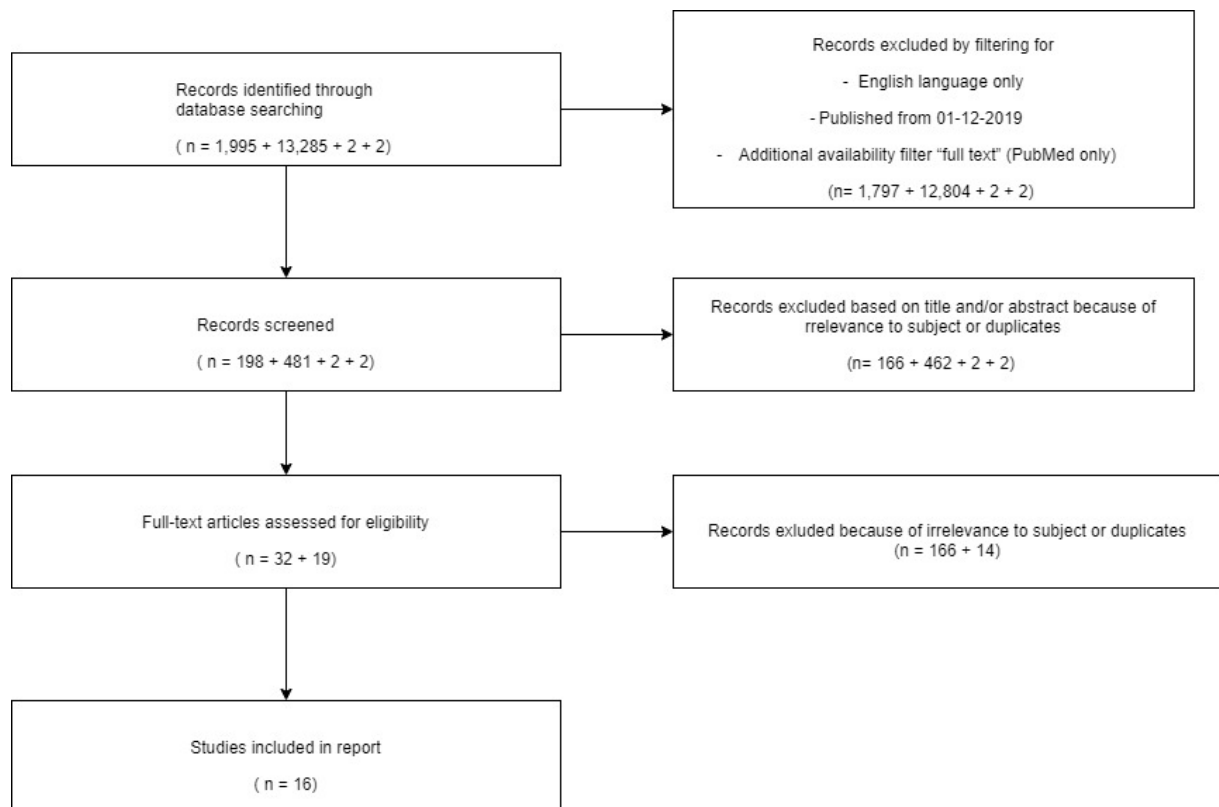


## Best Evidence Topic Report

Title	Which groups are at higher risk for complications caused by COVID-19?
Report by	Wim De Mol, Michaël Galouchka
Search checked by	Mieke Vermandere
Answerable question (PICO/PIRT/PEO/...)	P: Covid-19 patients I: risk factors C: baseline risk O: pneumonia, respiratory failure (ARDS), death
Search terms	<ul style="list-style-type: none"> <li>- MEDLINE (via PubMed): ("COVID-19" [Supplementary Concept] OR COVID19[tiab] OR covid-19[tiab] OR 2019-nCoV[tiab] OR SARS-CoV-2[tiab] OR SARS[tiab]OR "corona"[tiab] OR coronavirus[tiab]) AND (hospitalisation OR hospitalization OR pneumonia OR ARDS OR "respiratory failure" OR complications OR survival OR mortality OR death OR outcome) NOT MERS (n=1,995; filtered for <b>English only, publications starting 01-12-2019: n=231, additional filter "full text": n=198</b>)</li> <li>- Embase: ('covid 19' OR covid OR covid19 OR 'sars'/exp OR sars OR 'sars cov 2' OR '2019 ncov' OR corona OR 'coronavirus'/exp OR coronavirus) AND ('pneumonia'/exp OR pneumonia OR 'ards'/exp OR ards OR 'respiratory failure'/exp OR 'respiratory failure' OR 'hospitalization'/exp OR hospitalization OR 'complications'/exp OR complications OR 'death'/exp OR death OR 'mortality'/exp OR mortality OR 'survival'/exp OR survival) NOT mers (n=13,285; <b>n=481</b> when filtered for AND [1-12-2019]/sd AND [english]/lim )</li> <li>- TripDatabase: (title:covid-19 OR covid19 OR SARS-CoV-2 OR 2019-nCoV OR corona OR coronavirus OR SARS )(title:(hospitalisation OR hospitalization OR pneumonia OR ARDS OR "respiratory failure" OR complications OR survival OR mortality OR death OR outcome))(not MERS) from:2019 (<b>n=2</b>)</li> <li>- Cochrane: "covid-19" (<b>n=2</b>)</li> </ul>
Search date	19-03-2020
Search outcome (number of hits)	683 of which 667 irrelevant
Relevant papers (number of final inclusions)	16
Flow chart	



## Evidence table

Cfr attachment

## Conclusions of overall body of evidence:

### - Main results

#### 1) Risk factors for more severe disease:

- o Older age (2, 5, 6, 11, 12, 15)
- o Comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease (1, 2, 5, 6, 11)
- o History of smoking (4)
- o Longer time between illness onset and hospitalization (5)
  
- o Dyspnea (2, 5, 11)
- o High fever ( $\geq 39$  °C) (2, 4, 5)
- o Anorexia (11)
  
- o Coagulation dysfunction (longer PT, higher D-dimers) (2, 11)
- o Neutrophilia (2, 5, 11)
- o Organ dysfunction (liver damage (total bilirubin), renal dysfunction (urea, creatinine), LDH) (2)
- o Elevated inflammatory indicators in the blood (cardiac troponin, myoglobin, CRP, IL-6) (2, 3, 4, 5, 15)
- o Lower albumin levels (4, 15)

- o Elevated procalcitonin (5)
  - o Decreased lymphocyte ratio and lymphocyte count (2, 5, 11)
  - o lower oxyhemoglobin saturation (5)
  - o viral RNA detection in blood (8)
  - o high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1 $\alpha$ , and TNF $\alpha$  (14)
  - o Viral load (15)
  - o Viral detection in anal swab (8)
  
  - o High involvement of multiple lung lobes on chest CT (5)
  - o Radiological abnormalities at presentation (6)
- 2) Risk factors for mortality:
- o Older age (1, 2, 3, 10, 16)
  - o Comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease (2, 3)
  - o Obesity (16)
  
  - o Dyspnea (10)
  - o Presence of secondary infection (3)
  
  - o Neutrophilia (2, 11)
  - o Decreased lymphocyte count and ratio (2, 11)
  - o Organ dysfunction (liver damage (total bilirubin), renal dysfunction (urea, creatinine), LDH) (2, 11)
  - o Higher SOFA score (1, 7)
  - o Coagulation dysfunction (longer PT and aPTT, higher D-dimers, higher fibrin degradation product (FDP) levels) (1, 2, 9, 11)
  - o Elevated inflammatory indicators in the blood (cardiac troponin, myoglobin, CRP, IL-6) (2, 3, 4, 15)
- 3) No elevated risk for disease progression:
- o Pregnancy (13)

#### - Risks of bias

Most common risks for bias:

- small sample sizes
- retrospective methods
- short duration of follow-up
- single-center studies
- study population only including hospitalised patients

#### -Heterogeneity: statistical and/or clinical

High clinical heterogeneity due to very different endpoints in studies and different treatment protocols.

Low statistical heterogeneity: no conflicting results.

### **Clinical bottom line:**

Evidence is currently very limited due to the low amount and low quality of available studies.

Based on the current evidence, we conclude:

- Older age and comorbidities such as cardiovascular disease, diabetes mellitus and COPD have been described as risk factors for more severe COVID19-disease or mortality in multiple studies.
- Dyspnea may be predictive for more severe disease and higher likelihood of death
- While high fever ( $\geq 39$  °C) has been associated with higher likelihood of severe disease, it is not associated with higher mortality.
- Several other factors may be associated with higher risk for severe disease (anorexia, history of smoking, longer time between illness onset and hospitalization) or higher mortality (obesity, presence of secondary infection)
- Several test results may be associated with higher risk for severe disease or mortality. Neutrophilia, lowered lymphocyte count and ratio, elevated inflammatory parameters (cardiac troponin, myoglobin, CRP, IL-6) and coagulation dysfunction (most notably elevated D-dimers but also longer PT and aPTT and higher FDP) have been described the most.
- Radiologic abnormalities at presentation and involvement of multiple lungs on chest CT were associated with higher risk for severe disease progression.

### **References**

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#	Author, date and country	Study type	Main risks of bias	Patient characteristics	Intervention/ Index test / Exposure	Comparator	Outcome	Key results: RR, AR, NNT Sens/Spec, LR+/LR- HR, OR Other
1	Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. China, 2020 Mar	Retrospective cohort study	Late transfers to the two included hospitals Small sample size Short duration Retrospective method Inpatients only	All adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital who had been discharged or had died between Dec 29, 2019 and Jan 31, 2020.	Risk factor assessment	Survival	In-hospital death	Risk factors for death of adult patients with COVID-19: - Older age: OR 1.10, 95% CI 1.03-1.17, per year increase - Higher SOFA score: OR 5.65, 95% CI 2.61-12.23 - D-dimer >1 µg/L: OR 18.42, 95% CI 2.64-128.55

2	Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. China, 2020 Mar	Retrospective cohort study	<p>Selection of severely ill patients due to limited resources</p> <p>Small sample size</p> <p>Single-center study</p> <p>Retrospective method</p> <p>Inpatients only</p>	Patients aged 21 to 83 years with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China between December 25, 2019, and January 26, 2020	Risk factor assessment	No ARDS developed, survival	Development of ARDS or progression from ARDS to death	<p>Risk factors associated with the development of ARDS and progression from ARDS to death:</p> <ul style="list-style-type: none"> <li>- Older age (HR, 3.26 and HR, 6.17)</li> <li>- Neutrophilia (HR, 1.14; and HR, 1.08)</li> <li>- Organ and coagulation dysfunction (eg, higher lactate dehydrogenase [HR, 1.61; and HR, 1.30] and D-dimer [HR, 1.03 and HR, 1.02]).</li> </ul> <p>Risk factors for developing ARDS:</p> <ul style="list-style-type: none"> <li>- Dyspnea (difference, 33.9%)</li> <li>- Comorbidities such as hypertension (difference, 13.7%) and diabetes (difference, 13.9%).</li> <li>- High fever (<math>\geq 39</math> °C) (HR, 1.77).</li> <li>- Older age (<math>\geq 65</math> years old)</li> <li>- neutrophilia</li> <li>- elevated coagulation function–related indicators (PT and D-dimer)</li> </ul> <p>In the subgroup of patients who developed ARDS, patients who ultimately died were:</p> <ul style="list-style-type: none"> <li>- older (difference, 18.0 years)</li> <li>- lower proportion of high fever (difference, -31.8%)</li> <li>- higher proportions of hypertension (difference, 18.9%)</li> <li>- less likely to be treated with antiviral therapy (difference, -40.7%).</li> </ul> <p>For patients with ARDS who died, compared to those who survived 1) there was a significant elevation in:</p> <ul style="list-style-type: none"> <li>- the value of liver damage indices (total bilirubin [difference, 2.60 mg/dL])</li> <li>- renal dysfunction indices (urea [difference, 1.50 mM])</li> <li>- inflammation-related indices (IL-6 [difference, 3.88 pg/L])</li> </ul>
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3	Ruan Q, Yang K, Wang W, Jiang L, Song J. China, 2020 Mar 03	Retrospective multicenter observational study	Small sample size Retrospective method Inpatients only	150 hospitalised patients at Jin Yin-tan Hospital and Tongji Hospital with laboratory-confirmed infection of SARS-CoV-2.	Risk factor assessment	Overall survival	In-hospital death	Risk factors for mortality: -Older age (no exact numbers in article) -Cardiovascular disease (no exact numbers in article) -Presence of secondary infection (16% in nonsurvivors vs 1% in survivors) -Elevated inflammatory indicators in the blood (cardiac troponin, myoglobin CRP, IL-6)
4	Liu W, Tao ZW, Lei W, et al. China, 2020 Feb 28	Retrospective multicenter observational study	Small sample size Retrospective method Inpatients only	Seventy-eight patients with COVID-19-induced pneumonia admitted to 3 tertiary hospitals in Wuhan between December 30, 2019, and January 15, 2020	Risk factor assessment	disease improvement /stabilization	disease progression	Disease progression was associated with: -history of smoking (27.3% vs 3.0%) -higher maximum body temperature compared to improvement/stabilization group (38.2 [37.8, 38.6]°C vs. 37.5 [37.0, 38.4]°C) - higher CRP (38.9 [14.3, 64.8] vs. 10.6 [1.9, 33.1] mg/L, U = 1.315, P = 0.024) - lower albumin (36.62 ± 6.60 vs. 41.27 ± 4.55 g/L, U = 2.843, P = 0.006)



5	Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. China, 2020 Feb	Retrospective observational study	Small sample size and unbalance in sizes of “severe” and “ordinary” arms Short duration Retrospective method Inpatients only	83 patients with COVID-19 pneumonia with manifestations of pneumonia on CT	Clinical and chest CT features	Ordinary pneumonia	Severe/critical disease	<p>Compared with the “ordinary” group, the group of severe/critical patients:</p> <ul style="list-style-type: none"> <li>- was significantly older (mean age, 53.7 years [SD, 12.3] vs 41.9 years in ordinary group [SD,10.6]; P &lt;0.001)</li> <li>-had more comorbidities of systemic hypertension, heart disease, diabetes mellitus and chronic obstructive pulmonary disease (44.0% vs 6.9%)</li> <li>-had a longer time from illness onset to hospitalisation (8 days [6-12] vs 6 days [3-8.5])</li> <li>- had higher body temperature (38.0°C vs 37.6°C)</li> <li>- had higher incidences of cough (96.0% vs 70.7%), expectoration (36.0% vs 10.3%), dyspnea (28.0% vs 3.4%) and chest pain(16.0% vs 1.7%)</li> <li>- had increased neutrophil ratio (NEU% 80.08% vs 67.84%), C reactive protein (89.20mg/L [47.88-134.64 ]vs 9.59mg/L [2.07-29.89]and procalcitonin (0.086ng/mL vs 0.038ng/mL)</li> <li>- had decreased lymphocyte ratio (LYM% 13.20% vs 23.78%) and lymphocyte count (<math>0.70 \times 10^9/L</math> vs <math>1.23 \times 10^9/L</math>)</li> <li>- had lower oxyhemoglobin saturation (95.10% vs 97.00%)</li> </ul> <p>No significant differences of heart rate, respiratory rate and arterial pressure were found between the two groups.</p>
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								<p>CT findings of consolidation, linear opacities, crazy paving pattern, bronchial wall thickening, high CT scores (&gt;7) and extrapulmonary lesions were imaging features of severe/critical COVID 19 pneumonia.</p>
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6	Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, et al.  China, 2020 Feb	Retrospective multicenter observational study	Incomplete documentation of laboratory testing in some cases Cutoff of data on outcomes Clinically-driven data generation, not systematic Retrospective method Inpatients only	1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020	Risk factor assessment	Survival without admission to ICU or mechanical ventilation	Admission to ICU, the use of mechanical ventilation, or death.	Patients with severe disease were older than those with nonsevere disease by a median of 7 years. Moreover, the presence of any coexisting illness was more common among patients with severe disease than among those with nonsevere disease (38.7% vs. 21.0%). Presence of radiologic abnormalities at initial presentation was more likely in patients with severe disease ( No radiologic abnormalities were noted on initial presentation in 2.9% of the patients with severe disease and in 17.9% of those with nonsevere disease.)
7	Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al.  China, 2020 Feb	Retrospective single-center observational study	Small sample size Retrospective method Inpatients only	52 critically ill adult patients with SARS-CoV-2 pneumonia who were admitted to the intensive care unit (ICU) of Wuhan Jin Yin-tan hospital (Wuhan, China) between late December, 2019, and Jan 26, 2020.	Risk factor assessment	Overall survival	28-day mortality (ARDS, mechanical ventilation )	Compared with survivors, non-survivors were - older (64.6 years [11.2] vs 51.9 years [12.9]) - more likely to develop ARDS (26 [81%] patients vs 9 [45%] patients) - more likely to receive mechanical ventilation (30 [94%] patients vs 7 [35%] patients), either invasively or non-invasively.  Based on APACHE II score and SOFA score at ICU admission, non-survivors were in a more critical condition than survivors

8	Chen W, Lan Y, Yuan X, Deng X, Li Y, Cai X, et al.  China, 2020 Feb 26	Retrospective study	Very small sample size Retrospective method Inpatients only	57 patients with pneumonia-based diseases caused by 2019-nCoV, enrolled in or transferred to Guangzhou Eighth People's Hospital	Detectable 2019-nCoV viral RNA in blood or anal swabs	No detectable 2019-nCoV viral RNA in blood or anal swabs	Severe illness	-100% (6 out of 6) of those with detectable viral RNA in the blood progressed to severe illness - viral RNA was detectable in the blood in 6 out of 18 severe cases -positive anal swab was associated with a significantly elevated likelihood of severe illness (72.7% severe illness if anal swab positive, 23.5% severe illness if anal swab negative)
9	Tang N, Li D, Wang X, Sun Z.  China, 2020 Feb	Single-center retrospective study	Small sample size Short duration Retrospective method Inpatients only	183 consecutive patients with confirmed 2019-nCoV pneumonia in Tongji hospital	Abnormal coagulation parameters	Normal coagulation parameters	Death	Non-survivors revealed significantly higher D-dimer(2.12µg/mL [0.77-5.27] vs 0.61µg/mL [0.35-1.29]) and fibrin degradation product (FDP) levels (7.6µg/mL [4.0-23.4] vs 4.0µg/mL [4.0-4.3]), longer prothrombin time (15.5sec [14.4-16.3] vs 13.6sec [13.0-14.3]) and activated partial thromboplastin time (44.8sec [40.2-51.0] vs 41.2 [36.9-44.0]) compared to survivors on admission; 71.4% of non-survivors and 0.6% survivors met the criteria of disseminated intravascular coagulation during their hospital stay.
10	Liu K, Fang Y-Y, Deng Y, Liu W, Wang M-F, Ma J-P, et al.  China, 2020 Feb	Retrospective observational study	Small sample size Retrospective method, Inpatients only	137 patients admitted to the respiratory departments identified to be nucleic acid positive for 2019-nCoV in nine tertiary hospitals in Hubei province from December 30, 2019 to January 24, 2020	Clinical features	Recovered and discharged	Death	The risk of death was primarily associated with age, underlying chronic diseases, and shorter median interval from the appearance of initial symptoms to dyspnea. (no exact numbers in article)

11	Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al.  China, 2020 Feb	Retrospectives ingle-center case series	Small sample size Retrospective method, Inpatients only Short duration: many patients still hospitalized at submission of study	138 consecutive hospitalized patients with confirmed 2019- nCoV-infected pneumonia at Zhongnan Hospital of Wuhan University in Wuhan, China, from January 1 to January 28, 2020	Clinical features	Discharge, no transfer to ICU, overall survival	Transfer to ICU, death	Risk factors for transfer to ICU: older (median age, 66 years vs 51 years), underlying comorbidities (72.2% vs 37.3%), dyspnea (63.9% vs 19.6%), and anorexia (66.7% vs 30.4%).  In sequential blood analyses, nonsurvivors showed increasing neutrophil count, D-dimer, blood urea, and creatinine levels, and the lymphocyte counts continued to decrease until death.
12	Wang W., Tang J., Wei F.  China, 2020 Apr	Retrospective observational study		1975 patients with confirmed 2019-nCoV infection in mainland China	Risk factor assessment	Overall survival	Disease progressio n, death	Elderly people (>70 years) might have faster disease progression than younger people.
13	Chen H., Guo J., Wang C., Luo F., Yu X., Zhang W., Li J., Zhao D., Xu D., Gong Q., Liao J., Yang H., Hou W., Zhang Y.  England, 2020 Mar	Retrospective observational study	Small sample size, retrospective method, only third trimester patiënts	9 pregnant patients with laboratory confirmed covid-19 pneumonia.	Clinical features	Non- pregnant adult covid patiënts	Severe illness or death	Similar pattern of clinical characteristics to non-pregnant adult patients. However, none of the nine patients developed severe pneumonia, requiring mechanical ventilation, or died of COVID-19 pneumonia, as of Feb 4, 2020
14	Bassetti M., Vena A., Giacobbe D.R.  2020 Mar	Retrospective observational study	Small sample size	First 41 reported covid- 19 patients	Clinical features	Survival without admission to ICU	Admission to ICU or death	Increased serum levels of IL1B, IFN $\gamma$ , IP10 and MCP1 were registered in the study population compared with healthy subjects, and higher levels of GCSF, IP10, MCP1, MIP1A and TNF $\alpha$ were measured in ICU than in non-ICU

								2019-nCoV patients. (no exact numbers in article)
15	Liu Y., Yang Y., Zhang C., Huang F., Wang F., Yuan J., Wang Z., Li J., Li J., Feng C., Zhang Z., Wang L., Peng L., Chen L., Qin Y., Zhao D., Tan S., Yin L., Xu J., Zhou C., Jiang C., Liu L.  China, 2020 Mar	Single-center retrospective study	Small sample size	12 nCoV infected patients	Biochemical indexes, viral load and lung injury	Severity of lung disease	Severe lung injury	The viral load of 2019-nCoV detected from patient respiratory tracts was positively linked to lung disease severity. ALB, LYM, LYM (%), LDH, NEU (%), and CRP were highly correlated to the acute lung injury. Age, viral load, lung injury score, and blood biochemistry indexes, albumin (ALB), CRP, LDH, LYM (%), LYM, and NEU (%), may be predictors of disease severity. Moreover, the Angiotensin II level in the plasma sample from 2019-nCoV infected patients was markedly elevated and linearly associated to viral load and lung injury. (no exact numbers in article)
16	Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y., Xia J., Yu T., Zhang X., Zhang L.  England, 2020 Feb	Single-center retrospective study	Small size, short duration	99 Covid-19 cases	Clinical features	Overall survival	Death	Old age , obesity, and presence of comorbidity might be associated with increased mortality. (no exact numbers in article)

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