

Rapid Review Report

Review Title:	What are the risk factors for severity and death associated with COVID-19?
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Key Findings

- There is a growing body of research related to clinical characteristics and prognostic factors associated with COVID-19-related outcomes.
- The risk of severe COVID-19 infection and mortality increases with advancing age, male sex and presence of comorbid conditions such as diabetes mellitus, hypertension and cardiovascular disease.
- Information is limited about some risk factors such as smoking exposure, racial/ethnic identity that could contribute to better understanding of risk stratification and support early intervention.

Limitations

- Inconsistencies across studies related to operationalization and definition of

- outcomes including COVID 19 severity and disease progression.
- Within meta-analyses there were often multiple studies with overlapping cohorts that contributed to duplication of information.
- Information was often limited about measurement of non-clinical risk factors.
- Heterogeneity across studies with regard to period of observation and duration between symptom onset and admission to hospital.
- Information was limited about important covariates (e.g. smoking, ethnicity) in many studies for multivariable analyses.
- Many studies were available as pre-prints and had not been peer reviewed.
- Retrospective nature of studies precludes causal attribution.

GRADE of Evidence: B - Moderate

A grade of "B" is assigned when further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. The review may include one high quality study and/or several studies with some limitations.

For more information about how this rating was determined, visit https://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=grade

Background/Context

The Coronavirus disease (COVID-19) is a global public health concern that contributes substantially to morbidity and mortality for affected individuals and has social and economic implications for communities. Although work is ongoing to develop effective treatments and a vaccine, a better understanding of the risk factors associated with disease severity and poor outcomes is needed for early intervention to improve prognosis. Models can estimate future needs and demands on the health system and are key tools to inform planning for allocation of limited resources in affected communities but depend on key assumptions and risk estimates.

Purpose

The review was requested to canvass the literature for risk estimates of any risk factors associated with clinical progression of COVID-19 disease or mortality in order to inform critical assumptions of prediction models that are being developed. These models might inform decisions around risk stratification and rationalization of scarce resources.

Review Question(s)

- What are the risk factors for severity and death associated with COVID-19?

Method

The search strategy was developed by a team of medical librarians in collaboration with the modelling group to identify the most relevant concepts and sources of information. The search strategy details can be found in the Appendix. Time and language limits were applied consistent with the available resources. Articles were included if they examined the association between a risk factor (e.g. comorbidity) and either COVID-19 severity or death and reported a quantitative estimate such as odds ratio, relative risk or hazard ratio. It was anticipated that there would be inconsistencies in definition of severity (e.g. mechanical ventilation, ICU admission, Acute Respiratory Distress Syndrome (ARDS) and

death). Studies were excluded that did not explore an outcome of interest (either primary or secondary) and/or provide a risk estimate. As various study designs were allowed, primary studies were only included if they satisfied the criteria and were not already included in a meta-analysis. This reduced overlapping information from the same cohorts. The review was provided within a week of the initial request.

Summary of Evidence

The review identified 35 (23 meta-analyses) studies that reported risk estimates for risk factors that are associated with clinical COVID-19 disease progression including death. Among these studies, there were x systematic reviews and meta-analyses. Most of the studies originated from China likely reflecting the geographic region of earliest identification of the novel coronavirus. An exception is a large recent NHS study from the United Kingdom that explored risk factors for COVID-19 associated death in hospital (Williamson et al., 2020).

Several studies identified an elevated risk of COVID-19 severity and/or mortality associated with older age and/or being male (Biswas et al., 2020; Chen et al., 2020; Deng et al., 2020; Hwang et al., 2020; Jain et al., 2020; Matshushita et al., 2020; Mehra et al., 2020; Nasiri et al., 2020; Parochan et al., 2020; Rahman et al., 2020; Zhao, Li, Zhang et al., 2020; Williamson et al., 2020). Meng and colleagues (2020) examined the relationship between sex and progression of disease among severe COVID-19 patients in a single Chinese center. Compared to women, men had a trend toward a higher risk of mortality and a lower hospital discharge rate. Additionally, older age was associated with poorer prognosis and disease progression (OR = 10.968, 95% CI: 3.005–40.037; ≥80 years vs <59 years). After adjustment for comorbidities, respiratory symptoms and days between illness onset and admission and pathogens, elderly males (defined as >80 years old) were more likely to develop critically ill conditions than younger males (<59 years) [OR = 9.333, 95% CI: 1.62–53.85]. However, for females, the difference was not significant. Adjustment for age and other covariates, also showed that males were still more likely to die (OR = 3.824, 95% CI: 1.28–11.44) than females. The physiological and social changes of aging may account for sex-specific differences but still need to be explored.

Few studies examined other sociodemographic factors than age and sex (Bello-Chavallo et al., 2020; Williamson et al., 2020). Williamson and colleagues found that people from Asian and Black groups (vs White) had a substantially higher risk of death from COVID-19, only partially attributable to comorbidity, deprivation or other risk factors (HR 1.62; 95% CI 1.43-1.82). This is a gap in the literature that is important for planning responses for vulnerable populations that may be further disadvantaged by COVID-19.

In addition to demographic factors, the other major group of risks explored among studies included comorbid conditions. Guan and colleagues (2020) observed that the presence and number of comorbidities was associated with reaching a COVID-19 composite endpoint (admission to ICU, mechanical ventilation or death). In their study, the hazard ratio was 1.79 (95%CI 1.16-2.77) among patients with at least one comorbidity and increased to 2.59 (95%CI 1.61-4.17) among patients with two or more comorbidities. Chen, Yan and colleagues (2020) also found that the presence of any comorbidity increased risk of COVID-associated mortality (OR 2.87, 97% CI 2.5-3.29).

Risk estimates for the presence of specific comorbid conditions and COVID outcomes have been the focus of several systematic reviews and meta-analyses. Huang et al. (2020) reported that diabetes was

associated with composite poor outcome (RR 2.38 [1.88, 3.03], $p < 0.001$; I2: 62%) and its subgroup which comprised of mortality (RR 2.12 [1.44, 3.11], $p < 0.001$; I2: 72%), severe COVID-19 (RR 2.45 [1.79, 3.35], $p < 0.001$; I2: 45%), ARDS (RR 4.64 [1.86, 11.58], $p = 0.001$; I2: 9%), and disease progression (RR 3.31 [1.08, 10.14], $p = 0.04$; I2: 0%). Similarly, other reviews have observed an association between COVID-19 outcomes and prior cardiovascular disease or acute cardiac injury (Aggarwal et al., 2020; Gusik et al., 2020; Matshushita et al., 2020), hypertension (Lippi et al. 2020; Zuin et al., 2020) and chronic obstructive pulmonary disease (COPD) (Alqhatani et al., 2020; Zhao, Meng et al., 2020). Within the review, several studies also consistently found that the presence of multiple comorbidities including hypertension, diabetes and cardiovascular disease were associated with COVID-19 severity or mortality (Chen et al., 2020; Jian et al., 2020; Nasiri et al., 2020; Rahman et al., 2020; Wang et al., 2020; Yang et al., 2020; Zhang, Cui et al., 2020).

Only a few studies have explored the impact of obesity in relation to COVID-19 severity or disease progression (Bello-Chavallo et al., 2020; Zheng, Gao et al., 2020). In the former study, Bello-Chavallo and colleagues (2020) found that COVID-19 increased risk of mortality in obese individuals nearly six-fold (HR 5.954, 95%CI 4.939-7.178). Obesity also partially mediated the effect of diabetes on COVID-related outcomes. Diabetes mellitus increases the risk of hospitalization and obesity increases the risk of ICU admission and intubation. In the study by Zheng et al. (2020) among persons diagnosed with COVID-19 and metabolic-associated fatty liver disease (MAFLD), obesity increased the risk of severe COVID even adjusting for age, sex, smoking, diabetes, hypertension, and dyslipidaemia (AOR 6.32, 95%CI 1.16–34.54, $p = 0.033$). A recent UK study (Williamson et al, 2020) also found that obesity increased the risk of poor COVID-related outcomes (aHR 2.27; 95% CI 1.99-2.58) Class III obese vs non-obese). Williamson and colleagues (2020) also examined the effect of severe asthma (among other comorbidities) and demonstrated an association with COVID-19 hospital mortality (HR 1.25 CI 1.08-1.44).

Smoking behavior is a risk factor of interest that has been explored in several studies despite the challenges related to documentation of exposure in medical records (Alqhatani et al., 2020; Chen et al., 2020; Matshushita et al., 2020; Mehra & Desai, 2020; Patanavanich et al., 2020; Rahman et al., 2020; Zhao, Meng et al., 2020, Zhao, Li, et al., 2020; Zheng, Xu et al., 2020; Williamson et al., 2020). While smoking exposure is noted to be lower among persons hospitalized than the general population, the available information suggests that there is a higher proportion of smokers among severe cases. The growing popularity of electronic cigarettes is also an important area that needs further inquiry.

Conclusions

There is a growing body of research related to clinical characteristics and prognostic factors associated with COVID-19 related outcomes. An elevated risk of COVID-related disease progression/severity has been reported among men, older adults, and persons with multiple comorbidities (commonly diabetes, hypertension and cardiovascular disease). Studies that include smoking data are limited although the evidence is weighted towards an adverse impact on COVID-related outcomes. Similarly, obesity as a risk factor has seldom been examined in studies. Crude risk estimates have often been reported across studies limiting understanding of impact of confounding factors.

Glossary

(Optional, but useful if there are clinical/statistical terms being referenced in the document.)

Table 1: Summary of Literature

Ref	Sample/population	Method	Primary outcome measure	Additional findings	Quality of study
1.			[change title to reflect the outcome measure reported]		

See Excel spreadsheet

References Included in Summary

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Appendix: Evidence Search Details

Search Strategies

CINAHL

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S23	S20 OR S22	77
S22	S10 AND S21	42
S21	TX (((risk N1 (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or (risk N3 (regression or multivariate or multi-variate))) N3 (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*))	57,848
S20	S10 AND S13 AND S16 AND S19	47
S19	S17 OR S18	941,476
S18	TI (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*) OR AB (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*)	788,666
S17	(MH "Hospitalization+") OR (MH "Intensive Care Units+") OR (MH "Critical Care Nursing+") OR (MH "Critical Care+") OR (MH "Critical Illness") OR (MH "Severity of Illness") OR (MH "Patient Classification") OR (MH "Clinical Deterioration") OR (MH "Mortality+") OR (MH "Death+")	352,188
S16	S14 OR S15	1,144,660
S15	TI ((risk N1 (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or case control or cohort or (risk N3 (regression or multivariate or multi-variate))) OR AB ((risk N1 (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or case control or cohort or (risk N3 (regression or multivariate or multi-variate)))	673,599
S14	(MH "Risk Assessment") OR (MH "Odds Ratio") OR (MH "Prevalence") OR (MH "Case Control Studies+") OR (MH "Prospective Studies+")	787,032
S13	S11 OR S12	1,976,498
S12	TI (risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer or chemotherapy) OR AB (risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer or chemotherapy)	968,176
S11	(MH "Risk Factors+") OR (MH "Age Factors") OR (MH "Geographic Factors") OR (MH "Sex Factors") OR (MH "Race Factors") OR (MH "Comorbidity") OR (MH "Diabetes Mellitus+") OR (MH "Cardiovascular Diseases+") OR (MH "Hypertension+") OR (MH "Smoking+") OR (MH "Lung Diseases, Obstructive+") OR (MH "Neoplasms+") OR (MH "Chemotherapy, Cancer+") OR (MH "Radiotherapy+") OR (MH "Cancer Patients") OR (MH "Cancer Care Facilities")	1,709,552

S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 Limiters - Published Date: 20191201-20201231;
English Language 2,588

S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 14,514

S8 TX ("severe acute respiratory syndrome*") 3,676

S7 TX ((outbreak* or wildlife* or pandemic* or epidemic*) N1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)) 672

S6 TX (("seafood market*" or "food market*" or pneumonia*) N10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)) 454

S5 TX (respiratory* N2 (symptom* or disease* or illness* or condition*) N10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)) 1,247

S4 TX ("2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncover or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARSCoronavirus2 or "SARS-coronavirus-2" or "SARSCoronavirus 2" or "SARS coronavirus2" or SARSCoronavirus2 or "SARS-coronavirus-2" or "SARSCoronavirus 2" or "SARS coronavirus2") 2,246

S3 TX (coronavirus* or coronavirus* or coronavirinae* or CoV or HCoV*) 8,308

S2 TX ((corona* or corono*) N1 (virus* or viral* or virinae*)) 257

S1 (MH "Coronavirus Infections+") OR (MH "Coronavirus+") OR (MH "COVID-19") 4,737

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1 exp Coronavirinae/ or exp Coronavirus infection/ (21514)

2 (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj. (3649)

3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (710)

4 (coronavirus* or coronavirus* or coronavirinae* or CoV).ti,ab,kw. (19099)

5 ("2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncover or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARSCoronavirus2 or "SARS-coronavirus-2" or "SARSCoronavirus 2" or "SARS coronavirus2" or SARSCoronavirus2 or "SARS-coronavirus-2" or "SARSCoronavirus 2" or "SARS coronavirus2").ti,ab,kw. (7908)

6 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (542)

7 (("seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (1317)

8 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (99)

9 "severe acute respiratory syndrome*".ti,ab,kw. (5894)

10 or/1-9 (34858)

11 10 and 20191201:20201231.(dc). (9620)

12 risk factor/ or age/ or comorbidity/ or race/ or sex factor/ or exp diabetes mellitus/ or exp cardiovascular disease/ or exp hypertension/ or exp smoking/ or exp asthma/ or chronic obstructive lung disease/ or exp malignant neoplasm/ or exp chemotherapy/ or exp radiotherapy/ (9259019)

- 13 (risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer or chemotherapy).ti,ab. (5076382)
- 14 12 or 13 (10186079)
- 15 risk assessment/ or odds ratio/ or exp prevalence/ or exp case control study/ or cohort analysis/ (1873935)
- 16 ((risk adj (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or case control or cohort or (risk adj3 (regression or multivariate or multi-variate))).ti,ab. (2964396)
- 17 15 or 16 (3536815)
- 18 hospitalization/ or exp intensive care/ or exp intensive care unit/ or disease severity/ or critical illness/ or patient acuity/ or deterioration/ or terminal disease/ or exp mortality/ or exp death/ (2983521)
- 19 (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*).ti,ab. (4448056)
- 20 18 or 19 (5568249)
- 21 11 and 14 and 17 and 20 (290)
- 22 (((risk adj (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or (risk adj3 (regression or multivariate or multi-variate))) adj3 (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*).af. (195338)
- 23 11 and 22 (142)
- 24 21 or 23 (335)
- 25 limit 24 to (english language and exclude medline journals) (31)

Ovid MEDLINE(R) ALL 1946 to May 08, 2020

Run: May 11, 2020 16:05

- 1 exp coronavirus/ or exp coronavirus infections/ (17219)
- 2 ((corona* or coron*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (952)
- 3 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (18672)
- 4 ("2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARSCoronavirus2 or "SARS-coronavirus-2" or "SARSCoronavirus 2" or "SARS coronavirus2" or SARSCoronavirus2 or "SARS-coronavirus-2" or "SARSCoronavirus 2" or "SARS coronavirus2").ti,ab,kw,kf. (10826)
- 5 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (451)
- 6 (("seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (1221)
- 7 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (233)
- 8 "severe acute respiratory syndrome*".ti,ab,kw,kf. (5854)
- 9 or/1-8 (33131)
- 10 9 and 20191201:20201231.(dt). (12364)

- 11 risk factors/ or exp age factors/ or exp comorbidity/ or race factors/ or sex factors/ or exp diabetes mellitus/ or exp cardiovascular diseases/ or hypertension/ or exp smoking/ or exp lung diseases, obstructive/ or exp neoplasms/ or exp antineoplastic protocols/ or radiotherapy/ (6949423)
- 12 (risk factor* or comorbidit* or diabetes or cardiovascular disease* or heart disease* or hypertension or smoking or asthma* or chronic lung disease or chronic respiratory disease or chronic obstructive pulmonary disease or COPD or cancer or chemotherapy).ti,ab. (3557733)
- 13 11 or 12 (7979166)
- 14 exp risk assessment/ or odds ratio/ or prevalence/ or exp case-control studies/ or exp cohort studies/ (2606613)
- 15 ((risk adj (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or case control or cohort or (risk adj3 (regression or multivariate or multi-variate))).ti,ab. (2035955)
- 16 14 or 15 (3746974)
- 17 exp hospitalization/ or exp intensive care units/ or exp critical care/ or critical illness/ or mortality/ or exp patient acuity/ or clinical deterioration/ or exp death/ (771597)
- 18 (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*).ti,ab. (3120270)
- 19 17 or 18 (3457542)
- 20 10 and 13 and 16 and 19 (273)
- 21 (((risk adj (ratio? or prediction or assess* or factor* or stratif* or tool*)) or odds ratio? or prediction or prevalence or relative risk? or (risk adj3 (regression or multivariate or multi-variate))) adj3 (hospitalis* or hospitaliz* or hospital stay or intensive care unit* or ICU or critical* ill* or critical care or criticality or serious or severity or severe or deteriorat* or mortality or death or lethal* or poor prognosis or poor outcome*).af. (72115)
- 22 10 and 21 (103)
- 23 20 or 22 (295)
- 24 limit 23 to english language (276)

Sources

- Grey literature was included in this search
- Refer to the evidence search report for extensive sources.



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