COPD=Chronic obstructive pulmonary disease, IMD= Index of Multiple Deprivation score, PD =pulmonary disease

Discussion and conclusion

We included 11 studies assessing possible risk factors for hospitalisation, severe or critical disease, and death due to COVID-19 (median N=1,580; range: 442 to 17,425,445). We excluded studies with fewer than 400 participants, and studies that only reported results from univariate analyses, since several large studies with multivariate analyses had become available since we published the previous version of this rapid review (April 14th 2020),

In this review update, age stands out as the predominant individual risk factor for severe disease, and death due to COVID-19. Obesity (BMI>30), male gender and comorbidities are all factors that appear to be associated with increased risk. Race/ethnicity and deprivation score may also contribute additional risk. Currently, it is unclear whether smoking is a risk factor for serious progress and death due to COVID-19, as the results were inconsistent in the few studies reporting this outcome. The same goes for use of ACE inhibitors and ARBs.

The evidence base regarding important risk factors for severe COVID-19, or death is much stronger now. However, a majority of the included evidence is still from retrospective cohorts reported in unpublished preprints that have not been subjected to peer review. We did not perform a formal quality assessment of included studies (nor did we grade of the certainty of evidence), why the results from this review should be interpreted with caution. In addition, it should be noted that only associations are reported in the included studies, why cause and effect relationships cannot be confirmed or refuted.

The included studies were heterogeneous in terms of statistical methods used to analyse data, and procedures applied for selection of factors to include in the multivariate model. Some studies used Cox proportional hazard while others used logistic regression models. There was also large variability in the number of factors included in the multivariate model. Some studies only included risk factors based on their significance in univariate analysis, and effect estimates from such studies are not directly comparable studies including a large number of potential factors irrespective of findings from univariate analysis. We also found large variability in the way different factors were categorised, for example was age included as continuous factors

in some model and dichotomised in others. This heterogeneity impairs direct comparison of risk estimates across studies, and meta-analysis was therefore not feasible.

As mentioned above, age stands out as the predominant single risk factor for severe disease, and death due to COVID-19. This finding is consistent across nine of the 11 included studies, before and after adjustment for other risk factors. The two studies that did not show any significant associations with age were different from the other studies in terms of population (9, 13). In one of the studies, the cohort was comparatively younger than other cohorts, with 25 percent of the included participants being younger than 39 years old (9). The other study included only US veterans , and their population therefore had a narrower age span, and a very high proportion of men (13). This may be one explanation to the discrepancy in the results regarding age as a risk factors for hospitalisation.

The included evidence indicates that male gender, obesity (high BMI) male gender, other comorbidities, and race/ethnicity may contribute additional risk. However, not all studies included these outcomes in the analysis, and the results are not consistent for all outcomes. While results for obesity consistently suggest significant associations with severe COVID-19 and/or death, in the studies reporting this outcome, this is not the case for the other co-morbidities reported. A handful of studies, of which some were large, suggests that males are at greater risk than females for severe disease and death due to COVID-19, but not all studies showed a significant association. Evidence from a very large study suggest that race/ethnicity (and deprivation score), may be factors that need to be taken into account when developing interventions to prevent severe disease and death due to COVID-19, but the results were not consistent across the few studies reporting these outcomes. A majority of the included studies also suggest that co-morbidities may play a role as independent risk factors for COVID-19 mortality. The results however point in different directions, which in part may be due to differences in the number and type of comorbidities taken into account in the analysis, and differences in the methods used in the included studies. The evidence is not clear regarding whether smoking, or use of ACE inhibitors or ARBs increases the risk of severe disease and dying due to COVID-19, as few studies reported this outcomes, and the results were inconsistent.

In conclusion: Based on the data at hand, the elderly are clearly the main group at risk of severe illness, and death if infected by COVID-19. Males, people who are obese, with non-white ethnicity living in deprived areas, and people with other comorbidities, are groups that also appear to be at increased risk.

List of references

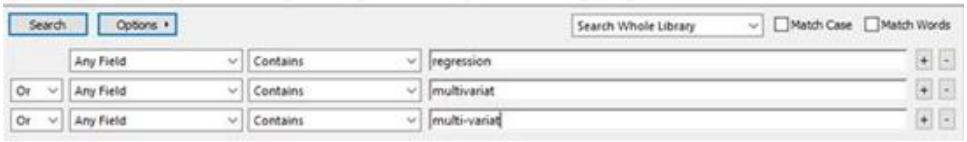
1. Brurberg K. Covid-19: Sammenheng mellom alder, komorbiditet og sykdomsalvorlighet – en hurtigoversikt: 1st update. Oslo, Norway: Norwegian Institute of Public Health (Folkehelseinstituttet); 2020.
2. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest. 2020.
3. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. medRxiv. 2020:2020.04.15.20067157.
4. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-Existing Characteristics Associated with Covid-19 Illness Severity. medRxiv. 2020:2020.04.29.20084533.
5. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology. 2020.
6. Nikpouraghdam M, Jalali Farahani A, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. Journal of clinical virology : official publication of Pan American Society for Clinical Virology. 2020;127:104378.
7. Petrilli CM JS, Yang J, Rajagopalan H, Donnell LF, Chernyak Y, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. medRxiv 2020:2020040820057794. 2020.
8. Sapey E, Gallier S, Mainey C, Nightingale P, McNulty D, Crothers H, et al. Ethnicity and risk of death in patients hospitalised for COVID-19 infection: an observational cohort study in an urban catchment area. medRxiv. 2020:2020.05.05.20092296.
9. Souza WMd, Buss LF, da Silva Candido D, Carrera JP, Li S, Zarebski A, et al. Epidemiological and clinical characteristics of the early phase of the COVID-19 epidemic in Brazil. medRxiv. 2020:2020.04.25.20077396.

10. Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. 2020:2020.05.06.20092999.
11. Zhang H, Shi T, Wu X, Zhang X, Wang K, Bean D, et al. Risk prediction for poor outcome and death in hospital in-patients with COVID-19: derivation in Wuhan, China and external validation in London, UK. medRxiv. 2020:2020.04.28.20082222.
12. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. 2020.
13. Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT, Skanderson M, et al. Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years. medRxiv. 2020:2020.04.09.20059964.

Appendix

Search strategy

We searched the EndNote database for NIPH 12th May for records added since the 1st update of the memo, i.e. 14th April, containing either of the words regression, multi-variate or multi-variate. We found 270 unique references using this method.



Our COVID-19 EndNote database contains records mainly retrieved from searches performed by Martha Knuth at Centers for Disease Control and Prevention (CDC). Below is the CDC search strategy for MEDLINE:

(coronavir* OR corona virus* OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR Coronavirus Infections/ OR Coronavirus/ OR betacoronavirus/

This strategy is adapted to the interfaces of the other 20+ databases searched. For a complete overview of databases and search strategies, go to the COVID-19 Research Articles Downloadable Database website.
https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html

Published by the Norwegian Institute of Public Health
May 2020
P. O. Box 222 Skøyen
NO-0213 Oslo
Tel: +47 21 07 70 00
www.fhi.no