Best Evidence Topic Report

Title	Which factors can help clinicians when to hospitalize patients infected with COVID-19?
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Search checked by	Prof. Dr. J. De Lepeleire and Prof. Dr. B. Schoenmakers
Clinical scenario	Clear guidelines regarding the question as to when to refer patients infected with COVID-19 to a hospital are missing. In our attempt to not see wood for the trees we try to analyse the existing literature for certain degrees of disease severity and specific clinical parameters that could guide health care providers trough this decision.
Answerable question (PICO)	P: all patients with suspected or clinically proven infection with COVID-19 I: serious course of disease C: mild course of disease O: signs and symptoms
Search terms	See search strategy in appendix (Figure 7).
Search date	March, 18, 2020
Search outcome (number of hits)	57 possible articles found across 3 platforms (Pubmed, Embase, Cochrane Library)
Relevant papers (number of final inclusions)	13 articles were included
Inclusion/exclusion criteria	Inclusion criteria: English, including patients infected with COVID-19, containing characteristics of hospitalized patients and/or symptoms of serious course of disease. Exclusion criteria: No full text available, other language than English, single case reports, no relevant information (characteristics hospitalized patients, risk factors, comparison severe versus non-severe infection)

Conclusions of overall body of evidence:

The National Early Warning Score (NEWS) is used in hospitals and care homes in the UK and is a standardized method to recognize acute illness. The following parameters need to be measured: temperature, heart rate, systolic blood pressure, respiratory rate, oxygen saturation and level of consciousness. Based on the obtained values a score will be given, which identifies patients at risk for severe deterioration (Table 4). In times like this, when we are facing a pandemic of Coronavirus Disease 2019 (COVID-19), a standardized tool like NEWS to decide whether a hospitalization is necessary or not would be very valuable for health care providers. Identifying risk factors and criteria for hospitalization would be very useful to help the general practitioners and other aid providers to evaluate the severity of the infection and refer the right patients for admission.

We searched the known literature on three different platforms (Pubmed, Embase and Cochrane library). In a total of 57 articles we thoroughly screened every article for these particular parameters and clinical events. We found 13 articles to be relevant to our design, however some data was missing or not mentioned. The studies are difficult to compare because of their heterogeneity. The used definition as to when the infection is defined as 'severe' also varies among the different studies (table 5). Another risk of bias is that all patients were already hospitalized when the studies were conducted, thus excluding the preceding events. No clear comparative studies were conducted which described hospitalization versus no hospitalization. Therefore we described some risk factors and essential parameters, mentioned in these articles, which could help general practitioners to decide on when to refer the patients for admission.

The most prominent symptoms (table 2 and 3) of an infection with COVID-19 were fever, coughing, fatigue or myalgia and dyspnea. A sore throat, rhinorrhea and diarrhea are described less frequently. The condition of patients with these symptoms can be mild or severe. An assessment of the need of hospitalization should be made, when a patient presents with these symptoms.

First, we give an overview of the different parameters, used in the NEWS (table 4). High temperature is present in the majority of the patients. Several studies describe a higher proportion of patients with fever and a higher temperature in the severe group, compared to the non-severe group. However, other studies didn't notice a significant difference between the two groups. The data are insufficient to determine a cut-off value for temperature, but they suggest that a higher temperature is possibly correlated with a more severe infection.

Although we expect a higher heart rate in the severe group, this finding was surprisingly not frequently seen in these studies. In a single study of 191 participants, all the patients with a heart rate > 125/minute (4%) were part of the group of patients who died during hospitalization.

In the NEWS criteria, a systolic blood pressure < 90 mmHg or > 220 mmHg is defined as the highest risk. These values were not seen in our data, not even in the severe groups. However, a systolic blood pressure < 90 mmHg or > 220 mmHg obviously seems to be a reason for hospitalization.

Respiratory rate seems to be a useful parameter to evaluate the severity of the patient's condition. Multiple studies showed that a significant higher percentage of patients who received ICU care or

died during hospitalization had a respiratory rate > 24/minute, in comparison to the group who did not receive ICU care or who survived.

Another important factor to determine the severity of the COVID-19 infection is the oxygen saturation. Different cut-off values are used in the different studies (90% or 93%). In a study of 69 patients with a mortality of 7.5%, the severe group was defined as an oxygen saturation < 90% and all the five patients who died were part of this group. Oxygen saturation is definitely an important parameter to take into account.

Level of consciousness was not mentioned in the studies we investigated, but it is clear that a reduced level of consciousness is a warning signal and that these patients need to get referred immediately.

Secondly, we would like to discuss some additional risk factors, like age and comorbidities (table 1). In almost all the studies that distinguish between severe and non-severe, the median age was higher in the severe group. We can conclude that an older age is a risk factor for a more severe course of the COVID-19 infection.

Diabetes, arterial hypertension and cardiovascular diseases are the most commonly described comorbidities. In most studies, a higher proportion of comorbidities was seen in the severe group which implies that having comorbidities is an additional risk factor and lowers the threshold for hospitalization.

As mentioned above, no comparison could be made between the different studies. This is merely a description of the different critical parameters and risk factors, mentioned in these studies and possibly useful in the decision whether to send the patient for hospitalization or not. More comparative high-quality studies are needed to investigate this research question.

Clinical bottom line: What is your response to the clinical scenario?

To summarize, there is limited evidence that the following signs from the NEWS criteria are suggestive of a more serious course of COVID: high temperature, a respiratory rate > 24/minute, oxygen saturation < 90%. The following signs from the NEWS criteria are suggestive for a more serious course of COVID based on common sense: systolic blood pressure < 90 mmHg or > 220 mmHg and a decreased level of consciousness. Moreover, other risk factors like age and possible comorbidities should be taken into account when this decision need to be taken.

Appendix:

The numbers of the articles of all the tables refer to the numbers of the reference list.

Table 1. Co-morbidities in % of the included patients.

Articles	# patients		Hypertension	Diabetes	Cardiovascular disease
Article 1	Total	21	/	/	/
	Severe	/			
	Non-severe	/			
Article 2	Total	1099	23.70%	7.40%	2.50%
	Severe	926	13.40%	16.20%	5.80%
	Non-severe	173	15.0%	5.70%	1.80%
Article 3	Total	41	15%	20%	15%
	Severe	13	15%	8%	23%
	Non-severe	28	14%	25%	11%
Article 4	Total	83	6.0%	7.8%	1.2%
	Severe	25	8%	28%	4%
	Non-severe	58	5.2%	0%	0%
Article 5	Total	78	/	/	/
	Severe	8			
	Non-severe	70			
Article 6	Total	46248	17% +/- 7%	8% +/- 6%	5% +/- 4%
	Severe				
	Non-severe				
Article 7	Total	50466	/	/	/
	Severe	9134			
	Non-severe	41332			
Article 8	Total	69	13%	10%	12%
	Severe	14	36%	43%	36%
	Non-severe	55	7%	2%	5%
Article 9	Total	201	19.40%	10.90%	4%
	Severe				
	Non-severe				
Article 10	Total	149	/	/	/
	Severe	3			
	Non-severe	146			
Article 11	Total	18	Any comorbidity: 28%		
	Severe	6	Any comorbidity: 67%		
	Non-severe	12	Any comorbidity: 8%		
Article 12	Total	140	30.80%	12.10%	5%
	Severe	58	37.90%	13.80%	6.90%
	Non-severe	82	24.40%	11%	3.70%
Article 13	Total	191	30%	19%	8%
	Severe				
	Non-severe				

Table 2. Clinical characteristics in % of the included patients.

Articles	# patients		Fever	Coughing	Fatigue	Sputum	Sore throat	Dyspnea
Article 1	Total	21	86%	57%	52%	29%		/
	Severe	/						
	Non-severe	/						
Article 2	Total	1099	88.70%	67.80%	38.10%	33.70%	13.90%	18.70%
	Severe	926	91.90%	70.50%	39.90%	33.40%	13.30%	37.60%
	Non-severe	173	88.10%	67.30%	37.80%	35.30%	14%	15.10%
Article 3	Total	41	98%	76%	44%	28%	/	55%
	Severe	13	100%	85%	54%	38%	/	92%
	Non-severe	28	96%	71%	39%	23%	/	37%
Article 4	Total	83	86.7%	78.3%	/	18.1%	7.2%	10.8%
	Severe	25	/	96%	/	36%	8.0%	28%
	Non-severe	58	86.2%	70.7%	/	10.3%	6.9%	3.4%
Article 5	Total	78						
	Severe	8						
	Non-severe	70						
Article 6	Total	46248	91 +/- 3%	67 +/- 7%	51 +/- 0%	/	/	30 +/- 4%
	Severe							
	Non-severe							
Article 7	Total	50466	89.10%	72.20%	42.50%	/	/	/
	Severe	9134						
	Non-severe	41332						
Article 8	Total	69	87%	55%	42%	29%	/	29%
	Severe	14	93%	57%	50%	29%	/	50%
	Non-severe	55	85%	55%	40%	29%	/	24%
Article 9	Total	201	93.50%	81.10%	32.30%	41.30%	/	39.80%
	Severe							
	Non-severe							
Article 10	Total	149	76.51%	58.39%	/	/	14.9%	1.34%
	Severe	3						
	Non-severe	146						
Article 11	Total	18	72%	83%	/	/	61%	11%
	Severe	6	100%	83%			50%	17%
	Non-severe	12	58%	83%			67%	8%
Article 12	Total	140	91.70%	75%	75%	/	/	36.70%
	Severe	58	96.20%	84.90%	73.60%			45.30%
	Non-severe	82	88.10%	67.20%	76.10%			29.90%
Article 13	Total	191	94%	79%	23%	23%	/	/
	Severe		94%	72%	28%	26%		
	Non-severe		94%	82%	21%	22%		

Table 3. Clinical characteristics in % of included patients

Articles	# patients		Rhinorree	Diarrhea	Myalgia
Article 1	Total	21	/	/	24%
	Severe	/			
	Non-severe	/			
Article 2	Total	1099	4.80%	3.80%	14.90%
	Severe	926	3.50%	5.80%	17.30%
	Non-severe	173	5.10%	3.50%	14.50%
Article 3	Total	41	/	3%	44%
	Severe	13		0%	54%
	Non-severe	28		4%	39%
Article 4	Total	83	/	8.4%	18.1%
	Severe	25		8.0%	20.0%
	Non-severe	58		8.6%	17.2%
Article 5	Total	78	/	/	/
	Severe	8			
	Non-severe	70			
Article 6	Total	46248	/	/	/
	Severe				
	Non-severe				
Article 7	Total	50466	/	/	/
	Severe	9134			
	Non-severe	41332			
Article 8	Total	69	/	14%	30%
	Severe	14		14%	14%
	Non-severe	55		15%	35%
Article 9	Total	201	/	/	/
	Severe				
	Non-severe				
Article 10	Total	149	3.36%	7.38%	3.36%
	Severe	3			
	Non-severe	146			
Article 11	Total	18	6%	17%	/
	Severe	6	0%	0%	
	Non-severe	12	8%	25%	
Article 12	Total	140	/	12.90	/
	Severe	58		15.80%	
	Non-severe	82		11.0%	
Article 13	Total	191	/	5%	15%
	Severe			4%	15%
	Non-severe			5%	15%

Table 4. NEWS criteria. sBP = systolic blood pressure, bpm = beats per minute, SaO2 = saturation

Articles	# patients		Respiratory rate	SaO2	SupplementoryO2 used	Fever (>37.5°C)	sBP (mmHg)	Heartritme (bpm)	Level of consciousness
						NEWS Criteria			
Article 1	Total	21				86%			
	Severe	/							
	Non-severe	/							
Article 2	Total	1099				88.70%			
	Severe	926				91.90%			
	Non-severe	173				88.10%			
Article 3	Total	41	>24/min: 29%			98%	125		
	Severe	13	>24/min: 29%			100%	145		
	Non-severe	28	>24/min: 29%			96%	125		
Article 4	Total	83	20			37.8° avg		90	
	Severe	25	21			38° avg		92	
	Non-severe	58	20			37.6° avg		89	
Article 5	Total	78							
	Severe	8				38.2° avg			
	Non-severe	70				37.5° avg			
Article 6	Total	46248							
	Severe								
	Non-severe								
Article 7	Total	50466							
	Severe	9134							
	Non-severe	41332							
Article 8	Total	69			64.2%	87%			
	Severe	14		<90%		93%			
	Non-severe	55		90%+		85%			
Article 9	Total	201							
	Severe								
	Non-severe								
Article 10	Total	149		97.43%	89.93%		129.98%	88.63%	
	Severe	3							
	Non-severe	146							
Article 11	Total	18	18/min	98%	33%				
	Severe	6	20/min	97%	100%				
	Non-severe	12	18/min	98%	0%				
Article 12	Total	140							
	Severe	58	30 or more	<93%					
	Non-severe	82	<30	94%+					
Article 13	Total	191	>24/min: 29%			94%	<90mmHg: 1%	>125/min: 1%	
	Severe		>24/min: 63%			94%	<90mmHg: 0%	>125/min: 4%	
	Non-severe		>24/min: 16%			94%	<90mmHg: 1%	>125/min: 0%	

Table 5. Used criteria for definition of 'severe' infection

Articles	# patients		Definition of 'severe'
Article 1	Total	21	-Severe respiratory distress (respiratory rate >30 breaths/min)
	Severe	/	-Requirement for oxygen treatment or mechanical ventilation
	Non-severe	/	-SpO2<90% on room air
Article 2	Total	1099	American Thoracic Society guidelines for community-acquired pneumonia:
	Severe	926	('severe' if 1 major of ≥3 minor criteria)
	Non-severe	173	

Minor criteria	Major criteria
-Respiratory rate > 30 breaths/min -PaO2/FIO2 ratio < 250 -Multilobar infiltrates -Confusion/disorientation -Uremia (blood urea nitrogen level > 20 mg/dl) -Leukopenia (white blood cell count , 4,000 cells/ml) -Thrombocytopenia (platelet count , 100,000/ml) -Hypothermia (core temperature , 368C) -Hypotension requiring aggressive fluid resuscitation	-Septic shock with need for vasopressors -Respiratory failure requiring mechanical ventilation

Articles	# patients		Definition of 'severe'
Article 3	Total	41	
	Severe	13	ICU-care
	Non-severe	28	No ICU-care
Article 4	Total	83	-Respiratory rate ≥30 breaths per minute
	Severe	25	-Finger of oxygen saturation ≤93% in a resting state
	Non-severe	58	-Arteria oxygen tension (PaO 2)/inspiratory oxygen fraction (FiO 2) ≤300 mmHg (1mmHg=0.133kPa) -Respiratory failure occurred and mechanical ventilation required -Shock occurred -Patients with other organ failure needed intensive care unit monitoring and treatment
Article 5	Total	78	-Respiratory distress, respiratory rate (RR) ≥30 breaths/min
	Severe	8	-Oxygen saturation ≤93% at rest
	Non-severe	70	-Partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300 mmHg (1 mmHg = 0.133 kPa)
Article 6	Total	46248	/
	Severe		
	Non-severe		
Article 7	Total	50466	/
	Severe	9134	
	Non-severe	41332	
Article 8	Total	69	Oxygen saturation <90%
	Severe	14	
	Non-severe	55	
Article 9	Total	201	/
	Severe		
	Non-severe		
Article 10	Total	149	CURB-65
	Severe	3	PSI score (class IV or V)
	Non-severe	146	
Article 11	Total	18	Extra ogyxen needed
	Severe	6	
	Non-severe	12	
Article 12	Total	140	-Respiratory distress, respiratory rate (RR) ≥30 breaths/min
	Severe	58	-Oxygen saturation ≤93% at rest
	Non-severe	82	-Partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300 mmHg (1 mmHg = 0.133 kPa)
Article 13	Total	191	/
	Severe		
	Non-severe		

Table 6: Study characteristics

Articles	Study date	Design	Study Location	Journal	Study advantages	Study downsides
Article 1	13/2/2020	Retrospective cohort study	Wuhan, China	Radiological society of North America	-Clear statistical results	-Limited population (21 patients) -Focussed on the radiological findings rather than the clinical characteristics
Article 2	28/2/2020	Multicentre comparison	China	New England Journal of Medicine	-Large study population -Multicenter -Comparison severe vs non-severe	-Some cases had incomplete documentation -Data regarding the clinical outcomes of the patients who remained in the hospital at the time of data cutoff were censored. -Patients who were treated at home were missed so the population represents the more severe cases of COVID-19. -Data was clinically generated and not systematically.
Article 3	15/2/2020	Multicentre comparison	Wuhan, China	The Lancet	-Laboratory-confirmed diagnosis -Difference of severity based on whether patient needed ICU care or not	-Limited population -Possible exposure bias (no kids or adolescents were used in this study)
Article 4	29/2/2020	Retrospective cohort study	China	Investigative radiology	-Comparison severe vs non-severe -Clear definition of severe cases -Multicenter	-Limited population of the severe group -All patients were already hospitalized, thus making it hard to reliably analyse the risk factors
Article 5	28/2/2020	Retrospective cohort study	Wuhan, China	Chinese Medical Journal	-Multicenter	-Limited population (78 patients)
Article 6	12/3/2020	Systematic review & meta-analysis	China	International Journal of Infectious Diseases	-Large study population (46248 patients) -Systematic review en meta-analysis	-High heterogeneity between centers -Different length of follow-up -No sensitivity and subgroup analysis were conducted, because only a few studies compared the comorbidities of severe and non-severe patients
Article 7	28/2/2020	Systematic review & Meta-analysis	China	Journal of Medical Virology	-Large study population (50466 patients) -Multicenter -Meta-analysis	-Large heterogeneity between the included studies -Publication bias -Population consisted of mainly hospitalized patients
Article 8	16/3/2020	Retrospective cohort study	China	Publication by Infectious Diseases Society of America	-Clear statistical results	-Limited population -Single center study -Possible bias with the measurements of oxygen saturation
Article 9	13/3/2020	Retrospective cohort study	China	JAMA Internal Medicine	-Clear statistical results	-Only hospitalization of patients with relatively severe COVID-19 pneumonia -Single center with limited study population -Possible selection bias
Article 10	26/2/2020	Retrospective cohort study	China	Joural of infection	-Reasonable study population (149) -Multicenter	-Mostly patients with mild disease used for follow-up
Article 11	3/3/2020	Descriptive case series	China	JAMA Internal Medicine	-Comparison severe vs non-severe	-Limited population (18) -Sample collection early during the course of illness was limited -Missing data
Article 12	19/2/2020	Retrospective cohort study	China	European Journal of Allergy and Clinical Immunology	-Reasonable study population (140) -Comparison severe vs non-severe	-Focus mainly on the laboratory characteristics of the disease
Article 13	11/3/2020	Retrospective cohort study	Wuhan, China	The Lancet	-Multicenter -Comparison survivor vs non-survivor -Clear statistical results	-Missing data -Patients were sometimes tranferred late in the disease proces -Patients still in the hospital at the end of the study were excluded (relatively more severe disease at an earlier stage)

Figure 7. Search strategy

Pubmed:

"severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe-acute-respiratory-syndrome-coronavirus-2 [tiab] OR "COVID-19" [Supplementary Concept] OR COVID-19 [tiab] OR Wuhan-coronavirus [tiab] OR Wuhan-seafood-market-pneumonia-virus [tiab] OR COVID19-virus [tiab] OR COVID-19-virus [tiab] OR coronavirus-disease-2019-virus [tiab] OR SARS-CoV-2 [tiab] OR SARS2 [tiab] OR 2019-nCoV [tiab] OR 2019-novel-coronavirus [tiab]

AND

 "Hospitalization"[Mesh] OR hospitalization* [tiab] OR hospitalized [tiab] OR hospitalization-criteria [tiab] OR reasons-for-hospitalization [tiab] OR patient-selection [tiab] OR "Risk Factors"[Mesh] OR risk-factor* [tiab] OR population*-at-risk [tiab] OR severe-symptom* [tiab] OR severe-manifestation* [tiab] OR predictor of hospitalization

Cochrane Library:

#1: [mh "Coronavirus"] OR [mh "Coronavirus Infection] OR [mh "Coronavirus Infections"] OR [mh "Severe Acute Respiratory Syndrome Virus"] OR [mh "Severe acute respiratory syndrome related coronavirus"] OR [mh "Severe acute respiratory syndrome-related coronavirus"] OR [mh "SARS (Severe Acute Respiratory Syndrome)"] OR [mh "SARS Associated Coronavirus"] OR [mh "SARS Coronavirus] OR [mh "SARS Related Coronavirus"] OR [mh "SARS Virus"] OR [mh "SARS-Associated Coronavirus"] OR [mh "SARS-CoV"] OR [mh "SARS-Related Coronavirus"]

#2: ("coronavirus" OR (coronavirus NEXT infection*) OR (severe NEXT acute NEXT respiratory NEXT syndrome NEXT virus) OR (severe NEXT acute NEXT respiratory NEXT syndrome NEXT related NEXT coronavirus) OR "sars" OR (sars NEXT associated NEXT coronavirus) OR (sars NEXT coronavirus) OR (sars NEXT related NEXT coronavirus) OR (sars NEXT virus) OR (sars NEXT associated NEXT coronavirus) OR (sarsNEXT cov) OR (sars NEXT related NEXT coronavirus) OR "covid19" OR (covid19 NEXT virus) OR (coronavirus NEXT disease NEXT 2019 NEXT virus) OR "sarscov2" OR "sars2" OR "2019ncov" OR (2019 NEXT novel NEXT coronavirus) OR (severe NEXT acute NEXT respiratory NEXT syndrome NEXT virus NEXT 2)):ti,ab,kw

#3 : #1 OR #2

#4: [mh "Hospitalization"] OR [mh "Hospitalizations"] OR [mh "Patient Selection"] OR [mh "Population at Risk"] OR [mh "Risk Factor"] OR [mh "Risk Factors"] OR [mh "Risk Assessment"] OR [mh "Risk Assessments"]

#5: ("hospitalization*" OR (patient NEXT selection) OR (population NEXT at NEXT risk) OR (risk NEXT factor*) OR (risk NEXT assessment*) OR "hospitalized" OR (hospitalization NEXT criteria) OR (reasons NEXT for NEXT hospitalization) OR (severe NEXT symptom*) OR (severe NEXT manifestation*)):ti,ab,kw

#6: #4 OR #5

#7: #3 AND #6

Embase:

('coronavirus 2019' OR covid) AND ('hospitalization'/exp OR 'hospital admission'/exp)

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