

# memo

## COVID-19-EPIDEMIC :

COVID-19: The relationship  
between age, comorbidity  
and disease severity  
– a rapid review, 1<sup>st</sup> update

**Title** COVID-19: The relationship between age, comorbidity and disease severity – a rapid review, 1<sup>st</sup> update

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# Key messages

This rapid review is an update of a version published March 26<sup>th</sup>, 2020 (1).

The findings in this memo are based on rapid searches in electronic databases, as well as manual searches on websites of health authorities in selected countries. Two researchers shared tasks related to study selection and synthesis of results. 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.

## **Association between single risk factors and severity of disease (univariate analyses)**

A consistent finding from analyses of single risk factors is that age is strongly associated with severity COVID-19. Other risk factors also seem to be associated with severe outcomes for COVID-19 patients, but these findings are difficult to interpret since most of these risk factors are also strongly associated with age. We therefore emphasize findings from multivariate analyses that take several risk factors, including age, into account simultaneously.

## **Multivariate analyses of age and comorbidities as predictors of disease severity**

We conclude that age stands out as the predominant single risk factor for severe disease.

The data indicates that comorbidities and other conditions may contribute additional risk, but this finding is less convincing than for age. Based on the findings from the largest study, patients with heart failure or a BMI>30 may be at particular risk, but this finding needs confirmation in future studies.

Based on the data at hand, the elderly are clearly the main group at risk of severe illness, among COVID-19 patients.

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# Hovedbudskap (Norwegian)

Denne hurtigoppsummeringen er en oppdatering av en tidligere versjon, publisert 26. mars, 2020 (1).

Resultatene i dette notatet er basert på raske søk i elektroniske databaser, og søk på nettsider til helsemyndigheter i utvalgte land. To forskere delte på oppgavene med å velge ut og sammenstille resultatene. Vi valgte denne framgangsmåten fordi det var viktig å få fram forskningsresultatene raskt, selv om det innebærer risiko for at vi kan ha oversett viktig dokumentasjon og kan ha gjort feilvurderinger underveis.

## **Sammenheng mellom enkelte risikofaktorer og sykdomsalvorlighet (univariate analyser)**

Analyser av enkeltfaktorer viser gjennomgående at det er en sterk sammenheng mellom alder og risiko for alvorlig forløp av covid-19. Andre risikofaktorer synes også være assosiert med alvorlige utfall for covid-19-pasienter, men disse resultatene er vanskelig å fortolke ettersom disse risikofaktorene også er sterkt knyttet til alder. Vi vektlegger derfor resultater fra multivariate analyser, som omfatter flere risikofaktorer inkludert alder, samtidig.

## **Multivariate analyser av alder og andre underliggende faktorer som prediktorer for alvorlig covid-19**

Vår konklusjon er at alder peker seg ut som den dominerende risikofaktoren for alvorlig forløp av covid-19.

Analysene som foreligger tyder også på at underliggende sykdommer og tilstander kan bidra til økt risiko, men disse resultatene er mindre overbevisende enn for alder. Basert på resultatene fra den største studien, kan pasienter med hjertesvikt eller BMI>30 være særlig utsatt, men dette bør bekreftes i flere studier før vi kan konkludere.

Ut fra informasjonen som foreligger, er de eldre den klart viktigste risikograppa for alvorlig sykdomsforløp ved covid-19.

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# 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 developing serious illness, published March 26<sup>th</sup> 2020 (1).

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# Method

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## Searches

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Research librarian Elisabet Hafstad conducted a search in the database of the Norwegian Institute of Public Health's systematic and living map on COVID-19 evidence<sup>1</sup>, using the terms “regression” or “multivariate” or “multi-variate”.

The database was last updated April 14<sup>th</sup> by searching the April 13<sup>th</sup> version of the Stephen B. Thacker CDC Library's collection of COVID-19 research articles (12582 references). The Centers for Disease Control and Prevention (CDC) search a wide range of databases, PubMed, Embase, 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>.

We also ran a supplementary search in the LitCovid-database, using the search string “systematic review” and “risk factors”.

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## Study selection

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We included publications assessing the importance of various demographic risk factors on the risk of COVID-19 related hospitalisation and severe disease. The factors of interest were primarily age, sex and comorbidities. Clinical and laboratory-based risk factors were not assessed in this report. We excluded studies with less than 50 participants due to lack of power.

Our primary interest was to identify studies where the relative importance of various risk factors was assessed using multivariate statistical models, but we also included systematic reviews and key studies assessing risk factors in univariate analysis.

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<sup>1</sup> <https://www.fhi.no/en/qk/systematic-reviews-hta/map/>

Two researchers shared the task of reviewing search results, selecting, assessing and summarising the research results. We only assessed the same studies if we judged it necessary.

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## **Peer review**

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Siri Laura Feruglio and Sara Sofie Viksmoen Watle (both Chief Medical Officers, Norwegian Institute of Public Health), briefly reviewed the draft before publication.

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.



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# Results

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## **Association between single risk factors and severity of disease**

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Multiple studies and systematic reviews report on the association between single risk factors and severity of COVID-19, typically by comparing the age or prevalence of comorbidity among COVID-19 patients with mild disease versus COVID-19 patients with severe disease.

A consistent finding in these univariate analyses is that age is strongly associated with severity of the disease (2-7). Other risk factors, such as diabetes, chronic respiratory disease and cardiovascular disease, also seem to be associated with more severe outcomes for COVID-19 patients (2, 3, 8, 9). However, these findings are difficult to interpret since most of the risk factors are also strongly associated with age. This makes it potentially misleading to assess single risk factors without also considering age.

We therefore emphasize findings from multivariate analyses that take several factors, including age, into account simultaneously.

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## **Multivariate analyses of age and comorbidities as predictors of disease severity**

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To explore which risk factors that best predict severity of the disease, we searched for studies where the relationship between disease severity and risk factors was analysed using multivariate analyses, i.e. where age can be controlled for to investigate the effect of other explanatory variables, and vice versa.

We included twelve studies reporting results from multivariate analyses of age and other demographic risk factors. Three of the included studies were also included in the first version of this rapid review. We distinguish between studies that explore risk factors associated with development of mild versus more severe disease, and studies investigating risk factors that predict critical disease or death.

## Risk factors predicting severe disease

We included six studies for this comparison, five from China and one from the US (Table 1). High age was identified as a risk factor for severe disease in most studies, as were comorbidities.

Most studies were too small to assess the relative importance of different comorbidities, but a study by Petrilli and co-workers contributes valuable data. The authors followed a cohort consisting of 4103 patients with COVID-19, and explored characteristics of patients admitted to hospital. 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 BMI, heart failure, chronic kidney disease, diabetes and male gender were identified as independent predictors of hospitalisation (Table 1).

**Table 1 Studies assessing risk factors predicting more severe disease**

Reference	Outcome	Factors tested	Factors included in multivariate model	
<b>Dong et al (10)</b> N=135 China	Mild vs Severe course	NA <sup>#</sup>	Age Comorbidity	OR 1.04 (1.01-1.97) OR 1.7 (1.1-2.8)
<b>Hu et al (11)</b> N=323 China	Favorable vs. unfavorable <sup>§</sup>	Age, BMI, CVD, diabetes, smok- ing	Age ≥65 Smoking Diabetes	OR 3.55 (1.63-7.73) OR 3.46 (1.18-10.17) OR 3.11 (1.16-8.37)
<b>Huang et al (12)</b> N=125 China	Mild vs severe course	Age, gender, hypertension, diabetes, BMI	Comorbidity	OR 15.7 (1.9-126.6)
<b>Ji et al (13)</b> N=208 China	Stable vs. progressive	Age Comorbidity	Age>60 Comorbidity	HR 3.0 (1.4-6.0) HR 3.9 (1.9-7.9)
<b>Liu et al (14)</b> N=78 China	Improvement vs progression	Age, cancer, COPD, diabetes, HT, gender, smoking	Age≥60 Smoking	OR 8.5 (1.6-44.9) OR 14.3 (1.6-25.0)
<b>Petrilli et al (15)</b> N=4103 US	Need for hospi- talisation	Age Cancer CAD CKD Diabetes Gender Heart failure	Age (65-74) Cancer CAD CKD Diabetes Male Heart failure	OR 10.91 (8.35-14.34) OR 1.24 (0.81-1.93) OR 0.88 (0.57-1.40) OR 3.07 (1.78-5.52) OR 2.81 (2.12-3.72) OR 2.80 (2.38-3.30) OR 4.29 (1.89-11.18)

Hyperlipidaemia	Hyperlipidaemia	OR 0.67 (0.51-0.87)
Hypertension	Hypertension	OR 1.23 (0.97-1.57)
BMI	BMI 30-40	OR 4.26 (3.5-5.2)
	BMI>40	OR 6.20 (4.21-9.25)
PD	PD	OR 1.33 (0.96-1.84)
Smoke	Smoke	OR 0.71 (0.57-0.87)

§ Unfavourable clinical outcome included death, progression from non-severe to severe/critical disease status or severe to critical status, and/or maintenance of severe or critical status.

#Data extracted from English abstract (publication in Chinese)

BMI (Body mass index), CAD (Coronary artery disease), CKD (Chronic kidney disease), COPD (Chronic obstructive pulmonary disease), CVD (Cardiovascular disease), PD (pulmonary disease)

### Risk factors predicting critical disease or death

We included seven studies for this comparison, six studies from China and one from the US. Most studies indicate that higher age also predicts progression to critical disease or death, but the evidence indicating that comorbidities play a role as an independent risk factor is less convincing.

In addition to studying risk factors for hospitalisation, 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 those admitted to hospital. Their findings suggest that some factors that seem to predict need for hospitalisation, do not seem to predict critical disease or death – only age and BMI remained statistically significant risk factors for critical disease or death.

We need to stress that the available data are from few and mostly small studies, so firm conclusions are not warranted.

**Table 2 Studies assessing risk factors predicting critical illness or in-hospital death**

Reference	Outcome	Factors tested	Factors included in multivariate model	
<b>Chen et al (16)</b> N=249 China	Need for intensive care	Age	Age	OR 1.06 (1.00-1.12)
		Gender	Male	OR 3.38 (0.77-14.9)
		Comorbidity	Comorbidity	OR 1.83 (0.50-6.75)
<b>Chen et al (17)</b> N=160 China	Mild vs critical	NA <sup>#</sup>	Heart disease	OR 16.6 (2.4-120.6)
<b>Du et al (18)</b> N=179 China	In-hospital death	Age	Age ≥ 65	OR 3.77 (1.15-17.39)
		Hypertension	CVD	OR 2.46 (0.76-8.04)
		CVD		

<b>Li et al (19)</b> <b>N=128</b> <b>China</b>	In-hospital death	Age, CHD, COPD, diabetes, gen- der, HT, malignancy, liver disease, smoking	Age	OR 1.06 (1.01-1.12)
<b>Liu et al (20)</b> <b>N=340</b> <b>China</b>	In-hospital death	Age Gender Comorbidity	Age Comorbidity	OR 1.05 (P=0.04) OR 3.42 (P=0.02)
<b>Petrilli et al (15)</b> <b>N=1582</b> <b>US</b>	Critical ill- ness <sup>&amp;</sup>	Age Cancer CAD CKD Diabetes Male Heart failure Hyperlipidaemia Hypertension BMI PD Smoke	Age (65-74) Cancer CAD CKD Diabetes Male Heart failure Hyperlipidaemia Hypertension BMI 30-40 BMI > 40 PD Smoke	OR 1.88 (1.20-2.95) OR 1.14 (0.67-1.91) OR 0.89 (0.55-1.41) OR 0.51 (0.29-0.89) OR 1.14 (0.83-1.58) OR 0.99 (0.74-1.33) OR 1.31 (0.73-2.34) OR 0.96 (0.68-1.37) OR 0.95 (0.68-1.33) OR 1.38 (1.03-1.85) OR 1.73 (1.03-2.90) OR 1.21 (0.79-1.86) OR 0.89 (0.65-1.21)
<b>Zhou et al (21)</b> <b>N=191</b> <b>China</b>	In-hospital death	Age, gender, CHD, COPD, dia- betes, HT, smok- ing	Age Heart disease	OR 1.10 (1.03-1.17) OR 2.14 (0.26-17.79)

<sup>&</sup>Care in the intensive care unit, use of mechanical ventilation, discharge to hospice, or death

<sup>#</sup>Data extracted from English abstract (publication in Chinese)

BMI (Body mass index), CAD (Coronary artery disease), CKD (Chronic kidney disease), COPD (Chronic obstructive pulmonary disease), CVD (Cardiovascular disease), HT (hypertension), PD (pulmonary disease)

## Discussion and conclusion

Several new multivariate analyses have become available since we published the previous version of this rapid review, March 26<sup>th</sup> 2020. The evidence base for assessing risk factors for severe COVID-19 is stronger now, but the quality of the data is impaired by small-sampled studies and methodological limitations. Hence, we still need more large and well-conducted studies to draw firm inferences about the relative importance of different risk factors.

There seems to be an abundance of publications reporting on small samples of patients, with simple univariate analyses of risk factors for severe COVID-19. In our view, such studies contribute little to improving our understanding of the importance of various risk factors. We encourage medical journals to refuse publication of additional research papers with small sample sizes, and to require multivariate analysis.

Despite the limitations mentioned above, we can conclude that age stands out as the predominant single risk factor for severe disease. This finding is consistent across all studies, before and after adjustment for other risk factors.

The data indicates that comorbidities, other conditions, and male gender may contribute additional risk, but these findings are less convincing than for age, since 1) data is sparser, 2) results are less consistent, and 3) the risk estimates are less precise. Based on the findings from the largest study (15), patients with heart failure or a BMI>30 may be at particular risk, but this finding needs confirmation in future studies.

Based on the data at hand, the elderly are clearly the main group at risk of severe illness, if infected by COVID-19.

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