

Symptomatology of Coronavirus Disease 2019 (COVID-19) - Lessons from A Meta-Analysis Across 13 Countries

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Abstract

Background: COVID-19 pandemic has resulted in varying clinical manifestations and mortality rates. There is no consensus on the symptomatology that would guide researchers and clinicians.

Objective: The objective of the study was to identify symptoms and their frequencies of coronavirus disease 2019 with a meta-analysis of studies from several countries. *Data sources:* A systematic review using PubMed and Google Scholar data sources and reference tracing were used to identify 7176 relevant articles. *Eligibility criteria:* Suitable articles were selected manually with selection criteria and 14 original articles included for meta-analysis. *Data abstraction analysis:* PRISMA guideline was used for abstracting data. Then a table was generated by feeding it with numbers and proportions of each symptom described in original studies. A meta-analysis was carried out using random effect models on each symptom separately across the studies and their prevalence rates and 95% confident intervals calculated.

Results: We identified 14 relevant scientific papers, either cross-sectional or cohort studies and analyzed. There were 2,660 cases of COVID-19. The majority were from China (n=2,439, 91.7%) and remainder from the Netherlands, Italy, Korea and India and one article from Europe. There was a total of 32 symptoms (i.e. present in >50% of patients): fever (79.56%, 95% CI: 72.17-86.09%), malaise (63.3%, 95% CI: 53.1 – 73.0%), cough (56.7 %, 95% CI: 48.6 - 64.6 %) and cold (55.6%, 95% CI: 45.2 – 65.7%). Symptoms of intermediate incidence (5-49%) were; anosmia, sneezing, ocular pain, fatigue, sputum production, arthralgia, tachypnea, palpitation, headache, chest tightness, shortness of breath, chills, myalgia, sore throat, anorexia, weakness, diarrhea, rhinorrhea, dizziness, nausea, altered level of consciousness, vomiting and abdominal pain. Rare symptoms (<5% of patients) were: tonsil swelling, haemoptysis, conjunctival injection, lymphadenopathy and rash were uncommon symptoms of coronavirus disease (<5%).

Conclusion and implications of key findings: We found (25/32) symptoms to be present in =>5% of cases which could be considered as “typical” symptoms of COVID-19. The list of symptoms we identified are different from those documents released by the WHO, CDC, NHS, Chinese CDC, Institute Pasteur and Mayo Clinic. The compiled list would be useful for future researchers to document a comprehensive picture of the illness.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the strain of coronavirus that causes coronavirus disease 2019 (COVID-19) has resulted in a pandemic with varying clinical manifestations. It has affected 216 countries or territories across the globe. Since the outbreak, it has claimed more than 423,000 lives and infected 7.5 million by mid-June 2020 according to the World Health Organization (WHO) ³. As COVID-19 spreads rapidly studies characterizing its clinical syndromes report a range of clinical features that differ from classic SARS like respiratory illness. This could be a result of host genetic and environmental factors or the virulence factors of the virus. There have been an estimated 198 sites in the SARS-CoV-2 genome that have undergone recurrent independent mutations suggesting an ongoing adaptation of COVID-19 to its human host⁴. Currently the clinical manifestations of the novel coronavirus portray a picture of multisystem involvement. The spectrum of clinical manifestations ranges from an asymptomatic carrier state to mild symptomatic disease with full recovery or progression to multi organ dysfunction and even sudden death. The classic clinical presentations when it was initially described was cough, shortness of breath or difficulty in breathing or at least two of the following symptoms including fever, chills, muscle pain, headache, sore throat and new loss of taste or smell⁵. Some presentations e.g. thromboembolism leading to multi-organ failure, stroke and cardiac complications like ischemic and rhythm abnormalities and skin manifestations such as petechial rashes and gastrointestinal symptoms; diarrhea, nausea and vomiting, which were thought as ‘atypical’ initially were found to be frequent as more cases with those presentations started emerging. Although many symptoms are described in literature, collective data from across different continents is not available. There is no consensus on ‘symptoms of COVID-19’ established up to now. We conducted this systematic review and meta-analysis to identify the common and uncommon symptoms of COVID-19 by analyzing selected studies around the world.

Methods

Study design: Systematic review with meta-analysis

We followed the recommendations of PRISMA and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines⁶.

Selection of studies and extraction of data: We (first two investigators themselves) used PubMed and Google scholar data bases to extract data. We searched the PubMed data base for suitable articles using the key words; “Symptoms of COVID-19 or 2019-nCoV or SARS-CoV-2” which produced 2761 articles on June 02nd 2019. Google scholar search with the same terms produced 2920 articles. “Clinical manifestations of COVID-19 or 2019-nCoV or SARS-CoV-2” produced 1466 articles on the same day. Further Google searches were carried out using references to trace important articles. This process of selection of articles is depicted in the flow diagram below.

Initial search results were first screened by the title and abstract. We included peer-reviewed articles that reported demographical, clinical features of cases confirmed using real-time reverse transcriptase polymerase chain reaction (RT-PCR). Only the original articles which had evaluated the clinical manifestations were included, with a minimum number of cases of 20 for the meta-analysis. Thus, case reports, review articles, letters and opinions were not included for meta-analysis. The inclusion and exclusion criteria are given below:

Inclusion criteria

1. Original studies evaluating symptoms of COVID-19 published before 2 June 2020 on persons confirmed with a positive PCR.
2. Predominately adult studies

3. Studies with more than 90 cases for China and at least 20 cases for other countries
4. Studies conducted in any country
5. Articles published in English language

Exclusion criteria

1. Predominately paediatric studies
2. Those articles that had not stated the frequencies and/or percentages of incidence of symptoms of COVID-19
3. Studies with less than 90 cases for China and less than 20 cases for other countries
4. Articles published in languages other than English

Please note that there were several studies from China; authors intentionally limited the number of studies from China when adequate numbers were included. This was to enable the inclusion of a diverse population in order to improve the generalizability of findings. We have limited the symptom analysis to mainly adult population, excluding primarily paediatric studies considering the potential variation in symptomatology, target groups and expertise of the authors. The authors' fluency in languages is limited to English on published articles leaving those published in other languages, excluded.

Study population: we included data from 14 studies, collecting 2660 individuals in to the analysis. Ages ranged from 0 to 94 years. It was not possible to calculate means and modes due to differences in the data given in the studies. However, the age and sex parameters are given separately for each study in table 01.

The disease severity included mild, moderate, severe/ critical and fatal representing a wider spectrum of disease. Each symptom was taken separately across the studies, including only those tested for that symptom, to avoid confounding by the investigator 'not checking' for the particular symptom. Meta-analysis was carried out studying each symptom separately and their frequencies were calculated and ranked in order. Figure 1 demonstrates the prevalence of all the symptoms and further describes the results of meta-analysis for each symptom separately. These symptoms are illustrated with the relevant system involved in Figure 2.

Among the selected studies for symptom analysis, 9 were from China⁷⁻¹³, one study per each country included from Netherlands¹⁴, India¹⁵, Korea¹⁶ and Italy¹⁷. Another article by Spiteri G et.al was included which represented the first 38 cases in Europe¹⁸. A large study which included data from 5700 COVID-19 patients in New York, was not include in to the meta-analysis. This is because the clinical characteristics assessed in this study were only fever and tachypnea present at triage. Fever was present only at triage in 30.7% and tachypnea in 17.3% of cases¹⁹. Here the symptoms before and after the triage was not taken in to account thus limiting the feasibility in our analysis¹⁹. Several other similar studies were excluded from the meta-analysis concerning the selection criteria; doubts raised on accuracy of data, inadequate information on symptoms studied etc.³¹⁻⁴³.

Methodology and results of these articles were also studied prior to selection, to assure the quality of information. After assessing the suitability of the articles, we selected 14 original studies for the meta-analysis. Those articles were used to generate a table consisting of sample size, number, percentage and prevalence of each symptom. The findings are presented in Table 1 as the Characteristics of studies. All the patients included were diagnosed to have COVID-19 by detection of nucleic acids (viral RNA detection by Reverse Transcription Polymerase Chain Reaction – RT-PCR).

Statistical analysis: All the symptoms encountered were considered for the analysis. Some symptoms were identified in all the studies (e.g. fever and cough), but certain symptoms were only described in one study (e.g. common cold, tonsil swelling, sneezing, palpitation, conjunctival congestion/ injection anosmia, rash, lymphadenopathy and malaise). Therefore, each symptom was considered separately and meta-analysis was carried out to obtain the prevalence of each symptom across all the studies. The sample size and number of events per each symptom in each study was considered in the analysis. Freeman-Tukey double arcsine transformation with inverse variance method was used to consider individual study weights. The overall prevalence of symptoms across studies along with 95% confidence intervals was calculated and symptoms were ranked in the ascending order as depicted in figure 1. R programming language version 3.6.3²² and Meta package²³ were used in the analysis.

Results

A total of 14 articles with original data describing the clinical manifestations of COVID-19 were retrieved. The largest study was done in China by Guan et.al⁷. Owing to the novelty of the current pandemic there were heterogeneity among the available data and not all symptoms were mentioned. The ages of patients varied from 0 to 94 years. All the studies were descriptive cross sectional or cohort studies and their characteristics are summarized in the Table 1.

Table1. Clinical characteristics of the studies used for meta-analysis

Study	Age (years)/ Sex	Study design and rating of quality of evidence ^a	Institute(s)/ Geography	Composition	Comments or additional information
CHINA Guan W N=1099	median age of 47, only 9 cases below 14 and 153 above 65, predominantly males 58.1%	Retrospective Cohort study Rating 3	552 hospitals distributed in 30 provinces, autonomous regions, and municipalities in mainland China	hospitalized as well as from outpatient departments (OPD)	Composition may represent wider spectrum of the disease from mild to severe.
CHINA Chen T N=274	median age 62.0 [44.0-70.0] with 53 below 40 and 153 above 60 and 62% were males	Retrospective case series Rating 4	Tongji Hospital	Only moderate-severe or critically ill patients have been included. OPD cases not included 113/274 died	Symptoms of those survived are mostly comparable to those died. Dyspnoea was commoner 62% in those died and only 31% in those recovered ^b
CHINA Chen J N=249	The median age was 51 years old (IQR, 36–64 years), and 126 (50.6%) were male	Retrospective cross sectional study Rating 3	Shanghai Public Health Clinical Centre (SPHCC)- hospitalized	22 (8.8%) -admitted to ICU 215 (86.3%) - were discharged 2 (0.8%) -died	Has studied the temporal clinical progression ; Median duration of fever was 10 days (95% CI – 8-11 days)
CHINA Shou F N=191	age 46 to 67, 62% males	Retrospective Cohort study Rating 3	Multicentre	They represent 50 (26%) ICU admitted cases, and 54 (28%) deaths. Disease severity ranges from general (38%), severe (35%) and critical (28%), thus excluding the milder fraction of the severity spectrum	
CHINA Sheng F N=161	age 45 (IQR 33.5-57) 49.7% males	Retrospective Cross sectional study Rating 4	Changsha Public Health treatment Center (CPHC)	30 of 161 were taken as severe and the rest were non-severe.	There was a statistically significant difference in age between the severe and non-severe groups ($p<0.05$), with
CHINA Wang D N=138	The median age 56 (IQR, 42-68), age range 22-92 75(73.9%) were men	Retrospective case series Rating 3	Zhongnan Hospital of Wuhan University	36/138 were admitted ICU and were older (median age, 66 [IQR, 57-78]) than non-ICU patients (median age of 51 [IQR- 37-62]), $P<0.001$.	ICU admitted patients were more likely to have pharyngeal pain, dyspnoea, dizziness, abdominal pain and anorexia.
CHINA Lui K N=137	Age range 20-83, with median 55+/-16. 61/137 (44.5%) were males	Retrospective cross sectional study Rating 3	Respiratory departments of nine tertiary hospitals in Hubei province	Discharged 44 (32.1%) Death 16 (11.7%) Inpatient treatment 77 (56.2%)	Higher mortality rate likely due to more critical patient cohort involved in the respiratory wards.
CHINA Chen N N=99	ages from 21-82, with a mean of 55.5 (SD 13.1) and 67% were males	Retrospective cross sectional study Rating 4	Jinyintan Adult Hospital in Wuhan	11 (11%) - died	49% of patients had an exposure to seafood market in Huanan. Article gives data only up to 25 Jan 2020 and outcomes were-11% deaths/ 31% discharged/ rest still hospital
CHINA Zhao X Y N=91	median age 46 and 53.8% were male	Crosssectional study Rating 4	hospitalized patients admitted in Jingzhou Central Hospital	30 (33%)- severely ill 2 (2.2%) – died 61 (67%) - only mild disease	Outcomes taken when 75 (82.4%) were still in hospital.
Study	Age (years)/ Sex	Study design and rating of quality of evidence ^a	Institute(s)/ Geography	Composition	Comments or additional information

N'lands Tostmann A N=90	aged 21-60 except those 03 above 60 and 82.9% were females	Cross sectional study Rating 4	Radbound university medical centre, Nimegen, The Netherlands	healthcare workers (HCW), diagnosed with COVID-19 during a screening done on 1,247 mildly symptomatic HCW	Symptoms analysed from a questioner given but only 803/1,247 Health care workers have responded by filling the questionnaire. They assessed early features of disease and the patients were otherwise healthy.
INDIA Gupta N N=21	aged 16-73 (mean 40.3) and 66.7% male	Case series Rating 4	Safdarjung Tertiary care Hospital, New Delhi	None given ICU care and only developed breathlessness and given oxygen	None had rhinitis or diarrhoea 61.9% of them were frequent travellers to Italy, and rest to other countries.
EUROPE Spiteri G N=38	ages 2-81 with median 42.6 and 25/38 were males	Cross sectional study Rating 4	Belgium (1), Finland (1), France (12), Germany (16), Italy (3), Russia (2), Spain (2) and Sweden (1)	Four needed respiratory support one French patient died	
KOREA Kim E S N=28	aged 42.6 +/- 13.4 and 53.6% males	Case series Rating 4	Multicentre ^c	6 (21.4%) – needed on oxygen on admission None - needed mechanical ventilation 22 (78.5%) – had pneumonia	None of these needed mechanical ventilation.
Colaneri M N=44	aged 10-94 with median of 67.5 and 28/44 were males	Cross sectional survey Rating 4	single centre in Pavia, Italy	2 - received sub-intensive care. 3 - admitted to ICU	Two died and 17 patients had developed severe disease Data analysed while 23 still in hospital.
a Quality Rating Scheme for Studies and Other Evidence					
<ol style="list-style-type: none"> 1. Properly powered and conducted randomized clinical trial; systematic review with meta-analysis 2. Well-designed controlled trial without randomization; prospective comparative cohort trial 3. Case-control studies; retrospective cohort study 4. Case series with or without intervention; cross-sectional study 5. Opinion of respective authorities; case reports 					
b. Features associated with higher mortality - ARDS, Type I respiratory failure, acute cardiac injury, heart failure, hypoxic encephalopathy, sepsis, alkalosis, AKI, DIC, hyperkalaemia, shock and acute liver injury were complications frequently observed in those who died than those recovered (n=161). Old age, male sex and presence of comorbidities were associated with higher mortality.					
c. Seoul National University Hospital, National Medical Centre and Seoul Medical Centre Incheon Medical Center, Incheon; Seoul National University Bundang Hospital and Armed Forces Capital Hospital, Seongnam; Myongji Hospital, Goyang; Gyeonggi Provincial Medical Center Ansung Hospital, Anseong; Wonkwang University Hospital, Iksan; Chonnam National University Hospital and Chosun University Hospital, Gwangju					

Clinical manifestations of COVID-19

We identified 32 symptoms mentioned in 14 studies. Table 2 summarizes clinical manifestation from those selected original articles with their frequencies. Those seen in more than 5% of the study populations were considered common and those less than 5% as uncommon.

Table 2
The frequencies of symptoms in each study and prevalence across the studies for each

Clinical feature	Prevalence From Meta- analysis	CHINA	CHINA	CHINA	CHINA	CHINA	CHINA	CHINA	CHINA	CH
		Guan W	Chen T	Chen J	Zhou F	Zheng F	Wang D	Kui L	Chen N	Zh
		Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Nu
		N = 1099	N = 274	n = 249	N = 191	N = 161	N = 138	N = 137	N = 99	N =
Fever	79.56 (72.17– 86.09)	975(88.7)	249(91)	217(87).1	180(94)	122(75.8)	136(98.6)	112(81.8)	82(83)	75
Cough	56.66 (48.59– 64.55)	745(67.8)	185(68)	91(36.5)	151(79)	101(62.7)	82(59.4)	66(48.2)	81(82)	59
Sputum production	22.43 (13.8– 32.41)	370(33.70)	83(30)		44(23)		37(26.8)	6(4.4)		
Shortness of breath	18.24 (12.07– 25.32)	205(18.7)	120(44)	19(7.6)		23(14.3)	43(31.2)	26(19%)	31(31)	
Tachypnoea	22.61 (3.94– 49.86)									11
Haemoptysis	2.31 (0.48– 5.28)	10(0.9)	7(3)					7(5.1%)		
Sneezing	40 (30.07– 50.35)									
Tonsil swelling	2.09 (1.32– 3.03)	23(2.1)								
Sore throat/ Pharyngalgia	14.19 (8.7– 20.68)	153(13.9)	12(4)	16(6.4)			24(17.4)		5(5)	19
Rhinorrhoea and/or nasal congestion	6.86 (2.91– 12.09)	53(4.8)		17(6.8)					4(4)	
Cold	55.56 (45.16– 65.72)									
Chest tightness	18.09 (1.66– 45.64)		103(38)						2(2)	21
palpitation	7.3 (3.46– 12.33)							10(7.3%)		
Chills	16.23 (6.49– 29.18)	126(11.5)								21
Fatigue (Tiredness)	37.1 (27.75– 46.96)	419(38.1)	137(50)	39(15.7)	44(23)	64(39.8)	96(69.6)	44(32.1)		35
Dizziness	8.1 (5.33– 11.35)		21(8)	28(11.2)			13(9.4)			3(3)

Clinical feature	Prevalence From Meta-analysis	CHINA Guan W	CHINA Chen T	CHINA Chen J	CHINA Zhou F	CHINA Zheng F	CHINA Wang D	CHINA Kui L	CHINA Chen N	CHINA Zhou
		Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)
		N = 1099	N = 274	n = 249	N = 191	N = 161	N = 138	N = 137	N = 99	N = 1099
Headache	15.58 (9.21–23.16)	150(13.6)	31(11)	28(11.2)		12(7.5)	9(6.5)	13(9.5%)	8(8)	
Altered consciousness	5.94 (1.49–12.73)								9(9)	3(3)
Abdominal pain	3.66 (1.39–6.76)		19(7)				3(2.2)			2(2)
Diarrhoea	8.26 (4.36–13.15)	42(3.8)	77(28)	8(3.2)	9(5)	17(10.6)	14(10.1)	11(8.0%)	2(2)	14
Anorexia/ Inappetence	17.62 (4.42–36.82)	-	66(24)	8(3.2)			55(39.9)			11
Conjunctival congestion/ injection	0.82 (0.36–1.45)	9(0.8)								
Clinical feature	Prevalence From Meta-analysis	CHINA Guan W	CHINA Chen T	CHINA Chen J	CHINA Zhou F	CHINA Zheng F	CHINA Wang D	CHINA Kui L	CHINA Chen N	CHINA Zhou
		Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)
		N = 1099	N = 274	n = 249	N = 191	N = 161	N = 138	N = 137	N = 99	N = 1099
Rash	0.18 (0–0.55)	2(0.2)								
Lymphadenopathy	0.18 (0–0.55)	2(0.2)								
Nausea	6.58 (4.09–9.56)	55(5.0)	24(9)		7(4)	6(3.7)	14(10.1)		1(1)	11
Vomiting	4.95 (2.86–7.54)	55(5.0)	16(6)		7(4)		5(3.6)		1(1)	
Myalgia	19.37 (14.47–24.77)	164(14.9)	60(22)		29(15)	18(11.2)	48(34.8)	44(32.1)	11(11)	15
Arthralgia/ Arthrodynia	26.24 (4.89–56.39)	164(14.9)								8(8)
Anosmia	46.84 (35.89–57.93)									
Malaise	63.33 (53.08–73.03)									

Clinical feature	Prevalence From Meta- analysis	CHINA	CHINA	CHINA	CHINA	CHINA	CHINA	CHINA	CHINA	CH
		Guan W	Chen T	Chen J	Zhou F	Zheng F	Wang D	Kui L	Chen N	Zh
		Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	Nu
		N = 1099	N = 274	n = 249	N = 191	N = 161	N = 138	N = 137	N = 99	N =
weakness	11.47 (0.41– 31.75)									
Asymptomatic	2.71 (0.96– 5.12)			7(2,8)						

Ranking of symptoms

The most prevalent clinical symptoms were fever (79.56%, 95% CI: 72.17–86.09%), malaise (63.3%, 95% CI: 53.1–73.0%), cough (56.7%, 95% CI: 48.6–64.6%) and cold (55.6%, 95% CI: 45.2–65.7%) observed in more than 50% of the study population. Anosmia (46.8%, 95% CI: 35.9–57.9%), sneezing (40%, 95% CI: 30.1–50.4%), fatigue (37.1%, 95% CI: 27.8–47.0%) and ocular pain (34.4%, 95% CI: 24.9–44.6%) are also quite common occurring in > 30% of cases. Gastro-intestinal symptoms are also seen frequently; anorexia (17.6%, 95% CI: 4.4–36.8%), diarrhea (8.3%, 95% CI: 4.4–13.2), nausea (6.6%, 95% CI: 4.1–9.6%) and vomiting (5.0%, 95% CI: 2.9–7.5%). According to our findings uncommon symptoms (< 5%) were tonsil swelling, hemoptysis, conjunctival injection/congestion, rash and lymphadenopathy. All those with a prevalence \geq 5% were considered common and therefore ‘typical symptoms’ of COVID-19.

There were symptoms noted only in one study (sneezing, tonsil swelling, cold, conjunctival injection/ congestion, ocular pain, rash, lymphadenopathy, anosmia and malaise) thus giving a poor statistical confidence on prevalence.

Discussion

This study was designed to identify the symptoms of COVID-19 and to rank them according to their frequencies of occurrence in a globally representative sample. This was difficult as the disease is novel and new symptoms and complications were frequently been reported. Our study recognizes 32 symptoms of coronavirus disease, which represent most organs and systemic features, thus defining this disease as a multisystem syndrome rather than a respiratory disease. There was no clear consensus as to what are the symptoms of novel corona virus disease until now. Manifestations are identified as we learn about it with the spread of the disease. The symptoms identified in the guidelines issued by the World Health Organization (WHO) ²⁵, The National Health Service (NHS) ²⁶, The Centers for Disease Control and Prevention (CDC) ²⁷, Chinese Center for Disease Control and Prevention (Chinese CDC) ²⁸, Institute Pasteur ²⁹, Mayo Clinic ³⁰ and in web-based trackers for self-assessment differ from that reported in our study. This comparison is shown in Table 3.

Table 3
– Comparison covid-19 symptoms identified with that of major publications

Clinical feature	Prevalence (%) From Meta-analysis	WHO ¹	NHS ²	CDC ³	Chinese ⁴ CDC	Institut Pasteur ⁵	Mayo Clinics ⁶
Fever	79.6	1	1	1	1	1	1
Cough	56.7	1	1	1	1	1	1
Sputum production	22.4						
Shortness of breath	18.2						
Tachypnoea	22.6						
Haemoptysis	2.3						
Sneezing	40.0						
Tonsil swelling	2.1						
Sore throat/ Pharyngalgia	14.2	1		1	1		1
Rhinorrhoea and/or nasal congestion	6.9	1		1	1		
Cold	55.6	1					
Chest tightness	18.1						
palpitation	7.3						
Chills	16.2						
Fatigue (Tiredness)	37.1	1		1	1		1
Dizziness	8.1						
Headache	15.6	1		1		1	1
Altered consciousness	5.9						
Abdominal pain	3.7						
Diarrhoea	8.3	1		1	1		1
Anorexia/ Inappetence	17.6						
Conjunctival congestion/ injection	0.9	1					
Rash	0.2						1
Lymphadenopathy	0.2						
Nausea	6.6			1			1
Vomiting	4.0			1			1
Myalgia	19.4	1		1	1	1	1
Arthralgia/ Arthrodynia	26.2						
Anosmia	46.8	1	1	1		1	1
Malaise	63.3	1					
weakness	11.8						
Asymptomatic	2.7						

We also found two studies which used such clinical criteria ⁵⁵⁻⁵.

We used original studies from different geographic locations having a range of severities to improve the generalizability of the information. However, nine studies representing about 90% of study population is from China, giving a publication bias for our statistical analysis. There is a significant variation in proportions of each symptom across countries and regions. This variability of presentations is likely to be due to the differences in demography of sample, virulence of strain of COVID-19, aggregation of severe cases in to certain centers with higher facilities and milder cases in to other care centers and variations in host response (both genetic and immunological) in different populations.

Wider spectrum of disease severity is covered by the included studies for the meta-analysis. Tostmann et al ⁽¹⁴⁾ has studied the COVID-19 in health care workers during a screening test while Chen T et al ⁽⁸⁾ included 113 fatal cases thus approaching the far severe aspect of the disease. However, the accessibility

to health care facility and some factors that could modify clinical features (e.g pregnancy, co-morbidities of individuals) were not taken in to account. The studies primarily on paediatric and neonatal population were identified but not included in this analysis and suggest the need of a different study for that⁴⁵⁻⁴⁹.

Older age, male sex, presence of comorbidities and certain symptoms were associated with poor outcome. The median age in the Italian study was high (median of 67.5 years), which may at least partially explain the higher fatality rates observed in this population⁽¹⁷⁾. Sex-disaggregated data suggests a slight male predominance which was also observed in mortality rates⁽²⁰⁾. Clinical data associated with disease evolution is critical knowledge especially in a new pandemic. Among the reported cases till February 2020, 14% of COVID-19 cases were severe, causing pneumonia and shortness of breath, and that of about 5% of patients had critical disease, including respiratory failure, septic shock, and multi-organ failure⁽²¹⁾. Host susceptibility is studied in detail by Shi Yu et al, including 487 patients outside Wuhan. They have developed a host risk score using 3 variables: age, sex and presence or absence of hypertension⁴⁴. Further analyses of the symptoms indicate that, certain symptoms like dyspnoea/ shortness of breath (62% in diseased vs. 31% in recovered), chest pain (49% in diseased vs. 30% in recovered) and altered consciousness (22% in diseased vs. 1% in recovered), are associated with higher mortality⁽⁸⁾.

Asymptomatic cases in this study was 9/287 (prevalence – 2.71%, 95% CI 0.96%- 5.12%) using data from articles by Chen J⁽⁹⁾ and Spiteri G⁽¹⁸⁾. This might not reveal the true picture, because a large scale screening tests done on populations at risk needed to assess this. However, a study done in Japanese Diamond Princess Cruise ship by Mizumoto K et el. shows valuable results. Here 3,711 patients were kept quarantined after finding one patient with COVID-19. Out of all, 634 cases became positive and 306 (48.3%) cases were symptomatic and 328 (51.7%) were asymptomatic⁽²⁴⁾

In this study, we did not concentrate on the chronology of development of symptoms and complications which is also very important for clinicians when assessing patients, and need to be addressed in detail separately. However, temporal clinical progression has been assessed by Chen J et al (N = 249) in their study⁹. There had been reports of possible 'reactivation' of COVID-19 after recovering from the first infection³⁷; the symptoms of such cases are not taken in to this review.

The results of our systematic review highlight the common and uncommon clinical symptoms which will help clinicians across the globe in the diagnosis and management of suspected cases of COVID-19, especially during the early phase. This will help in defining the disease presentation and improves diagnostic skills. These common and uncommon symptoms could be utilized in studying patients and designing future research.

There are a multitude of other uncommon or rare manifestations of COVID-19 not described in these studies presented from many countries that have been mainly the focus of case reports⁵⁰⁻⁵⁴.

Limitations

Some symptoms assessed were only present in one or two studies and other studies have not recorded them or not inquired about them making them statistically less reliable on their frequencies.

We have not focused on the chronology of symptom development and complications. Reports in languages other than English were not included

Conclusions

There are 32 symptoms of COVID-19 representing multiple organs and systemic features. Fever is the most common symptom followed by malaise, cough, cold and anosmia. Researchers and clinicians should be aware of a comprehensive list of symptoms to describe the illness and for research.

List Of Abbreviations

COVID-19 - Coronavirus Disease 2019

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

CI - Confidence Interval

WHO - World Health Organization

NHS - The National Health Service (United Kingdom)

CDC - Centers for Disease Control and Prevention (United State of America)

Chinese CDC - Chinese Centers for Disease Control and Prevention

MOOSE - Meta-analysis of Observational Studies in Epidemiology

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus-2

RT-PCR - Reverse Transcriptase Polymerase Chain Reaction

PCR - Polymerase Chain Reaction

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The pooled articles, data-sheets and analytic results are available with the authors for future references

Competing interests:

There are no competing interests.

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Authors' contributions:

CG: Conceptualization, search of data sources, initial draft writing and updating manuscript

DH: Search of data sources, Initial draft writing, updating manuscript, and designing figure 02 info graphic. .

DE: Meta-analysis and compilation of statistics section of manuscript

SJ: Update and finalizing the manuscript.

All authors have read and approved the manuscript

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We included the data from published literature and the consent was not applicable data collection and for publications.

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Figures

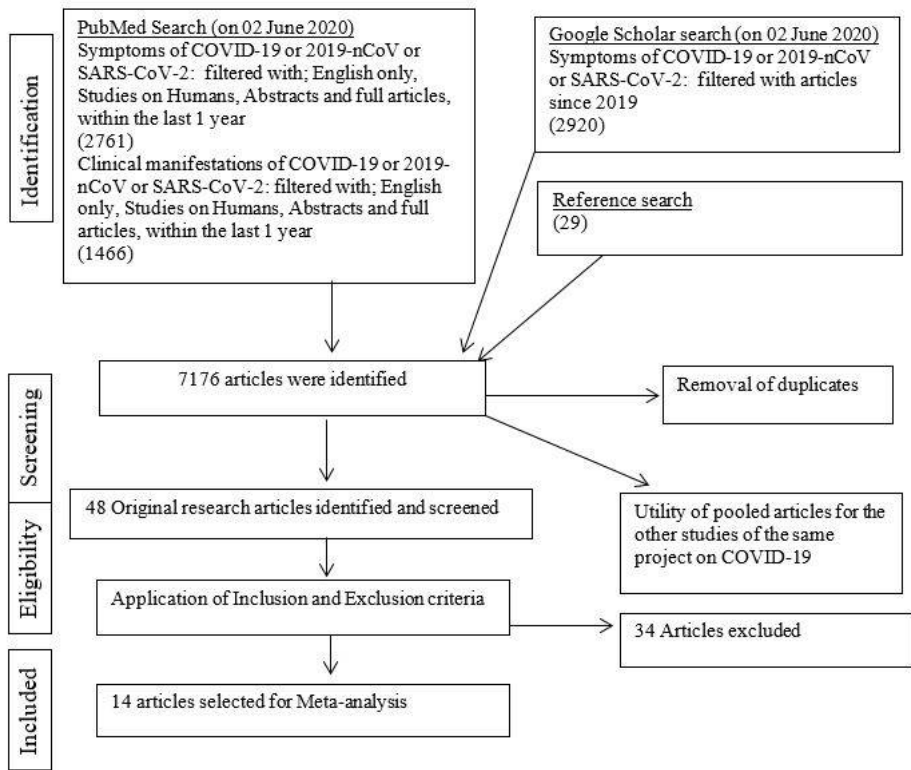


Figure 1

Flow diagram

Generalized Symptoms

- Fever
- Chills
- Malaise
- Myalgia
- Arthralgia/ Arthrodynia
- Fatigue
- Weakness
- Lymphadenopathy

CNS Symptoms

- Headache
- Dizziness
- Altered consciousness

Ophthalmological Symptoms

- Ocular pain
- Conjunctival congestion/injection

Upper Respiratory Symptoms

- Cough
- Sputum production
- Sneezing
- Sore throat/ Pharyngalgia
- Common cold
- Anosmia
- Rhinorrhoea and/or nasal congestion
- Tonsil swelling

Cardiac Symptoms

- Palpitations

Lower Respiratory Symptoms

- SOB
- Tachypnoea
- Chest tightness
- Haemoptysis

Dermatological manifestations

- Rash

GI Symptoms

- Anorexia
- Diarrhoea
- Nausea /vomiting
- Abdominal pain



SOB – Shortness of breath (dyspnoea)

Colour code

In red – System

In blue – common symptoms (>5% prevalence)

In grey – uncommon symptoms (<5% prevalence)

Figure 2

Symptoms of COVID-19

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMA2009checklist.doc](#)
- [Figure1.ResultsofMetaanalysis.docx](#)