

## Best Evidence Topic Report 9

### Titel:

Welke zijn de alarmsymptomen bij patiënten met vermoeden van een COVID-19 infectie?

### Auteurs:

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### Antwoord op klinische vraag:

Patiënten die op de ICU moeten worden opgenomen, hebben vaak al ARDS, acuut hartfalen, acuut nierfalen of shock, dus een vroegere diagnose is noodzakelijk. In het algemeen hebben oudere patiënten met onderliggende comorbiditeiten (d.w.z. diabetes, hypertensie, chronische obstructieve longziekte) sneller zorg nodig en krijgen vaker een behandeling op de ICU. Sommige van de meest ernstig zieke patiënten met COVID-19-infectie vertonen vaker kortademigheid, hoesten en misselijkheid, volgens studies met een lage bewijskracht.

### Disclaimer:

Deze rapporten zijn ontwikkeld volgens de methode van de Best Evidence Topics, kortweg bestBETs. Een bestBET beoogt een antwoord te geven op een specifieke klinische vraag, geformuleerd op basis van het op dit ogenblik best beschikbare bewijs. Omwille van de beperkte beschikbaarheid van wetenschappelijk bewijs voor COVID-19 topics, worden ook studies van lagere kwaliteit gebruikt. BestBETs bevatten geen aanbevelingen. Studenten 3e Master geneeskunde van de KU Leuven werkten deze topics uit onder begeleiding van twee docenten, waarna ze volgens een vast stramien een eindrapport opstellen. Voor de validatie van deze rapporten, konden we beroep doen op de expertise van CEBAM, die de rapporten rigoreus toetste aan vooropgestelde kwaliteitscriteria.

## Best Evidence Topic Report

<b>Title</b>	What are alarm signs and symptoms when infected with COVID-19?																
<b>Report by</b>	Jolien Van de Wijer & Phoebe Van der Donckt, medical students																
<b>Search checked by</b>	Prof. Dr. Ann Van de Bruel																
<b>Clinical scenario</b>	The population included consists of patients with a severe type of Covid-19 infection. We looked at alarm signs and symptoms that were typical for patients who stayed at ICU or had a high mortality rate.																
<b>Answerable question (PICO/PIRT/PEO/...)</b>	<ul style="list-style-type: none"> <li>- P: patients with severe Covid-19 infection</li> <li>- I: stay at ICU or mortality</li> <li>- O: signs and symptoms</li> </ul>																
<b>Search terms</b>	<ul style="list-style-type: none"> <li>- (covid-19 OR coronavirus covid-19 OR SARS-CoV-2) AND (symptoms OR signs) AND (intensive care OR mortality OR ICU) (Pubmed, Embase, Cochrane, NEJM, BMJ, The Lancet/ScienceDirect)</li> <li>- covid-19 OR coronavirus covid-19 OR SARS-CoV-2 (Annals of Int Med)</li> </ul>																
<b>Search date</b>	18-03-2020																
<b>Search outcome (number of hits)</b>	357 articles																
<b>Relevant papers (number of final inclusions)</b>	9 articles																
<b>Flow chart</b>	See appendix																
<b>Inclusion and exclusion criteria</b>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 33%;"></th> <th style="width: 33%;">Inclusion</th> <th style="width: 33%;">Exclusion</th> </tr> </thead> <tbody> <tr> <td>Population</td> <td>Adults</td> <td>Children</td> </tr> <tr> <td></td> <td>Severe covid 19 infection</td> <td>No Covid-19 infection</td> </tr> <tr> <td>Language</td> <td>English</td> <td>Other languages</td> </tr> <tr> <td>Full text</td> <td>Available</td> <td>Unavailable</td> </tr> </tbody> </table>			Inclusion	Exclusion	Population	Adults	Children		Severe covid 19 infection	No Covid-19 infection	Language	English	Other languages	Full text	Available	Unavailable
	Inclusion	Exclusion															
Population	Adults	Children															
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Full text	Available	Unavailable															

Author, date and country	Study type	Patient characteristics	Intervention/Index test/Exposure	Comparator	Outcome	Key results: RR, AR, NNT Sens/Spec, LR+/LR-HR, OR Other	Main risks of bias
Alfonso J. Rodriguez-Morales et al., 13/03/2020, Colombia	Systematic review and meta-analysis	656 (not only adult) patients with confirmed COVID-19, mean age 51.97 years old; from 01/01/2020 to 23/02/2020	ICU/death	No need for ICU	clinical, laboratory, imaging features, and outcomes	among the patients, 20.3% (95%CI 10.0–30.6%) who required ICU, 32.8% presented with ARDS (95%CI 13.7–51.8), 13.0% with acute cardiac injury (95%CI 4.1–21.9%), 7.9% with acute kidney injury (95%CI 1.8–14.0%), 6.2% (95%CI 3.1–9.3%) with shock and 13.9% (95%CI 6.2–21.5%) had fatal outcomes	<ul style="list-style-type: none"> <li>- Few studies are available for inclusion.</li> <li>- Most studies are from China.</li> <li>- More detailed patient information, particularly regarding clinical outcomes, was unavailable in most studies at the time of analyses.</li> </ul>
Fei Zhou et al., 09/03/2020, China	Retrospective cohort study	191 adult hospitalized patients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan	In-hospital death	Survival	demographic, clinical, treatment, and laboratory outcomes	increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03–1·17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score (5·65,	<ul style="list-style-type: none"> <li>- Not all laboratory tests were done in all patients.</li> <li>- Patients were sometimes transferred late in their illness to the two included hospitals.</li> </ul>

		Pulmonary Hospital (Wuhan, China); from 29/12/2020 to 31/01/2020				<p>2.61–12.23; <math>p &lt; 0.0001</math>) on admission</p> <p>The Sequential Organ Failure Assessment (SOFA) Score is a mortality prediction score that is based on the degree of dysfunction of six organ systems (respiratory, liver, coagulation, cardiovascular, central nervous system, renal). The score is calculated on admission and every 24 hours until discharge using the worst parameters measured during the prior 24 hours.</p>	<ul style="list-style-type: none"> <li>- The estimated duration of viral shedding is limited.</li> <li>- Patients still in hospital as of Jan 31, 2020, and thus relatively more severe disease at an earlier stage were excluded.</li> <li>- Small sample size.</li> </ul>
Qin C. et al., 12/03/2020, China	Retrospective, single-centered study	452 patients with COVID-19 at Tongji hospital; from January 10 to	Severe group Those who met the criterion as follows were defined as severe-type: 1.	Non-severe group	Demographic and clinical data; expression of infection	Severe patients were significantly older (median age, 61 years [IQR, 51-69] vs 53 years	<ul style="list-style-type: none"> <li>- A retrospective, single center and small sample study of patients</li> </ul>

		February 12, 2020	Respiratory distress with the respiratory rate over 30 per minute; 2. Oxygen saturation $\leq$ 93% in the resting state; 3. Arterial blood oxygen partial pressure (PaO <sub>2</sub> ) / oxygen concentration (FiO <sub>2</sub> ) $\leq$ 300mmHg.		related biomarkers, inflammatory cytokines and lymphocyte subsets by flow cytometry	[IQR, 41-62]; P < 0.001); The proportion of men in the severe group (54.2% men) had no significant difference with the non-severe group; Of the 452 patients with COVID-19, 201 (44.0%) patients had chronic diseases (i.e., hypertension, diabetes, chronic obstructive pulmonary disease), and a higher percentage in the severe cases (146[51.0%]) than the mild cases (55[33.1%]); Severe patients were significantly more likely to have short of breath and fatigue (58.4% vs 39.2%; P < 0.001; 51.4% vs 39.2%; P = 0.014; respectively) than non-severe patients.	- admitted to hospital. Patients with COVID-19 who have bacterial co-infection or superinfection might affect the results of immune response.
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<p>Yang X. et al., 24/02/2020, China</p>	<p>Retrospective, single-centered study</p>	<p>52 patients from Dec 24, 2019, to Jan 26, 2020, who had been diagnosed with SARS-CoV-2 pneumonia, according to WHO interim guidance, and who were critically ill.</p>	<p>Critically ill patients Critically ill patients were defined as those admitted to the intensive care unit (ICU) who required mechanical ventilation or had a fraction of inspired oxygen (FiO<sub>2</sub>) of at least 60% or more.</p>	<p>Non-critically ill patients</p>	<p>28-day mortality after ICU admission; incidence of SARS-CoV-2-related acute respiratory distress syndrome (ARDS); the proportion of patients requiring mechanical ventilation.</p>	<p>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), and more likely to receive mechanical ventilation (30 [94%] patients vs 7 [35%] patients), either invasively or non-invasively.</p>	<ul style="list-style-type: none"> <li>- Only 52 critically ill patients were included.</li> <li>- Some specific information from the ICU was missing</li> <li>- A retrospective study</li> </ul>
<p>Wang Z. et al., 16/03/2020, China</p>	<p>Observational study – Cohort study</p>	<p>69 confirmed COVID-19 patients on main campus of Union hospital; from January 16 to January 29, 2020</p>	<p>SpO<sub>2</sub>&lt;90% group</p>	<p>SpO<sub>2</sub>≥90% group</p>	<p>epidemiological, clinical, laboratory, radiologic features; prognosis</p>	<p>The median age of the SpO<sub>2</sub>≥90% group was 37.0 years (IQR 32.0-51.0), whereas the median age of the SpO<sub>2</sub>&lt;90% group was 70.5 years (IQR 62.0-77.0). Patients of the SpO<sub>2</sub>&lt;90% group showed more underlying comorbidities when compared with the SpO<sub>2</sub>≥90% group, such as hypertension</p>	<ul style="list-style-type: none"> <li>- The size of the cohort is limited.</li> <li>- The outcome data of two patients in the SpO<sub>2</sub>&lt;90% group was missing</li> </ul>

						(5[36%] vs 4[7%], p=0.014), cardiovascular disease (5[36%] vs 3[5%], p=0.07), and diabetes (6[43%] vs 1[2%], p<0.001). So, the elderly and the patients with underlying comorbidities are prone to develop severe condition.	
Guan WJ. et al., 28/02/2020, China	Observational study – Cohort study	1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China between December 11, 2019 and January 29, 2020.	Severe disease The degree of severity of Covid-19 (severe vs. nonsevere) at the time of admission was defined using the American Thoracic Society guidelines for community-acquired pneumonia.	Non-severe disease	The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death. Secondary end points were the rate of death and the time from symptom onset until the composite end point and until each component of	Patients with severe disease were older than those with nonsevere disease by a median of 7 years; 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%).	<ul style="list-style-type: none"> <li>- Some cases had incomplete documentation of the exposure history and laboratory testing</li> <li>- The incubation period could be estimated in only 291 of the study patients.</li> <li>- Many patients remained in the hospital and the outcomes were unknown at the time of data cut-off.</li> <li>- Missed patients who were</li> </ul>

					the composite end point.		asymptomatic or had mild cases and who were treated at home
Zhang JJ. et al., 19/02/2020, China	Observational study – Cohort study	140 hospitalized COVID-19 patients, with confirmed result of SARS-CoV-2 viral infection. From January 16 to February 3, 2020	Severe group Severe COVID-19 was designated when the patients had one of the following criteria: (a) respiratory distress with respiratory frequency $\geq 30/\text{min}$ ; (b) pulse oximeter oxygen saturation $\leq 93\%$ at rest; and (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, $\text{PaO}_2/\text{FiO}_2$ ) $\leq 300$ mm Hg.	Non-severe group	clinical and laboratory characteristic of hospitalized patients; reveal the relationship between SARS-CoV-2 infection, immune response, allergy, and clinical manifestations, with a special focus on asthma, COPD, and smoking behaviour.	Median age was 64 years in severe cases, compared to 51.5 years in nonsevere cases ( $P < .001$ ); More comorbidities (79.3% vs 53.7%, $P = .002$ ) in severe cases, compared to nonsevere cases; No difference was identified for the occurrence rates of most signs and symptoms between nonsevere and severe patients, and only two symptoms (cough and nausea) were more commonly experienced in severe group ( $P = .023$ and $0.027$ , respectively).	- Small sample population

<p>Han Q. et al., 25/02/2020 , China</p>	<p>Narrative review</p>	<p>Patients with Covid-19</p>	<p>death</p>	<p>Survival</p>	<p>the nature of the 2019-nCoV and its clinical characteristics and therapeutics</p>	<p>The mortality rate was higher in elder patients with chronic diseases (diabetes, hypertension and angiocardopathy, etc.) and intensive care patients reaching 17-38% in recent reports</p>	<p>- No description of search strategy, included studies and selection criteria.</p>
<p>Dawei Wang, 18/03/2020 , China</p>	<p>Retrospective, single-center case series</p>	<p>138 consecutive hospitalized adult patients with confirmed NCIP (novel coronavirus (2019-nCoV)–infected pneumonia) at Zhongnan Hospital of Wuhan University in Wuhan, China; from 01/01/2020 to 28/01/2020</p>	<p>patients who required ICU care</p>	<p>patients who did not receive ICU care</p>	<p>epidemiological, demographic, clinical, laboratory, radiological, and treatment outcomes</p>	<p>Patients treated in the ICU (n = 36), compared with patients not treated in the ICU (n = 102), were older (median age, 66 years vs 51 years) (p&lt;0,05), were more likely to have underlying comorbidities (26 [72.2%] vs 38 [37.3%]) (p&lt;0,05), and were more likely to have dyspnea (23 [63.9%] vs 20 [19.6%]) (p&lt;0,05), and anorexia (24 [66.7%] vs 31 [30.4%]) (p&lt;0,05).</p>	<p>- Respiratory tract specimens were used to diagnose NCIP through RT-PCR. The serum of patients was not obtained to evaluate the viremia. - Hospital-related transmission/ infection could not be definitively proven but was suspected and presumed based on timing and patterns of exposure to infected patients and</p>

							<p>subsequent development of infection.</p> <ul style="list-style-type: none"><li>- Among the 138 cases, most patients are still hospitalized at the time of manuscript submission.</li></ul>
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## Conclusion of overall body of evidence

### - Main results

The only systematic review and meta-analysis available showed that patients who were taken care of at ICU often presented with ARDS, acute cardiac injury, acute kidney injury and some of them in shock.

The smaller retrospective studies showed a higher amount of older patients (>60 years) in the severe group of Covid-19 patients, the group with a high mortality or in the group treated at ICU. In the group with a severe infection contained more patients with underlying chronic diseases (i.e. hypertension, diabetes, chronic obstructive pulmonary disease) and with a higher SOFA-score. Patients treated in the ICU were more likely to have dyspnea and compared with patients not treated in the ICU.

The cohort studies also showed a higher median age in the group of patients with a severe infection and a higher amount of underlying comorbidities (i.e. hypertension, cardiovascular diseases, diabetes). Only cough and nausea were more commonly observed in the severe group. The studies with the lowest evidence showed a higher chance of treatment in the ICU in elder patients with chronic diseases (i.e. diabetes, hypertension). Patients treated in the ICU had a higher mortality rate.

### - Risks of bias

A problem in all studies is the selection bias. All studies, except for one, were conducted in China, so most of the patients were Chinese. It is not quite sure that for instance people of the Caucasian race would present with similar symptoms to classify them into severe and non-severe cases and if this would influence the need for ICU or mortality.

Another problem are the small sample sizes, so the power of the articles included, is limited. With such size it is difficult to draw a firm conclusion regarding our research questions.

### - Heterogeneity: statistical and/or clinical

In most studies, they use different criteria for describing severe/non-severe/critically ill. It is difficult to compare such groups, although almost all studies include a criterion with  $SpO_2 \leq 93\%$ . The scientific evidence of most studies could be better. We could only include one review and meta-analyse, the rest of the articles are at best cohort studies. This is something that we have to keep in mind reading the conclusion to our research question.

## Clinical bottom line

### - What is your response to the clinical scenario?

Patients who need to be hospitalized in the ICU often already present with ARDS, acute cardiac injury, acute kidney injury or shock so an earlier diagnosis is necessary. In general, the elder patients with underlying comorbidities (i.e. diabetes, hypertension, chronic obstructive pulmonary disease) need more attention and need a treatment in the ICU more often. Some of the patients in the severe group of covid-19 infection were more likely to show dyspnea, cough and nausea in studies with low evidence.

## References

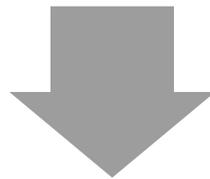
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## **Appendix**

### **Flowchart**

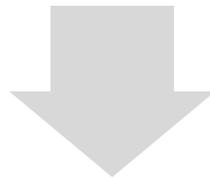
Search 18/03/2020 databases Medline, Embase, Cochrane, NEJM, Annals of Int Med, BMJ and The Lancet/ScienceDirect with terms (covid-19 OR coronavirus covid-19 OR SARS-CoV-2) AND (symptoms OR signs) AND (intensive care OR mortality OR ICU) or (covid-19 OR coronavirus covid-19 OR SARS-CoV-2) or (covid-19 OR coronavirus covid-19 OR SARS-CoV-2) AND (symptoms OR signs) or (covid-19 OR coronavirus covid-19 OR SARS-CoV-2) AND (symptoms OR signs) AND (intensive care OR mortality OR ICU); 2019-2020

Result: 357 articles



First selections after reading title/abstract

Result: 17 articles



Second selection after reading full text/eliminating duplicates

Result: 9 articles

**Table 1**

SOFA score	0	1	2	3	4
<b>Respiration</b>					
PaO <sub>2</sub> /FIO <sub>2</sub> (mmHg) (kPa)	> 400 > 5.3)	301–400 (4.1–5.3)	201–300 (2.8–4.0)	101–200 (1.4–2.7)	≤ 100 ≤ 1.3)
<b>Coagulation</b>					
Platelets (x10 <sup>3</sup> /mm <sup>3</sup> )	> 150	101–150	51–100	21–50	≤ 20
<b>Liver</b>					
Bilirubin (mg/dl) (μmol/l)	< 1.2 < 20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	≥ 12.0 ≥ 204)
<b>Cardiovascular</b>					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
<b>Central nervous system</b>					
Glasgow coma score	15	13–14	10–12	6–9	< 6
<b>Renal</b>					
Creatinine (mg/dl) (μmol/l) or urine output	< 1.2 < 110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) < 500 ml/day	> 5.0 > 440) < 200 ml/day

\* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)