Which symptoms and clinical signs should be included in the clinical risk assessment of patients with a (suspicion of) Covid-19 infection and what are their demonstrative and exclusive powers?
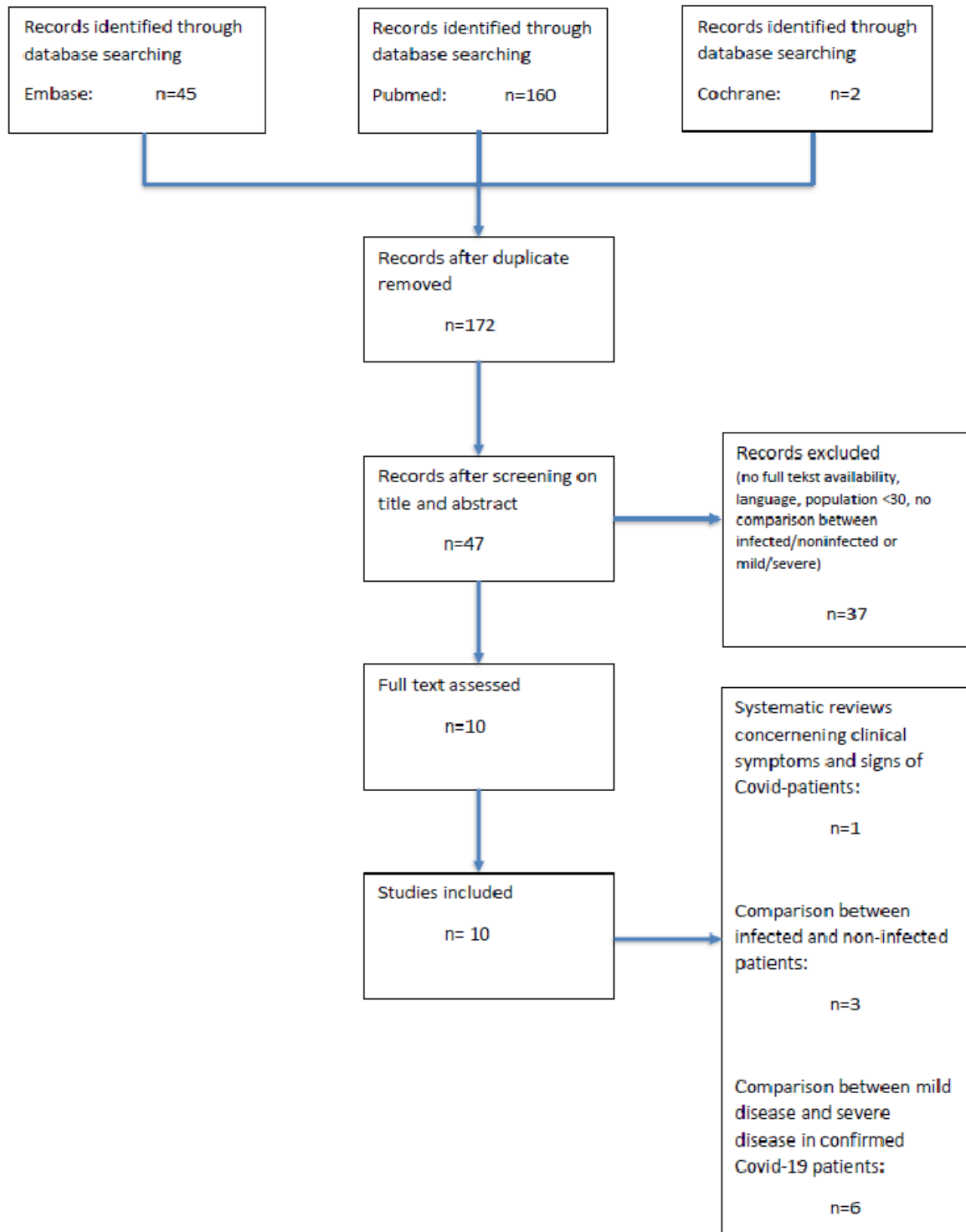
Clinical problem	There are difficulties with clinical differentiation between infections caused by the novel Covid-19-virus and other viral infections of the respiratory tract.

3 part question	
Patient characteristic	All patients with (suspicion of) a Covid-19 infection
Intervention(s)	/
Comparison	Comparison of symptoms/signs between Covid-19 positive and negative patients and between mild and severe Covid-19 patients.
Relevant Outcome(s)	symptoms and clinical signs

Best Evidence Topic Report	
Title	Which symptoms and clinical signs should be included in the clinical risk assessment of patients with a (suspicion of) Covid-19 infection and what are their demonstrative and exclusive powers?
Report by	Desiree Schrijnemakers and Tom Robben, 3rd master in Medicine students Supervised by Dr. Brigitte Schoenmakers, general practitioner
Search checked by	Desiree Schrijnemakers (medicine student, master), Tom Robben (medicine student, master), Prof. Dr. Birgitte Schoenmakers (professor of General Practice)
Clinical scenario	1. Comparison of frequencies of symptoms in Covid-19-positive patients vs Covid-19 negatieve patients 2. Comparison of frequencies of symptoms in mild Covid-19 patients vs severe Covid-19 patients
Answerable question (PICO)	See above
Search terms	**Medline**: 1.(((covid-19) OR SARS-CoV-2)) AND ((symptoms) OR signs)) AND clinical **Embase**:1. ('covid 19' OR 'sars cov 2') AND clinical AND assessment 2.('covid 19' OR 'sars cov 2') AND clinical AND (symptoms OR signs) **Cochrane library**: Covid-19 OR Sars-CoV-2
Search date	17/03/2020 and 18/03/2020

Search outcome (number of hits)	**Medline**: *160* papers found of which *118* irrelevant (1st selection) and *33* not meeting the inclusion criteria (2nd selection) **Embase**: 2 searches combined: *45* papers found of which *40* irrelevant or duplicates (1st selection) and *5* not meeting the inclusion criteria (2nd selection) **Cochrane library**: *2* papers found of which *2* irrelevant (1st selection)
Relevant papers (number of final inclusions)	11
Flow chart	see below
Inclusion criteria	-A comparison of symptoms was made between Covid-19-positive and Covid-19-negative patients OR a comparison of symptoms was made between mild and severe Covid-19 cases
Exclusion criteria	-Study population smaller than 30 people -Study population consisting of children -No comparison of symptoms was made between Covid-19-positive and Covid-19-negative patients OR no comparison of symptoms was made between mild and severe Covid-19 cases -Full article text was not available -Article is not available in English

1. Flowchart of the study selection process

Records identified through database searching	Records identified through database searching	Records identified through database searching
Embase: n=45	Pubmed: n=160	Cochrane: n=2

Records after duplicate removed

n=172

Records after screening on title and abstract

n=47

Records excluded (no full tekst availability, language, population <30, no comparison between infected/noninfected or mild/severe)

n=37

Full text assessed

n=10

Systematic reviews concernening clinical symptoms and signs of Covid-patients:

n=1

Studies included

n= 10

Comparison between infected and non-infected patients:

n=3

Comparison between mild disease and severe disease in confirmed Covid-19 patients:

n=6

2. Evidence table:

Database	Author, date, country	Evidence level - study type	Number of patients	Patient characteristics	Intervention	Comparison	Outcome	Key results (only significant results are listed)	Main risks of bias
PUBMED	Sun P et al, Feb 28 2020, China	3A - systematic review	50466	Patients with SARS-CoV-2 infection	Covid 19 +	not applicable	frequencies of clinical symptoms	**Incidences of symptoms/clinical signs in confirmed Covid-19 patients:** fever:0.891 (95% CI: 0.818, 0.945), cough:0.722 (95% CI: 0.657, 0.782), muscle soreness or fatigue: 0.425 (95% CI: 0.213, 0.652), acute respiratory distress syndrome (ARDS): 0.148 (95% CI: 0.046,0.296). For further results, see article.	Publication bias for ARDS (Egger test)
PUBMED	Zhu W et al, Mar 13 2020, China	3B – case control study	116	All patients suspected for Covid-19 infection who presented at the ED of the USTC hospital, China between Jan 24 and Feb 20.	Covid 19 +	covid19 -	frequencies of clinical symptoms	Presence of fever: RR (95%C.I.)=1,24 (1,01-1.53); p=0,04. Peak body temperature: Mean difference +- SE= 0,20 +- 0,068 ; p=0,003.	Selection bias
PUBMED	Zenghui C et al., Mar 14 2020, China	3B – case control study	33	All patients with confirmed pneumonia in a fever observation department in Shangai, China. Admission between Jan 19 and Feb 6, 2020.	covid19 + pneumonia	covid19 – pneumonia	frequencies of clinical symptoms	no significant differences in symptoms/clinical signs between the 2 groups	Selection bias
PUBMED	Zhao D et al, Mar 12 2020, China	4 – case series	34	All patients with confirmed pneumonia at the Anhui hospital, China. Admission between Jan 23 and Feb 5.	covid19 + pneumonia	covid19 - pneumonia	frequencies of clinical symptoms	no significant differences in symptoms/clinical signs between the 2 groups	Selection bias

Database	Author, date, country	Evidence level - study type	Number of patients	Patient characteristics	Intervention	Comparison	Outcome	Key results (only significant results are listed)	Main risks of bias
PUBMED	Tian S et al, Feb 27 2020, China	3B- case control study	262	All hospitalized Covid-19 positive patients (RT-PCR +) in the hospitals across Beijing transferred to the designed hospitals for treatment of the Covid-19 cases. Admission till Feb 10, 2020.	severe cases	non severe cases, no pneumonia, no symptoms	frequencies of clinical symptoms	Presence of shortness of breath: RR (95%C.I.)=23,5 (7,1-77,8); p<0,0001	Selection bias
PUBMED	Zhang JJ et al, Feb 19 2020, China	3B- case control study	242	All hospitalized patients in Hospital n°7 in Wuhan,China with confirmed Covid-19 infection. (admission between Jan 16 and Feb 3, 2020)	severe cases	non-severe cases	frequencies of clinical symptoms	Presence of cough: RR (95%C.I.)=1,26 (1,03-1,55); p=0,023	Attrition bias + Selection bias
PUBMED	Li K et al, Feb 29 2020, China	3B- case control study	83	Patients hospitalized with confirmed COVID-19 pneumonia (RT-PCR positive and abnormal CT-scan) in the hospitals of Chonqing. Admission between Jan 2020 and Feb 2020.	severe cases	non-severe cases	frequencies of clinical symptoms	Presence of cough: RR (95%C.I.)=1,36 (1,13-1,63); p=0,0001. Presence of sputum/expectoration: RR(95%C.I.)=3,48 (1,39-8,74); p=0,0079. Presence of shortness of breath: RR (95%CI.I)=8,12 (1,81-36,4); p=0,0062. Presence of chest tightness: RR(95%C.I.)=9,28 (1,09-78,9); p=0,041.	Selection bias
PUBMED	Liu W et al, Feb 28 2020, China	3B- prospective case control study	78	All hospitalized patients in three tertiary hospitals in Wuhan,China with confirmed Covid-19 pneumonia (admission between Dec 30 2019 and Jan 15 2020)	progression group	remission or stabilisation group	frequencies of clinical symptoms	Presence of shortness of breath: RR (95%C.I.)=2,61 (1,28-5,32); p=0,0083	Selection bias
PUBMED	Huang C et al, Feb 15 2020, China	3B- prospective case control study	41	All hospitalised patients with confirmed covid-19 infection (RT-PCR) (admission between Dec 16 2019 and Jan 2 2020)	ICU	no ICU	frequencies of clinical symptoms	Presence of shortness of breath: RR(95%C.I.)=2,49 (1,49-4,18); p=0,001. Presence of chest tightness: RR(95%C.I.)=2,49 (1,49-4,18); p=0,001.	Attrition bias
PUBMED	Wang D et al, Feb 7 2020, China	4 – case series	138	All consecutive patients with confirmed NCIP admitted to Zhongnan Hospital of Wuhan University from January 1 to January 28, 2020	ICU	no ICU	frequencies of clinical symptoms	Presence of sore throat: RR (95%C.I.)= 2,83 (1,40-5,73); p=0,0037. Presence of chest tightness: RR (95%C.I.)=3,26 (2,05-5,18); p<0,0001	Selection bias

3. Quality analysis of the included studies:

Art 1: Sun P. et al.:

- Clearly defined inclusive and exclusive criteria and strict control of included studies.
- Included studies are 10 retrospective studies with a large heterogeneity
- A very large study population, however the study subjects were in-patients who have been diagnosed with Covid-19 infection. So the incidence of severe pneumonia or the fatality rate in the total infected population could be much lower than these study results show.
- All not-published articles were excluded. They performed an Egger test, which showed publication bias for the ARDS-meta-analysis.

Art 2: Zhu W et al.:

- Only patients who were suspected for Covid-19 infection based on the guidelines of the Chinese Health Department were admitted to the hospital, included in the study, and tested for Covid-19 infection. There is a risk of selection bias because a first selection of patients was already made outside the hospital. This way, patients with atypical symptoms were not included in the study. This makes the study population probably more homogeneous than the average population.

Art 3: Cheng Z. et al.:

- Clearly described methodology and methods, but exclusion criteria are not mentioned.
- Patients were first evaluated bij specialists who decided if testing for Covid-19 and CT for detection of pneumonia were necessary. Only patients with proven pneumonia were included. 5 patients who tested negative for Covid-19 infection and had no pneumonia were not included in the study. This leads to a risk of selection bias.

Art 4: Zhao D. et al.:

- It remains unclear how patients were enrolled in the study. The inclusion and exclusion criteria are not specified. Were all patients who had been admitted to the hospital between January 23 and February 5 included in the study, or did the researchers make a selection? Further, the authors report that no patients with severe infection were included in the study. Was this done deliberately? This leads to a significant risk of selection bias.

Art 5: Tian S. et al.:

- All included patients had been diagnosed in other hospitals before being transferred to the designated hospital where the data collection took place. There is a risk of selection bias because a first selection of patients was already made outside the hospital. This way, patients with atypical symptoms were not included in the study.
- Clear definitions of confirmed cases, suspected cases, mild and severe cases and non-pneumonia and asymptomatic cases.
- Data was collected and evaluated by two independent reviewers.
- The ordinary group included mild cases of pneumonia, non-pneumonia and asymptomatic cases. However there is no further subanalysis of characteristics between these groups. Thus significant selection bias.

Art 6: Zhang JJ. et al.:
- Significant differences in characteristics of the two groups were found. Severe cases had a significantly higher age and more comorbidities than the nonsevere cases. This leads to a risk of selection bias.

- Not all symptoms have been questioned for every included patient. This leads to a risk of attrition bias.

<u>Art 7: Li K. et al.:</u>

- Clearly defined inclusion and exclusion criteria of the study population. Clearly defined group characteristics: ordinary or severe.
- Only patients with abnormal signs on CT-scan were included. Seven patients diagnosed with Covid-19 were excluded because their CT-scan showed no abnormal signs. No information about their baseline characteristics or follow-up is known. This might lead to selection bias.

<u>Art 8: Liu W et al.:</u>

- Clear inclusion criteria of patients and clear criteria for the three clinical types (common, severe and critical) and division into the two outcome groups: progression or remission/stabilisation.
- The results mainly focus on the comparison of characteristics between the progression group and the remission group. However, when evaluating these characteristics, they do not take the initial state of the patient into account. No comparison in characteristics within the earlier assigned clinical types (common, severe, critical) has been made. This leads to a great risk of selection bias. Among the common-type group there were 8 out of 62 patients who showed progression. Among the severe-type group 3 out of 8 patients showed progression.

<u>Art 9: Huang C. et al.:</u>

- Patients were included when their Covid-19 infection was confirmed by RT-PCR.
- Clear difference between outcomes: ICU-care required versus no ICU-care required
- Not all symptoms have been questioned for every included patient. This leads to a risk of attrition bias.

<u>Art 10: Wang D. et al.:</u>

- All patients enrolled were diagnosed with Novel Corona Infection Pneumonia (NCIP) according to WHO interim guidance. They were all in-hospital patients, who have been diagnosed with Covid-19. Not all covid-19 require hospitalisation, so the incidence of ICU-admittance in the total infected population would be lower than shown in this study.

4. **Summary of the findings**

In this Best BET we aimed to answer two questions. The first one being whether it is possible to differentiate between a respiratory infection caused by the novel Covid-19 virus and ordinary respiratory infections based on clinical assessment alone, and what symptoms and clinical signs are key in that differentiation. The second question was whether it is possible to differentiate between a mild Covid-19 infection and a severe Covid-19 infection based on onset symptoms and onset clinical signs.

To answer these two questions we performed two analyses. For the first analysis we included 3 observational studies that compared symptoms of Covid-19 positive patients and Covid-19 negative patients with respiratory complaints. The number of symptoms and signs broken down by Covid-19 positive and Covid-19 negative patients, for each of the individual studies, are listed in the sheet *'analysis'* of the attached excel file. The most reported symptoms were fever, cough and expectoration, but also dyspnea, myalgia, fatigue, sore throat, headache, chest tightness, haemoptysis, lung auscultation and diarrhea were compared. In general, there were no consistent

differences in symptoms and clinical signs between the Covid-19 positive and negative groups. This means that with the data currently available there is no evidence for any of the symptoms or clinical signs to be a good indicator for the presence or absence of a Covid-19 infection. According to the analyzed studies a Covid-19 infection has practically the same symptomatology as other viral upper airway infections. It comes as no surprise that these studies come to this conclusion, knowing that all patients tested in these studies had symptoms that were suspicious for Covid-19 positivity.

In a second analysis we clustered 6 observational studies that examined the difference in initial symptoms between mild and severe Covid-19 infections. The number of symptoms and signs broken down by mild and severe Covid-19 patients, for each of the individual studies, are listed in the sheet *'analysis'* of the attached excel file. Here the most common symptoms were fever, cough, myalgia and fatigue. Other symptoms that were analyzed were expectoration, sore throat, headache, dyspnea, hemoptysis and diarrhea. The only consistent difference in symptom onset between severe and mild Covid-19 cases was shortness of breath. All 4 studies that examined shortness of breath as a symptom showed a significantly higher prevalence in the group of severe cases compared to the mild cases. The relative risks (RR) variated between 2.5 and 23.5. Figure 1 gives an overview of the relative risks reported in the individual studies. In addition, 3 out of 4 studies that reported on the prevalence of chest tightness, found significantly higher rates in the severe group, the RR being between 1.52 and 9.28. We can therefore say that there is mild evidence of higher prevalences of shortness of breath and chest tightness in severe cases compared to mild cases. Careful interpretation of these statements is advised, knowing that they are based on observational studies.
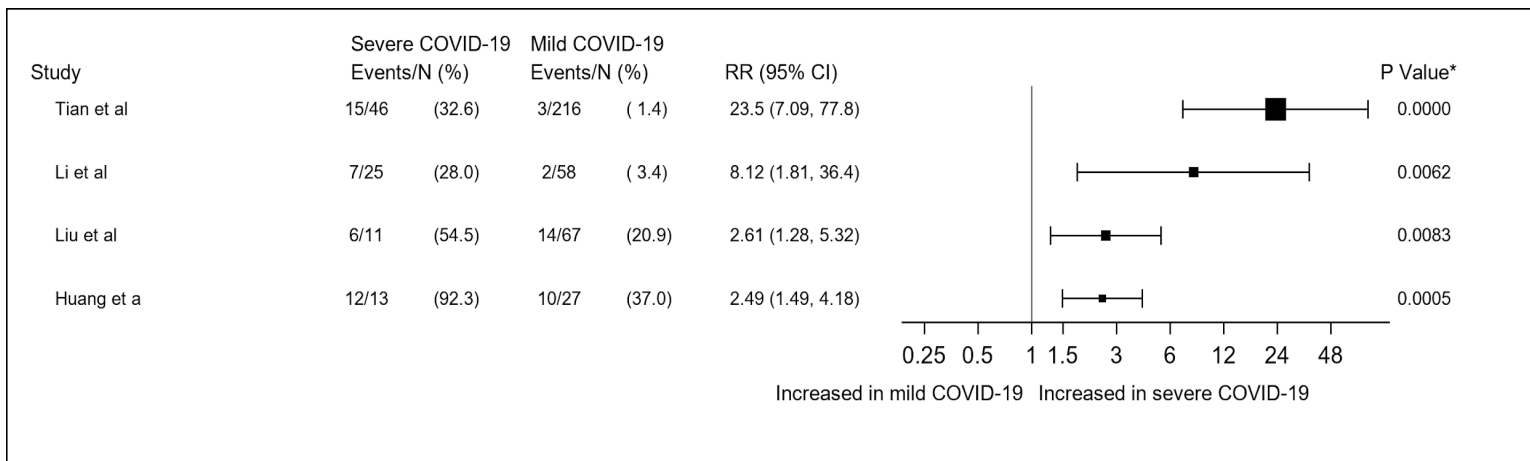
Study	Severe COVID-19 Events/N (%)		Mild COVID-19 Events/N (%)		RR (95% CI)	P Value*
Tian et al	15/46	(32.6)	3/216	(1.4)	23.5 (7.09, 77.8)	0.0000
Li et al	7/25	(28.0)	2/58	(3.4)	8.12 (1.81, 36.4)	0.0062
Liu et al	6/11	(54.5)	14/67	(20.9)	2.61 (1.28, 5.32)	0.0083
Huang et a	12/13	(92.3)	10/27	(37.0)	2.49 (1.49, 4.18)	0.0005

0.25 0.5 1 1.5 3 6 12 24 48

Increased in mild COVID-19   Increased in severe COVID-19

Figure 1: Forest plot of the symptom 'shortness of breath' in studies comparing severe vs mild cases

Overall we can state that there was a big heterogeneity between studies. Especially the studies that compared symptoms of mild cases with symptoms of severe cases were very heterogeneous, because the division between mild and severe cases was not done based on the same parameters and cut-offs. Therefore, results were not formally pooled. The heterogeneity of the studies makes it difficult to draw reliable conclusions.

5. Comments

We compared our outcomes with the systematic review by *Sun P. et al.* who performed a meta-analysis on 10 retrospective observational studies that reported clinical symptoms of Covid-19

positive patients. They also found that fever and cough followed by muscle soreness or fatigue are the most common symptoms of Covid-19 infected patients. Diarrhea, hemoptysis, headache, sore throat, shock and other symptoms were found to be rare.

Symptoms of Covid-19 infection are non-specific. Initially the diagnosis relied on epidemiological factors like recent journeys to Wuhan and other affected areas or close contact to a confirmed case. However, with Covid-19 being so diffusely spread, these factors have become less important (except for the contact with a confirmed case).

6. Conclusion

The most reported symptoms in Covid-19 positive patients were: fever, cough, dyspnea, fatigue and myalgia. There were no significant differences in the prevalences of these symptoms between Covid-19 positive and Covid-19 negative patients. None of these symptoms can therefore be used as a reliable indicator for presence or absence of Covid-19 infection.

The included studies that compared mild and severe Covid-19 cases were too heterogeneous to draw reliable conclusions. Shortness of breath and chest tightness were the only symptoms that were consistently higher in the severe group. According to these individual studies, these two symptoms might therefore be used as an indicator of a more severe course of the Covid-19 infection.

Our results confirm the overall presumption that clinical symptoms of a Covid-19 infection do not significantly differ from other viral respiratory infections. This has very likely contributed to the spread of Covid-19, making it currently the biggest health issue of our time.

7. Clinical bottom line

The most reported symptoms of Covid-19 positive patients are:

- fever
- cough
- dyspnea
- fatigue and myalgia

No onset symptoms were found to be good differentiators between Covid-19 positive infections and Covid-19 negative infections. Health care workers should be cautious in their contact with all patients showing these symptoms.

Shortness of breath and chest tightness tend to be indicators of a more severe course of the Covid-19 infection.

It is important to notice that these results are based on observational studies with limited level of evidence.

References

1. Sun P., Qie S., Liu Z., Ren J., Li K., Xi J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. *Journal of Medical Virology.* 2020. https://doi.org/10.1002/jmv.25735

2. Zhu W., Xie K., Lu H., Xu L., Zhou S., Fang S. Initial clinical features of suspected Coronavirus Disease 2019 in two emergency departments outside of Hubei, China. *Journal of Medical Virology.* 2020. https://doi.org/10.1002/jmv.25763

3. Zenghui C., Yong L., Qiqi C., Le Q., Zilai P., Fuhua Y., Wenjie Y. Clinical Features and Chest CT Manifestations of Coronavirus Disease 2019 (COVID-19) in a Single-Center Study in Shanghai, China. *American Journal of Roentgenology.* 2020;0 0:0, 1-6. https://doi.org/10.2214/AJR.20.22959

4. Zhao D., Yao F., Wang L., Zheng L., Gao Y., Ye J., Guo F., Zhao H., Gao R. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. *Clinical Infectious Diseases.* 2020. https://doi.org/10.1093/cid/ciaa247

5. Tian S., Hu N., Lou J., Chen K., Kang X., Xiang Z., Chen H. et al. Characteristics of COVID-19 infection in Beijing. *Journal of infection.* 2020. https://doi.org/10.1016/j.jinf.2020.02.018

6. Zhang JJ., Dong X., Cao YY., Yuan YD., Yang YB., Yan YQ., Akdis CA., Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy.* 2020. https://doi.org/10.1111/all.14238

7. Li K., Wu J., Wu F., Guo D., Chen L., Fang Z., Li C. The Clinical and Chest CT Features Associated with Severe and Critical COVID-19 Pneumonia. *Investigative Radiology.* 2020. https://doi.org/10.1097/RLI.0000000000000672

8. Liu W., Tao ZW., Lei W., Ming-Li Y., Kui L., Ling Z., Shuang W. et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chinese Medical Journal.* 2020. https://doi.org/10.1097/CM9.0000000000000775

9. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet.* 2020 Feb 15;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

10. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061–1069. https://doi.org/10.1001/jama.2020.1585