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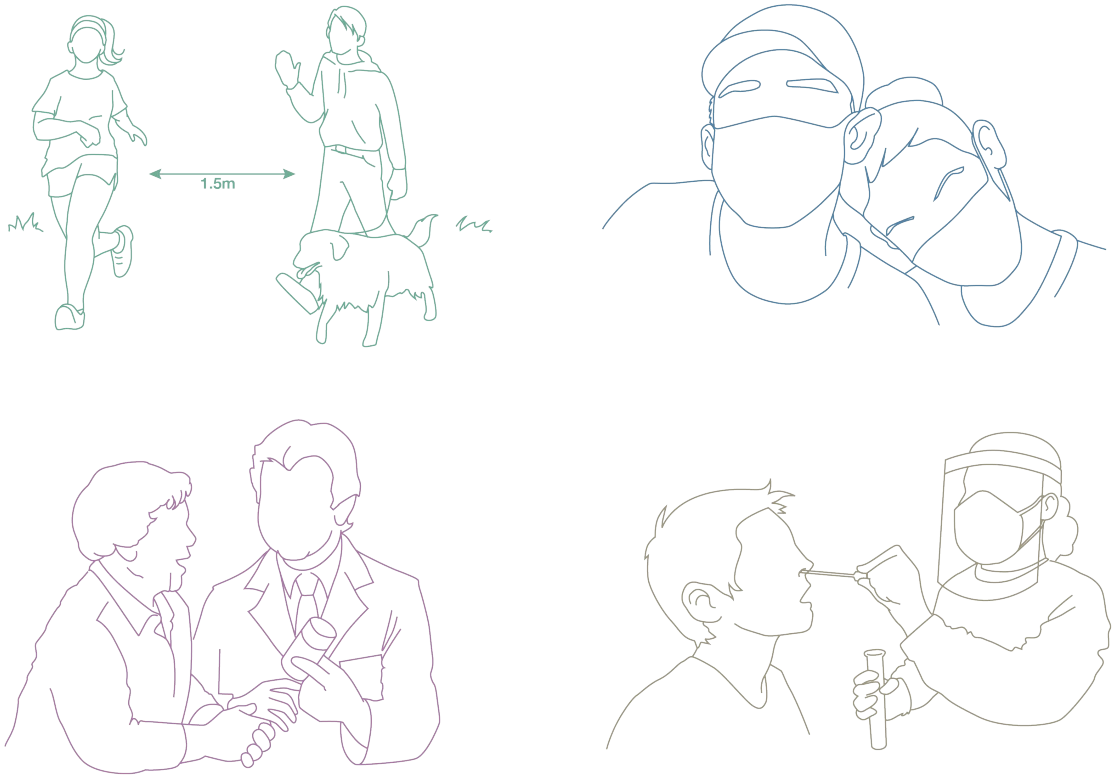

REVIEW OF META-ANALYSES: RISK FACTORS ASSOCIATED WITH SEVERE COVID-19 OUTCOMES

Eden Barrett, Amelia Lisbeth Joshy, Rubijayne Cohen, Suji O'Connor, Katherine Thurber, Lucy Kirk and Ellie Paige

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ANU COLLEGE OF HEALTH AND MEDICINE COVID-19 EVIDENCE TEAM

Research School of
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ANU College of
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Acknowledgement of Country

We acknowledge and celebrate the First Australians on whose traditional lands we work and meet, and pay our respect to the Elders past, present and emerging.

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Correspondence to:

Name: Eden Barrett
Position: Research Assistant
Australian National University

E: eden.barrett@anu.edu.au

Summary

A rapid evidence summary of meta-analyses published up until 23 June 2020 was conducted to examine factors associated with severe cases of SARS-CoV-2. The factors investigated were comorbidities, demographic characteristics and lifestyle factors. Due to the large volume of literature in this space, the rapid evidence summary was restricted to meta-analyses of good or fair quality published up to 23 June 2020. Evidence is only summarised for risk factors where there were five or more meta-analyses on the topic.

Definitions and measures of severity varied between meta-analyses. Some analysed associations with specific outcomes such as mortality or admission to intensive care unit (ICU) separately. However, many used a broad composite endpoint referred to as severe disease or composite poor outcome. This composite outcome often included both mortality and ICU admission, as well as other indicators of severe disease including acute respiratory distress syndrome (ARDS), requirement of mechanical ventilation, refractory or progressive disease, or severe disease as defined by accepted guidelines[1-4].

Of the 22 meta-analyses found (**Table 1**), studies contributing data to the meta-analyses were mostly exclusively of hospitalised patients within China, with limited data available from the United States (US), the United Kingdom (UK), Iran, Italy, Brazil, France, Japan, Canada, Spain, Italy, Germany, Turkey and South Korea. Many of the meta-analyses were published at around the same time and there is overlap in the studies included as well as in the original data sources contributing to the studies. We have reported the number of unique studies contributing to the meta-analyses on each topic, but nonetheless there will be substantial overlap in the data presented. While most of the studies used odds ratios (ORs) to express how much more likely severe outcomes were in people with the risk factor compared to those without, some reported this in terms of the relative risk (RR). Since ORs can approximate RRs where the outcome is not common[5] (as is generally the case of severe COVID-19 outcomes), we have presented these risk measures together except where there was a notable difference in the magnitude of the effect reported. Risk measures have been reported to two decimal places within this review except where an included meta-analysis has only reported results to one decimal place. Additional information on the search strategy and methods used for assessing quality is provided in the Appendix.

Consistent with earlier evidence summaries done by the Australian National University's College of Health and Medicine COVID-19 Evidence Team[6; 7], there is good evidence that people of older age and with specific existing chronic conditions, including hypertension, cardiovascular diseases (CVD), cerebrovascular disease, diabetes, and chronic obstructive pulmonary disease (COPD) have a greater risk of severe COVID-19 outcomes. Evidence on the individual risk factors is summarised below.

Hypertension: All 14 meta-analyses (129 unique studies) analysing the association between hypertension and severe COVID-19 outcomes found a significant positive association[8-21]. The odds of severe disease or composite poor outcomes in people with hypertension compared to those without ranged from 1.97 to 3.65 times as high. People with hypertension were between 1.5 to 3.67 times as likely to die as people without hypertension.

Cardiovascular disease (CVD): There was consistent evidence of an association between CVD and severe COVID-19 outcomes within all 13 meta-analyses (80 unique studies) that examined the relationship [8-17; 21-23]. People with CVD were 2.23 to 5.19 times as likely to experience severe disease as people without CVD, and 2.5 to 4.85 times as likely to die. One meta-analysis reported markedly higher odds of mortality for people with versus without CVD (11.08, 95% CI: 2.59, 47.32); however, this meta-analysis included only three studies each with less than 225 people, and there was substantial uncertainty around the estimate (wide confidence intervals)[22]. Results were similar between reviews that defined the exposure as CVD or coronary heart disease specifically.

Cerebrovascular diseases: All six meta-analyses (31 unique studies) examining the association between cerebrovascular diseases or history of stroke and severe COVID-19 found a significant positive association[10; 12; 14-16; 23]. People with cerebrovascular diseases were 1.88 to 4.69 times as likely to experience severe disease as those without[10; 15; 16; 23]. The risk of mortality in people with CeVD was 2.38 to 4.92 times as high[12; 14; 23].

Diabetes: There was consistent evidence from all 12 meta-analyses examining diabetes (120 unique studies) that severe COVID-19 outcomes occurred more frequently among people with diabetes compared to those without[8-17; 24; 25]. People with compared to without diabetes were 1.6 to 3.68 times as likely to experience severe disease or composite severe outcomes. A similar relationship was observed for mortality; those with compared to without diabetes were around 2 times as likely to die.

Chronic Obstructive Pulmonary Disease (COPD): Ten meta-analyses (65 unique studies) examined chronic obstructive pulmonary disease (COPD) as a risk factor[9-13; 15-17; 26; 27]. Of note, one meta-analysis (of seven studies total) included one study which grouped COPD and asthma together as 'respiratory diseases'[9]. There was consistent evidence that presence of COPD was associated with increased odds of having severe COVID-19 outcomes, but no significant association with mortality, in most of the included meta-analyses. There was a fair amount of uncertainty in the magnitude of effects of these estimates with the estimated odds ratio of severe COVID-19 outcomes ranging from 3.08 to 6.42 with substantial amounts of uncertainty (i.e. wide confidence intervals) within individual meta-analyses. There was no evidence of an association between COPD and mortality in three out of the four meta-analyses that examined this outcome[12; 26; 27], noting that these three meta-analyses had few studies contributing data (ranging from 2 to 4 studies). The single meta-analysis that found a significant association with mortality (OR 3.53; 95% CI: 1.79, 6.96) included data from seven studies[11].

Chronic Kidney Disease (CKD): Six meta-analyses (42 unique studies) examined the relationship between chronic kidney disease and severe COVID-19 outcomes[8; 10; 12; 14-16]. Findings were generally consistent with an association with severe disease/composite severe outcomes and mortality, but not all review findings were significant. Of the four meta-analyses[8; 10; 15; 16] that examined severe disease or composite severe outcomes, the two meta-analyses with the largest number of studies contributing data (11 and 26 studies, respectively) found that the odds of severe outcomes were around 2 times as high in people with CKD compared to those without[8; 16]. The ORs reported in the other two meta-analyses were consistent (ranging from 1.5 to 2.5) but did not reach statistical significance, likely due to the fewer studies contributing data to these analyses (4 studies in each meta-analysis)[10; 15].

Two meta-analyses specifically examined mortality as an outcome. They found that the risk of mortality in people with CKD compared to those without was around 4.2 times as high, and the odds of mortality were 9 times as high, but there was a large degree of uncertainty in these estimates (wide confidence intervals)[12; 14].

Cancer: Seven meta-analyses (65 unique studies) examined the relationship between cancer and severe COVID-19 outcomes[9-11; 14-16; 28]. There was consistent evidence from three meta-analyses that cancer is associated with increased odds (around two-fold) of having severe disease or composite severe outcomes[10; 15; 16]. One meta-analysis with data from nine different studies found a similar odds ratio of 1.6 for composite severe COVID-19 outcomes but this did not reach statistical significance[9]. Three meta-analyses[11; 14; 28] examined the association between cancer and mortality, with two finding that the risk of dying was around 1.7 to 3 times higher for those with cancer compared to those without[11; 28], while the third meta-analysis[14] found an association in the same direction but which was not statistically significant. The most comprehensive of these meta-analyses used data from 32 studies and five countries, finding that cancer among people with COVID-19 increased the risk of all-cause mortality by 1.66 (95% CI: 1.33-2.07; 8 studies) and ICU admission by 1.56 times (95% CI: 1.31, 1.87; 26 studies)[28]. A limitation across all studies is that cancers were grouped together thereby somewhat limiting clinical relevance.

Smoking status: Six meta-analyses (27 unique studies) examined the associations between smoking status and COVID-19 outcomes[9; 10; 12; 26; 27; 29]. There appears to be consistent evidence for an increased risk of severe COVID-19 outcomes among smokers, but there was no strong evidence for an increased risk of mortality. Four meta-analyses found higher odds of severe disease or poor composite outcome among smokers (defined as current smokers, former and current smokers combined, or not defined) ranging from 1.34 to 2.04[9; 10; 27; 29]. When smoking status was defined as current smokers only, one meta-analysis found a 45% higher risk of severe disease among current smokers compared to non-smokers (95% CI: 1.03, 2.04)[26]. Although two more meta-analyses reported consistent ORs for current smokers compared to non-smokers (1.12 and 1.55), these did not reach significance[27; 29]. Two small meta-analyses (including 2 and 5 studies each) did not find a significant association between smoking status and mortality[12; 29]. One of these meta-analyses included studies defining smokers as former and current smokers combined, and then as current smokers only, but results did not differ appreciably between exposure definitions. Notably, definition of smoking status exposure, including duration of smoking, has not been provided within most of the studies included within meta-analyses. Meta-analyses that restrict analyses to current smokers therefore often have a smaller total sample (2 to 10 studies) compared to those that don't make this restriction (4 to 18 studies), which may impact the strength and significance of associations found.

Age: The relationship between age and severe COVID-19 outcomes was significant in all five meta-analyses (67 unique studies)[9; 11; 12; 14; 16]. Zheng et al. reported that the odds of severe disease in people over 65 years compared to younger people were 6.01 times (95% CI: 3.95, 9.16) as high[9], while Parohan et al. reported that the odds of mortality in a similar age group (≥65yrs) compared to younger people were 4.59 times as high (95% CI: 2.61, 8.04). People who had died were roughly 14 to 16 years older than people who survived in two meta-analyses[12; 14]. However, Toraih et al. found only a modest difference in the ages of those who experienced poor outcomes compared to those that didn't (standardised mean

difference 1.01 years, 95% CI: 0.72, 1.31) in a review of 53 studies[16]. With the exception of the meta-analyses by Zheng et al. which only included two studies, all analyses examining the association between age and severe COVID-19 showed high heterogeneity, indicating inconsistency between individual studies.

As older people often have more comorbidities than younger people, it is possible that the association between age and severe COVID-19 outcomes is at least partly explained by existing comorbidities. Some meta-analyses attempted to untangle this by examining age-stratified associations between individual risk factors and severe disease, often finding stronger associations in younger rather than older age groups, but these analyses did not fully account for other co-morbidities[19; 24; 25; 28; 29].

Sex: Seven meta-analyses (86 unique studies) examined the role between sex (male/female) and severe COVID-19 outcomes[9-14; 16]. The odds of severe disease or composite severe outcomes were similar across the four meta-analyses[9; 10; 13; 16] that examined it (increased odds of severe outcomes ranging from 1.14 to 1.7) but results were not statistically significant for two of the meta-analyses[10; 13]. The most comprehensive and recent of these included data from 54 studies and 12 countries, estimating that the odds of composite severe outcomes were 1.5 times as high for males compared to females (95% CI: 1.34, 1.69)[16]. Three studies considered mortality as the outcome, finding that males were around 1.3 to 1.5 times as likely to die as females[11; 12; 14]. Overall, while there is evidence that the odds of severe COVID-19 outcomes or death might be slightly higher among males compared to females, it is not clear what is driving these differences. Many of the meta-analyses did not clearly identify what factors were adjusted for in the estimates that were extracted. It is possible and likely that the small differences observed between males and females might be due to different comorbidity and/or risk factor profiles rather than an independent relationship between sex and severity of COVID-19 outcomes.

Additional factors: Table 1 also presents associations found for liver disease within meta-analyses that examined multiple risk factors, although evidence has not been summarised (<5 meta-analyses available)[8; 10; 14; 15]. Meta-analyses are available for several other risk factors that have not been summarised in this review of reviews, including alcohol intake, medication use (angiotensin-converting enzyme inhibitors and angiotensin receptors blockers), pregnancy, and primary or acquired immunodeficiency [30-36].

Table 1. Factors associated with severe COVID-19 outcomes: a review of meta-analyses [a]

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Wang et al.[8]	April 6, 2020	China	34 studies	6263 hospitalised patients (1727 severe)	Severe disease (undefined but including at least ICU admission, ARDS and mortality.)	Hypertension Diabetes CVD CKD Liver disease	OR 2.92 (95% CI: 2.35, 3.64) (n=33), mod heterogeneity[b] OR 2.61 (95% CI: 2.05, 3.33) (n=31), mod heterogeneity OR 3.84 (95% CI: 2.90, 5.07) (n=23), low heterogeneity OR 2.22 (95% CI: 1.14, 4.31) (n=11), mod heterogeneity OR 0.86 (95% CI: 0.42, 1.75) (n=9), no heterogeneity	Fair
Zheng et al.[9]	March 20, 2020	China	13 studies	3027 hospitalised patients (527 events)	Composite outcome: ICU admission, refractory disease, severe disease, SpO2<90%, ARDS, mortality	Male sex Age (>65yrs) Hypertension Diabetes CVD COPD[c] Cancer Smoking	OR 1.77 (95% CI: 1.43, 2.19) (n=13), no heterogeneity OR 6.01 (95% CI: 3.95, 9.16) (n=2), no heterogeneity OR 2.72 (95% CI: 1.60, 4.64) (n=10), high heterogeneity OR 3.68 (95% CI: 2.68, 5.03) (n=11), mod heterogeneity OR 5.19 (95% CI: 3.25, 8.29) (n=10), low heterogeneity OR 5.15 (95% CI: 2.51, 10.57) (n=7), mod heterogeneity OR 1.60 (95% CI: 0.81, 3.18) (n=9), no heterogeneity OR 2.04 (95% CI: 1.32, 3.15) (n=5), no heterogeneity	Good
Li et al.[10]	April 14, 2020	China	12 studies	2445 hospitalised patients (479 severe)	Severe disease (undefined but including at least ICU admission)	Any morbidities Male sex Hypertension Diabetes CVD (CHD) CeVD COPD Cancer CKD Liver disease Smoking	OR 3.07 (95% CI: 1.56, 6.05) (n=5), high heterogeneity OR 1.14 (95% CI: 0.91, 1.43) (n=11), no heterogeneity OR 2.40 (95% CI: 1.47, 3.90) (n=8), mod heterogeneity OR 3.17 (95% CI: 2.26, 4.45) (n=8), mod heterogeneity OR 2.66 (95% CI: 1.71, 4.15) (n=8), no heterogeneity OR 2.68 (95% CI: 1.29, 5.57) (n=4), mod heterogeneity OR 5.08 (95% CI: 2.68, 9.63) (n=7), no heterogeneity OR 2.21 (95% CI: 1.04, 4.72) (n=5), no heterogeneity OR 1.50 (95% CI: 0.58, 3.85) (n=4), mod heterogeneity OR 0.44 (95% CI: 0.13, 1.51) (n=4), no heterogeneity OR 1.70 (95% CI: 1.20, 2.41) (n=5), mod heterogeneity	Fair
Parohan et al.[11]	May 1, 2020	China, Iran, Italy	14 studies	29,909 patients (including hospitalised and ED admissions) (1445 deaths)	Mortality	Male sex Age (≥65yrs) Hypertension Diabetes CVD COPD Cancer	OR 1.50 (95% CI: 1.06, 2.12) (n=5), high heterogeneity OR 4.59 (95% CI: 2.61, 8.04) (n=6), high heterogeneity OR 2.70 (95% CI: 1.40, 5.24) (n=8), high heterogeneity OR 2.41 (95% CI: 1.05, 5.51) (n=7), high heterogeneity OR 3.72 (95% CI: 1.77, 7.83) (n=9), high heterogeneity OR 3.53 (95% CI: 1.79, 6.96) (n=7), high heterogeneity OR 3.04 (95% CI: 1.80, 5.14) (n=7), mod heterogeneity	Good

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Tian et al.[12]	April 24, 2020	China, US	14 studies	4659 hospitalised patients (1189 deaths)	Mortality	Age	MD 15.56y (95% CI: 12.48, 18.64) (n=10), high heterogeneity	Good
						Male sex	OR 1.78 (95% CI: 1.30, 2.42) (n=14), high heterogeneity	
						Hypertension	OR 2.53 (95% CI: 2.07, 3.09) (n=11), low heterogeneity	
						Diabetes	OR 1.97 (95% CI: 1.67, 2.31) (n=12), no heterogeneity	
						CVD (CHD)	OR 3.81 (95% CI: 2.11, 6.85) (n=12), mod heterogeneity	
						CeVD	OR 4.92 (95% CI: 1.54, 15.68) (n=6), mod heterogeneity	
						COPD	OR 2.09 (95% CI: 0.49, 8.90) (n=4), mod heterogeneity	
						CKD	OR 9.41 (95% CI: 3.23, 27.40) (n=6), no heterogeneity	
						Smoking	OR 1.77 (95% CI: 0.83, 3.81) (n=4), low heterogeneity	
Jain & Yuan[13]	March 5, 2020	China	7 studies	1813 hospitalised patients (315 severe, 116 ICU)	Severe disease (undefined but including as specified by guidelines criteria) ICU admission[d]	Male sex	Severe: OR 1.15 (95% CI: 0.89, 1.48) (n=5), no/low heterogeneity ICU: OR 1.55 (95% CI: 1.02, 2.36) (n=3), no/low heterogeneity	Fair
						Hypertension	Severe: OR 1.97 (95% CI: 1.40, 2.77) (n=3), no/low heterogeneity ICU: OR 3.65 (95% CI: 2.22, 5.99) (n=3), heterogeneity indicated	
						Diabetes	Severe: OR 3.12 (95% CI: 1.00, 9.75) (n=3), heterogeneity indicated ICU: OR 2.72 (95% CI: 0.70, 10.60) (n=3), heterogeneity indicated	
						CVD	Severe: OR 2.70 (95% CI: 1.52, 4.80) (n=3), no/low heterogeneity ICU: OR 4.44 (95% CI: 2.64, 7.47) (n=3), no/low heterogeneity	
						COPD	Severe: OR 6.42 (95% CI: 2.44, 16.90) (n=3), no/low heterogeneity ICU: OR 17.80 (95% CI: 6.56, 48.20) (n=3), no/low heterogeneity	

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Martins-Filho[14]	April 6, 2020	China	4 studies	852 hospitalised patients (249 deaths)	Mortality	Age	MD 13.8 yrs (95% CI: 8.0, 19.7), high heterogeneity	Fair
						Male sex	RR 1.3 (95% CI: 1.1, 1.4), no heterogeneity	
						Any morbidities	RR 1.6 (95% CI: 1.4, 2.0), no heterogeneity	
						Hypertension	RR 1.5 (95% CI: 1.1, 2.1), high heterogeneity	
						Diabetes	RR 1.6 (95% CI: 1.1, 2.2), low heterogeneity	
						CVD	RR 3.0 (95% CI: 1.2, 7.6), high heterogeneity	
						CeVD	RR 3.3 (95% CI: 1.8, 6.2), no heterogeneity	
						Lung disease	RR 3.5 (95% CI: 2.0, 6.3), no heterogeneity	
						Cancer	RR 1.5 (95% CI: 0.6, 3.8), no heterogeneity	
						CKD	RR 4.2 (95% CI: 1.4, 12.8), low heterogeneity	
						Liver disease	RR 4.2 (95% CI: 0.3, 66.5), heterogeneity not reported	
Wang[15]	March 1, 2020	China	6 studies	1558 hospitalised patients (324 severe)	Severe disease (ICU admission or 'clinical symptoms' (undefined))	Hypertension	OR 2.29 (95% CI: 1.69, 3.10) (n=6), low heterogeneity	Good
						Diabetes	OR 2.47 (95% CI: 1.67, 3.66) (n=6), mod heterogeneity	
						CVD	OR 2.93 (95% CI: 1.73, 4.96) (n=4), no heterogeneity	
						CeVD	OR 3.89 (95% CI: 1.64, 9.22) (n=3), mod heterogeneity	
						COPD	OR 5.97 (95% CI: 2.49, 14.29) (n=6), no heterogeneity	
						Cancer	OR 2.29 (95% CI: 1.00, 5.23) (n=4), no heterogeneity	
						CKD	OR 2.51 (95% CI: 0.93, 6.78) (n=4), no heterogeneity	
						Liver disease	OR 0.67 (95% CI: 0.30, 1.49) (n=5), no heterogeneity	
Toraih[16]	May 8, 2020	China, US, Brazil, UK, mixed[e]	56 studies	17,794 hospitalised patients (3038 events)	Composite outcome: severe disease (ARDS, mechanical ventilation, ICU admission), ICU admission, cardiac injury, mortality.	Age	SMD 1.01 (95% CI: 0.72, 1.31) (n=53), high heterogeneity	Fair
						Male sex	OR 1.50 (95% CI: 1.34, 1.69) (n=54), low heterogeneity	
						Hypertension	OR 2.22 (95% CI: 1.75, 2.81) (n=50), high heterogeneity	
						Diabetes	OR 1.88 (95% CI: 1.59, 2.24) (n=51), low heterogeneity	
						CHD	OR 3.42 (95% CI: 2.65, 4.42) (n=40), mod heterogeneity	
						CeVD	OR 4.49 (95% CI: 2.72, 7.40) (n=21), mod heterogeneity	
						COPD	OR 3.08 (95% CI: 2.36, 4.03) (n=35), low heterogeneity	
						CKD	OR 2.75 (95% CI: 1.77, 4.28) (n=26), low heterogeneity	
						Cancer	OR 1.97 (95% CI: 1.41, 2.76) (n=31), low heterogeneity	

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Liu[17]	April 25, 2020	China, US, Italy, France	24 studies	10,948 hospitalised patients (2699 events)	Severe disease (undefined), ICU admission, Mortality	Any morbidities	Severe: OR 3.50 (95% CI: 1.78, 6.90) (n=3), mod heterogeneity ICU: OR 3.36 (95% CI: 1.67, 6.76) (n=2), low heterogeneity Mortality: OR 2.09 (95% CI: 0.26, 16.67) (n=3), high heterogeneity	Fair
						Hypertension	Composite: OR 2.84 (95% CI: 2.22, 3.63) (n=9), low heterogeneity	
						Diabetes	Composite: OR 2.61 (95% CI: 1.93, 3.52) (n=10), low heterogeneity	
						CVD/CAD	Composite: OR 4.18 (95% CI: 2.87, 6.09) (n=8), low heterogeneity	
						COPD	Composite: OR 3.83 (95% CI: 2.15, 6.80) (n=10), no heterogeneity	
Pranata[18]	April 7, 2020	China	30 studies	6560 hospitalised patients (1642 events)	Composite outcome: mortality, severe disease[f], ARDS[g], ICU admission, disease progression	Hypertension	Composite: RR 2.11 (95% CI: 1.85, 2.40) (n=30), mod heterogeneity Mortality: RR 2.21 (95% CI: 1.74, 2.81) (n=11), high heterogeneity Severe: RR 2.04 (95% CI: 1.69, 2.47) (n=12), low heterogeneity ARDS: RR 1.64 (95% CI: 1.11, 2.43) (n=2), no heterogeneity ICU care: RR 2.11 (95% CI: 1.34, 3.33) (n=3), low heterogeneity Disease progression: RR 3.01 (95% CI: 1.51, 5.99) (n=2), no heterogeneity	Good
Zhang[19]	March 20, 2020	China	18 studies	4505 hospitalised patients (674 severe, 115 deaths)	Severe disease[f] Mortality	Hypertension	Severe disease: OR 2.27 (95% CI: 1.80, 2.86) (n=12), low heterogeneity Mortality: OR 3.48 (95% CI: 1.72, 7.08) (n=6), mod heterogeneity	Good
Zuin[20]	March 23, 2020	China	3 studies	419 hospitalised patients (86 deaths)	Mortality	Hypertension	OR 3.36 (95% CI 1.96, 5.74) (n=3), low heterogeneity	Good

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Li et al.[21]	April 14, 2020	China	10 studies	3118 hospitalised patients (511 deaths)	Mortality	CVD Hypertension	OR 4.85 (95% CI: 3.06, 7.70) (n=8), low heterogeneity OR 3.67 (95% CI: 2.31, 5.83) (n=7), mod heterogeneity	Good
Aggarwal[22]	April 20, 2020	China US	18 studies	4858 patients (1257 severe, 518 deaths)	Severe disease[f] Mortality	CVD	Severity: OR 3.14 (95% CI: 2.32, 4.57) (n=13), no heterogeneity Mortality: OR 11.08 (95% CI: 2.59, 47.32) (n=3), mod heterogeneity	Good
Pranata[23]	April 10, 2020	China, Iran	16 studies	4448 hospitalised patients (1201 events)	Severe disease[f] Mortality	CVD CeVD	Composite: RR 2.23 (95% CI: 1.71, 2.91) (n=12), mod heterogeneity Severe: RR 2.25 (95% CI: 1.51, 3.36) (n=6), high heterogeneity Mortality: RR 2.25 (95% CI: 1.53, 3.29) (n=6), low heterogeneity Composite: RR 2.04 (95% CI: 1.43, 2.91) (n=12), high heterogeneity Severe: RR 1.88 (95% CI: 1.00, 3.51) (n=7), high heterogeneity Mortality: RR 2.38 (95% CI: 1.92, 2.96) (n=5), no heterogeneity	Good
Huang et al.[24]	April 8, 2020	China Japan[h]	30 studies	6452 hospitalised patients (834 events)	Mortality, severe disease[f], ARDS[g], ICU admission, disease progression	Diabetes	Composite outcome: RR 2.38 (95% CI: 1.88, 3.03) (n=30), mod heterogeneity Mortality: RR 2.12 (95% CI: 1.44, 3.11) (n=10), high heterogeneity Severe: RR 2.45 (95% CI: 1.79, 3.35) (n=13), mod heterogeneity ARDS: RR 4.64 (95% CI: 1.86, 11.58) (n=2), low heterogeneity ICU: RR 1.47 (95% CI: 0.38, 5.67) (n=3), high heterogeneity Disease progression: RR 3.31 (95% CI: 1.08, 10.14) (n=2), no heterogeneity	Fair

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Kumar et al.[25]	April 22, 2020	China, US, France	33 studies	16,003 patients (including hospitalisations and 6637 cases from registry data) (2827 events)	Mortality, severe disease[f]	Diabetes	Composite outcome: OR 2.49 (95% CI: 1.98, 3.14) (n=33), high heterogeneity Mortality: OR 1.90 (95% CI: 1.37, 2.64) (n=9), low heterogeneity Severe disease: OR 2.75 (95% CI: 2.09, 3.62) (n=24), high heterogeneity	Good
Alquahtani[26]	March 24, 2020	China, US	15 studies	2473 hospitalised patients (577 events)	Severe disease (ICU admission, severe symptoms (undefined), requiring oxygenation or mechanical ventilation, death) Mortality	COPD Smoking (current only)	Severe: RR 1.88 (95% CI: 1.4, 2.4) (n=7), no heterogeneity Mortality: RR 1.10 (95% CI: 0.6, 1.8) (n=2), no heterogeneity Severe: RR 1.45 (95% CI: 1.03, 2.04) (n=2), no heterogeneity	Fair
Zhao et al.[27]	March 22, 2020	China	11 studies	2002 hospitalised patients (334 events)	Mortality, severe disease[f]	COPD Smoking	Mortality: OR 1.93 (95% CI: 0.59, 7.43) (n=2), mod heterogeneity Severe: OR 4.38 (95% CI: 2.34, 8.20) (n=10), mod heterogeneity Severe: OR 1.98 (95% CI: 1.29, 3.05) (n=7), mod heterogeneity Severe current smokers only: OR 1.55, 95% CI: 0.83, 2.87	Good

Author, ref	Search until	Regions	No. studies	Sample size and setting	Outcome/s	Risk factors	Results	Quality
Giannakoulis et al.[28]	April 27, 2020	China, US, Italy, UK, Iran	32 studies	46,499 patients including hospitalisations, outpatients and ED admissions, and 2653 cases from registry data (2034 deaths, 3220 ICU)	Mortality, ICU admission/severe disease[f]	Cancer	Mortality: RR 1.66 (95% CI: 1.33, 2.07) (n=8), low heterogeneity ICU: RR 1.56 (95% CI: 1.31, 1.87) (n=26), mod heterogeneity	Good
Karanasos[29]	May 4, 2020	China, US	22 studies	7148 hospitalised patients (1989 events)	Severe disease (ICU admission, severe disease (undefined), invasive ventilation, disease progression, refractory disease) Mortality	Smoking	Severe: OR 1.34 (95% CI: 1.07, 1.67) (n=18), mod heterogeneity Severe current smoking only: OR 1.12, (95% CI 0.84, 1.50) (n=10), mod heterogeneity Mortality: OR 1.45 (95% CI 0.78, 2.72) (n=5), low heterogeneity Mortality current smoking only: OR 1.57 (95% CI 0.75, 2.31) (n=2), no heterogeneity	Good

[a] ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ED, emergency department; ICU, intensive care unit; MD, mean difference; OR, odds ratio; RR, relative risk; SMD, standardised mean difference; SpO2, oxygen saturation.

[b] The values of the I2 statistic were interpreted as follows: 0% indicates no heterogeneity, 25% indicates low heterogeneity, 50% indicates moderate (mod) heterogeneity and 75% indicates high heterogeneity[37]. Where only tau-squared was provided (Jain & Yaun et al.), <0.001 indicates no/low heterogeneity and ≥0.001 indicates heterogeneity.[38]

[c] Includes one study that examined COPD and asthma as combined 'respiratory diseases'.

[d] One included study groups ICU admission, mechanical ventilation or death as a single ICU outcome

[e] One included study analyses data from hospitals in the US, Canada, Spain, Italy, Germany, France, UK, Turkey, China, South Korea and Japan.

[f] Includes only articles that have defined severe disease according to specified guidelines or established characteristics. Guidelines vary but include the World Health Organisation (WHO)-China Joint Mission on COVID-19, the American Thoracic Society/Infectious Disease Society of America criteria for defining severe community acquired pneumonia in the *Diagnosis and Treatment of Adults with Community-acquired Pneumonia*, the Chinese National Health Commission severe case definition in the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*, and the WHO severity criteria in the *Clinical management of severe acute respiratory infection when COVID-19 is suspected*. Briefly, the following characteristics are commonly included in severe disease definitions: respiratory distress with respiratory rate ≥30 breaths/min, pulse oximeter

oxygen saturation ≤93% at rest, oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) ≤ 300mm Hg, requirement for mechanical ventilation, ICU admission and/or critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure)[1-4].

[g] ARDS was defined as per WHO *Clinical management of severe acute respiratory infection (SARI) when COVID-19 is suspected*.[2]

[h] Study analyses data from a hospital in Japan treating patients from a cruise ship. Patients' nationality reported as from Asia, Europe, North America, Oceania and others.

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Appendix

Search strategy

We searched PubMed, Web of Science and the Cochrane library for systematic reviews and meta-analyses published up until 23 June 2020. The search terms used were: systematic, meta, COVID-19, SARS-CoV-2, severe, critical, death, mortal, comorbid, prognosis, intensive, risk and ventilation.

Inclusion/exclusion criteria

The rapid evidence summary was restricted to include systematic reviews and meta-analyses published in peer-reviewed journals. Included articles must have made a statistical comparison of at least one potential factor (e.g. demographic characteristic or comorbidity) between severe and non-severe patient groups. Furthermore, due to the large volume of literature in the space, we have here only summarised evidence on factors for which there were at least five fair or good quality meta-analyses available. Quality of meta-analyses was assessed using the National Institute of Health quality assessment tool for systematic reviews and meta-analyses[39].

Search results

Our search strategy returned 924 results. Duplicates were removed, leaving 428 articles for abstract and title screening. After abstract and title screening, 111 articles remained to be read in full. After excluding articles that did not meet inclusions, 39 articles remained. Articles were mainly excluded because they were not systematic review and meta-analyses, they were unpublished preprints, or they did not compare exposures between severe and non-severe groups. For the purpose of this evidence summary, we then determined factors for which there were not at least five meta-analyses, resulting in a further exclusion of seven articles. Quality assessment was conducted by two authors. Ten articles were removed for being of poor quality. After excluding articles that did not meet inclusion criteria, 22 meta-analyses were extracted and summarised (**Table 1**).

COLLEGE OF HEALTH AND MEDICINE

The Australian National University
Canberra ACT 2601 Australia

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