Original article

Clinical manifestations of COVID-19; what have we learned from the global database?

Mohd S.Ibrahim[1,], Nurulhuda M. Hassan[2], Aniza A. Aziz[3], Harmy M. Yusoff[4], Nor K. Esa[5], Mokhairi Makhtar[6], Nor Iza A. Rahman[7], Samhani Ismail[8], Ras A. Ramli[9], Nyi Nyi Naing[10], Hafizan Juahir[11]*

Abstract

Background: There is a need to analyze a worldwide database of the coronavirus disease of 2019 (COVID-19) pandemic.This may prove valuable to facilitate better strategies and planning on prevention, screening, surveillance, early diagnosis, containment and treatments. ***Method:*** We extracted 14,259 case reports of COVID-19 dated 11th November 2019 to 18th March 2020 from Johns Hopkins University Repository Online Databaseof 58 countries. After extensive data preprocessing, a multi-disciplinary expert researcherthen conducted series of vetting to categorizefree-text description of symptoms into discreet standardizedcategories.Continuous variables were presented by using median and inter-quartile range whereas categorical variables were presented by frequency and percentage***. Result***: A total of 2191 cases (15.4%) were included for demographic analysis. The median age was46 years (IQR26 years) with 787 (35.9%) cases involved patients aged of 60 and above while patients less than18 years of age were reported in 79 (3.6%) cases. Majority of the patients were males (n=1227, 56.7%). There were a total of 20standardized categories ofCOVID-19symptoms.The most prevalent were fever (74.8%), non-productive cough (42.2%), fatigue (13.1%), sore throat (12.8%) and shortness of breath (11.7%). Other symptoms with frequency of more than 1% were chest discomfort, nasal congestion, muscular pain, chills and rigors, headache, diarrhoea, expectoration and joint pain. Other more uncommon symptoms reported include loss of appetite, conjunctivitis, toothache and abdominal pain. Asymptomatic manisfestations were reported in 8 cases (1.0%).All population are susceptible to COVID-19 especially the older age group. There were 20 standardized categories of symptoms wherefever, non-productive cough, fatigue, sore throat and shortness of breath were the most commonly reported. ***Conclusion***: Findings of this study contribute to a deeper understanding on COVID-19 and may prove useful for researchers to better-design screening and surveillance strategies via more accurate risk-prediction modelling.

Keyword: coronavirus disease; multi-disciplinary; symptoms; surveillance; COVID-19

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Background

The COVID-19 pandemic has triggered an unprecedented global crisis which reverberates across almost every aspect of human life. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been found to be the aetiological agent

1. Mohd S. Ibrahim
2. Nurulhuda M. Hassan
3. Aniza A. Aziz
4. Harmy M. Yusoff
5. Nor K. Esa

   Faculty of Medicine, Universiti Sultan Zainal Abidin, 20400 Kuala Terengganu, Terengganu, Malaysia.
6. Mokhairi Makhtar, Faculty of Informatics and Computing, Universiti Sultan Zainal Abidin (UniSZA) Gong Badak Campus, 21300 Kuala Nerus, Terengganu, Malaysia.
7. Nor Iza A. Rahman
8. Samhani Ismail
9. Ras A. Ramli
10. Nyi Nyi Naing, Faculty of Medicine, Universiti Sultan Zainal Abidin, 20400 Kuala Terengganu, Terengganu, Malaysia.
11. Hafizan Juahir, East Coast Environmental Research Institute (ESERI),Universiti Sultan Zainal Abidin (UniSZA), Gong Badak Campus, 21300 Kuala Nerus, Terengganu, Malaysia.

Correspondence: Nyi Nyi Naing, Faculty of Medicine, Universiti Sultan Zainal Abidin, 20400 Kuala Terengganu, Terengganu, Malaysia. e-mail: syedhatim@unisza.edu.my

responsible for the pandemic, which mainly manifest as acute respiratory syndrome.[1-3] From the initial reported cases of pneumonia in Wuhan[4], related to contact history with a seafood market; the disease has now progressed by human-to-human transmission.[5, 6] On 30th January 2020, the disease was regarded as a global emergency by the World Health Organization (WHO) and subsequently declared as a pandemic on 11th March 2020.

Outbreak from coronaviruses family is not new. The outbreaks of Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012 were both originated from the same group of coronaviruses.[7] However, there were substantial genetic dissimilarity between the pathogens and the SARS-CoV-2[1], as well as some differences in the clinical manifestations.[8] For SARS-CoV-2, being a novel virus, clinical symptoms may emerge and become more established with time. The typical clinical symptoms has been reported such as fever, dry cough, shortness of breath, headache and progressive respiratory failure that may lead to death.[7] Most reviews of clinical characteristics were based from patients in China.[9, 10] These symptoms have to be reviewed with time as more patients are infected worldwide to paint a clearer clinical picture of its differentiating features compared to other causes of acute respiratory syndrome.

Moreover, there are evidence of accelerated community spread across many countries and the severe illness proportion is particularly high among the adults with ≥50 years of age and among those with chronic diseases and comorbid health conditions.[8] Given its speed of spreading, countries with resources to conduct mass diagnostic testing such as South Korea has been recognized as successful in containing the outbreak and mitigate its economic impact.[11-14] Yet, not all countries have the capacity to observe the same comprehensive strategies due to constraints in resources such as financial, expertise, logistics, and short supply for materials for testing itself such as the chemical reagents and the testing kits. Hence, a robust and validated screening model could prove useful to improve the efficiency of diagnostic testing when capacity is limited.

In view of this, we agreed that an updated analysis of worldwide cases of COVID-19 for its clinical features would be appropriate in order to support clinicians and expert researchers to better-design a screening model to facilitate cost-effective strategy for mass diagnostic testing. This would help for situations where resources are limited so prioritize testing is warranted to curb the spread of this rapidly transmissible virus. During the early stage of the pandemic, China has started extensive collaborations with international institutions and established a publicly available database of line list of cases through coordinating with Johns Hopkins University.[15] In our university, we formed a task force team consisting of multi-disciplinary experts for the purpose of evaluating the clinical features of the cases reported in the thousands of articles and reports pertaining to COVID-19. In this article, we report the demographic and clinical symptoms of systematic mapping of 14,259 reports of real COVID-19 cases; mainly from the John Hopkin University's Respository data hub on COVID-19.[16]

Methodology

As part of the complex process of reviewing the literature, an officer from the university library with expertise in information searching and two data analyst experts were given the task for article search and scoured thousands of articles and reports pertaining to COVID-19.

Articles were extracted using PubMed, Embase, and Google Scholar search engines using searching terms "COVID-19", "SARS-CoV-2", and "2019-nCoV" in titles, abstracts and keywords. We divided the literature into peer-reviewed papers and reports of real cases. Afterwards, the review articles, clinical reports, case reports pertaining to clinical manifestations of COVID-19 were closely reviewed. In addition to these articles, we found a public domain data repository hub and explored it for supportive descriptive information on COVID-19 demographic and clinical characteristics. The Data Repository Hub on COVID-19 is provided by Johns Hopkins University Center for Systems Science and Engineering.[16]

These data are copyrighted materials of John Hopkins University and has been published for public access for academic and research purposes.[16] The data from 11th November 2019 were extracted on 18th March 2020.

The collection of the cases extracted from the John Hopkins University'shub were then compiled in an excel table format for further refinement. Using complex nested Microsoft Excel formula and Visual Basic Application (VBA) coding, the data was systematically refined, recategorized, re-mapped and re-coded.The Figure 1 below demonstrates

methodological steps to extract and analyse the clinical symptoms and presentations of the COVID-19 cases:

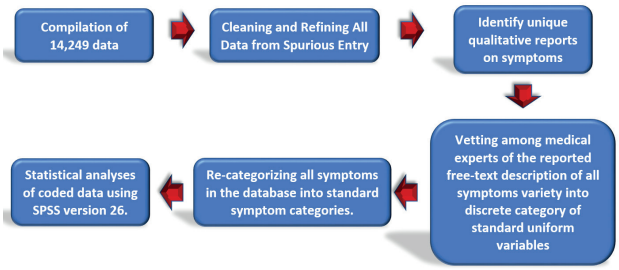

Fig. 1. The process of refining data forstatistical analyses

Inclusion criteria were the cases being diagnosed as having COVID-19 by laboratory investigation. For analyses of age, gender and symptoms, only reports which contain information on these aspects were included. Continuous variables were presented by using median and inter-quartile range whereas categorical variables were presented by frequency and percentage. Statistical analyses were conducted using SPSS version 26.

Ethical clearance: None required

Results

A collection of 14,259 reports of COVID-19 cases from 354 online resources in the hub were compiled in an excel table format for further analysis. The cases were from 58 countries, with majority from China and South Korea (Table 1). From these cases, 2191 cases (15.4%) were having reports on age while 2165 (15.1%) cases contain reports on gender. Table 2 showed the age group and gender of the patients. The median age was 46 years (Interquartile range 26 years). A total of 787 (35.9%) cases were attributed to patients from the age of 60 and above. Majority of the patients with COVID-19 were males (n=1227, 56.7%).

For clinical manifestation analysis, 763 cases (5.4%) were included as they had reports of symptoms. Table 3 showed the clinical symptoms according to frequency and relative frequency. A total of 20 standardized categories of clinical symptoms of COVID-19 disease were identified. The most prevalent symptoms was fever, where 74.8% of patients experienced it. Other symptoms reported by more than 10% of patients were cough (42.2%), fatigue (13.1%), sore throat (12.8%) and shortness of breath (11.7%). Symptoms experienced by 1 to 10% of patients were chest discomfort, nasal congestion, muscular pain, chills and rigors, headache, diarrhoea, expectoration and joint pain. Other more uncommon symptoms reported include loss of appetite, conjunctivitis, toothache and abdominal pain.

Table 1. Frequency distribution of cases according to country of origin (n=14,259)

No	Country	Frequency
1	China	10643
2	South Korea	1052
3	Japan	921
4	Italy	591
5	Singapore	184
6	Hong Kong	94
7	Thailand	81
8	Germany	74
9	France	58
10	Spain	47
11	Iran	46
12	Malaysia	40
13	Bahrain	37
14	Kuwait	35
15	Taiwan	34
16	Vietnam	32
17	Australia	30
18	Missing Data	26
19	Canada	22
20	UAE	21
21	United Arab Emirates	20
22	UK	20
23	USA	18
24	United States	17
25	United Kingdom	12
26	Switzerland	11
27	Sweden	10
28	India	6
29	Oman	6
30	Iraq	6
31	Israel	5
32	Russia	4
33	Lebanon	4
34	Austria	4
35	Norway	4
36	Croatia	4
37	Finland	3
38	Philippines	3
39	Romania	3
40	Phillipines	3

No	Country	Frequency
41	Nepal	2
42	Cambodia	2
43	Sri Lanka	2
44	Belgium	2
45	Egypt	2
46	Pakistan	2
47	Afghanistan	2
48	Algeria	2
49	Georgia	2
50	Netherlands	2
51	North Macedonia	1
52	Greece	1
53	Brazil	1
54	Nigeria	1
55	Estonia	1
56	San Marino	1
57	Lithuania	1
58	Ecuador	1
	Total	**14259**

Note: Data from 11th November 2019 to 18th March 2020

Table 2. Sociodemographic characteristics of the cases

Sociodemographic data		n (%)
Age (n=2191)	Less than 18 years old	79 (3.6%)
	18 to 29	251(11.4%)
	30 to 39	370 (16.9%)
	40 to 49	335 (15.3%)
	50 to 59	369 (16.8%)
	60 and above	787 (35.9%)
Gender (n=2165)	Male	1227 (56.7%)
	Female	938 (43.3%)

Note: Data from 11th November 2019 to 18th March 2020

Table 3: Clinical symptoms of the cases (n=763)

No	Symptoms	Count	Percentage
1	Fever	571	74.8%
2	Non-productive cough	322	42.2%
3	Fatigue	100	13.1%
4	Sore throat/ dry mouth/ dry throat	98	12.8%
5	Shortness of breath	89	11.7%
6	Chest pain/ discomfort	63	8.3%
7	Rhinorrhoea/ nasal congestion/ sneezing	46	6.0%
8	Muscular pain/ stiffness	40	5.2%
9	Chills/ rigors	35	4.6%
10	Headache	31	4.1%
11	Expectoration	25	3.3%
12	Diarrhoea	18	2.4%
13	Nausea/ vomiting	17	2.2%
14	Joint pain	13	1.7%
15	Asymptomatic	8	1.0%
16	Loss of appetite	5	0.7%
17	Dizziness	2	0.3%
18	Conjunctivitis	2	0.3%
20	Toothache	1	0.1%
21	Abdominal pain	1	0.1%

Note: Data from 11th November 2019 to 18th March 2020

Discussion

Comparison with other existing reports from the literature

This study contributes an overview of the common clinical symptoms of COVID-19 and its demographic data for this infection from a worldwide database. The median age in our analysis was consistent with previous review,[10] while another review showed a median age of 47 years old, with majority were males (58.1%).[9] There were quite a number of cases in the adolescent and children age group (n=79, 3.6%), which was not shown from earlier reports.[17, 18]

Some findings for the clinical symptoms from this database were comparably similar to previous report among 1099 patients in China[9] and a case series of 138 admitted patients in China;[10] where the most common symptoms were fever, followed by cough and fatigue. In the analysis of 1099 patients byGuan, Ni [9] sputum production, shortness of breath, myalgia, sore throat, headache and chills were other symptoms that had a prevalence of more than 10%. A stark difference in the previous reviews[9, 10] were a higher number of patients had sputum production at 33.7%[9] and 26.8%[10] ; compared to our analysis in which only 3.3% experience expectoration. Nasal congestion or rhinorrhoea was relatively more common in our analysis at 6%, compared to less that 5% in previous reviews.[9, 19] This symptom was thought to be rare and more of a common cold symptom.

Another difference that our current analysis found

Table 4: Cases with reports on symptoms according to countries(Note: Data from 11th November 2019 to 18th March 2020)

No	Country	No of cases reporting symptoms (n=763)	Fever	Dry Cough	fatigue	Sore throat	Shortness of Breath	chest pain/ dis-comfort	Rhinorr-hoea/ nasal conges-tion/ sneezin	mus-cular pain/ stiff-ness	chills/ rigors	Head-ache	expecto-ration	diarr-hoea	Nausea/ vomiting	joint pain	Asymp-tomatic	Loss of Appe-tite	dizzi-ness	conjunc-tivitis	Tooth-ache	Abdo-minal Pain
1	China	298	220	110	39	26	41	39	15	19	8	6	9	7	6				2			
2	Japan	278	228	115	54	32	31	15	9	4	11	19	14	7	9	13	3	5			1	1
3	Hong Kong	43	27	27	1	5	4		3	2	2		2	4	1							
4	Taiwan	23	11	14	1	6	3	2	3	1	1	1										
5	South Korea	22	14	10		5	1	2	1	7	5	1										
6	Malaysia	15	9	7	1	3			1								3					
7	Unspecified	14	7	7		5	5	3	2	2	1											
8	Thailand	13	12	6	1	2				3	2	2										
9	Singapore	12	12	3		2					1											
10	Vietnam	12	7	5	2	1	1	1	4			2										
11	Germany	4	4	3		3				2	2											
12	France	3	2	3	1	1			1		2									1		
13	United States	3	2	2			1		1						1							
14	Spain	3	2	1		2			1													
15	Cambodia	2	2						2													
16	Russia	2	2	2		2			2													
17	Sweden	2	1	2		1	1	1	1													
18	Nepal	1	1	1			1															
19	Philippines	1		1		1																
20	Belgium	1															1					
21	Italy	1	1																	1		
22	Lebanon	1	1																			
23	Nigeria	1															1					
24	Lithuania	1																				
25	Netherlands	1																				
26	Ecuador	1	1																			
27	USA	1	1	1																		
28	Canada	1	1	1																		
29	Sri Lanka	1	1																			
30	Phillipines	1	1	1		1																
31	Finland	1	1																			
	Total	**763**	**571**	**322**	**100**	**98**	**89**	**63**	**46**	**40**	**35**	**31**	**25**	**18**	**17**	**13**	**8**	**5**	**2**	**2**	**1**	**1**

was chest discomfort as a symptom of COVID-19 at 8.3% prevalence. This symptom is not surprising as pleuritic chest pain is one of the established symptoms of pneumonia where there may be inflammation of the pleura due to the infection. However it was not reported in the previous reviews.[9, 10, 18, 19] The pain may be induced by inflammatory mediators released into the pleural space or when there is inflammation at the parietal pleurae at the periphery of the rib cage and lateral hemidiaphragm which are innervated by intercostal nerves.[20] Other than that, conjunctival injection which was not reported in initial reports[10, 18, 19] was present at 0.3% in our analysis and was found in a more recent review.[9]

Contribution to screening and surveillance modelling

With this understanding, we hope this study can better-contribute to the development of screening and surveillance model for COVID-19. As per our initialmotivation which drives this review, we believe extensive active case detection, contact-tracing and comprehensive mass diagnostic testing of the population are still the key strategy to contain the outbreak of the disease. However, since this is not possible in all situations[21-24], screening and surveillance model based on combined key epidemiological information and associated symptoms are highly valuable to improve the efficiency and effectiveness of mass diagnostic testingwhen resources are limited. Information from this may facilitate more accurate risk-prediction modelling of the targeted population.This hopefully will navigate for a better resource allocation and more systematic planning to manage groups of population according to their risk of contracting the SARS-CoV-2 infection.

Asymptomatic infection

There have been much debates surrounding asymptomatic SARS-CoV-2 infections and risk of infecting others among infected individuals who do not exhibit any symptoms.[25-27] The initial comprehensive joint WHO-China report[25] stated only small proportion or less than 1% of confirmed cases were truly asymptomatic and suggested their risk of infecting others were likely even lower. Our study showed consistent results with only 8 out of 763 cases (1.05%) were asymptomatic.Yet, we believe a cross-sectional reading of data, including this study, needs to be interpreted with caution since it is possible for these patients to develop symptoms when they progress throughout the course of the disease. This may have an important repercussion to screening strategy where once-off screening will likely be less useful than full surveillance of daily screening so any symptoms of the disease can be identified at the earliest stage possible.Fortunately, this can be conveniently achieved through use of technology such as dedicated web-based or mobile-apps screening for use among mass population.

Nonetheless, completely asymptomatic infection from prospective observation has also been reported. For example, on 12th April 2020, the Health Director-General (DG) of Malaysia[26] revealed specialreport on cases among 41high school students who underwent the first phase of quarantine due to history of close contact with individuals with confirmed infection. Theywere initially tested negative twice at the beginning and middle of March 2020. However, they were tested positive on March 30th and underwent further two-weeks quarantine. They were released from quarantine on April 12th following negative test results just prior to discharge. Throughout these periods of quarantine, only one of them reported symptoms of coughing whereas the remaining 40 students (97.6%) were free from any symptoms. The prevalence of asymptomatic infection among the elderly population has also been reported higher than the initial WHO-China report.[25] An observational study among the elderly population at various long term care facilities in King County, Washington, reported 7 out of 167 (4.19%) of all residents with confirmed diagnosis were asymptomatic throughout the period of care.[27]

Therefore, while surveillance with daily screening of symptoms may have been highly valuable to improve efficiency of resource allocation for mass testing, they are not to replace the core epidemiological strategy on comprehensive active case detection and contact tracing. Findings of our study and reports from the literature and case reports therefore demonstrate any comprehensive screening modelling and surveillance strategy must not be relying solely on epidemiological risk factors or solely on symptoms. Rather it must incorporate both to better improve the accuracy of risk-prediction and subsequently more robust screening and surveillance strategies.

Limitations

The main challengeof this study was the lack of complete reports from the data itself. Although a large amount of cases of COVID-19 was found in the database, only 763 cases actually described the

clinical symptoms that the patient presented with. Likewise, only 2191 (15.4%)and 2165 (15.2%) of cases were providing reports on age and gender respectively. In spite of collecting a comprehensive data from a total of 58 countries, majority of cases with reports on symptoms were mainly from China and Japanas shown in Table 4. This showed that there was much to be done to improve the data coordination for a pandemic of this scale.

Another limitation of our study is the fact that COVID-19 itself is a novel pathology. Therefore, there is a possibility that new clinical features of the disease will be identified at a later stageas more cases are reported worldwide. For example, there were recent publication from prominent medical websites in otolaryngology[28] and dermatology[29] which reported anosmia/hyposmia and skin rashes as two other possible symptoms associated with the disease.There was also recent news headlines in the United Kingdom on possible toxic shock syndrome associated with severe illnesses of COVID-10 among children.[30]The extent of prevalence and significance ofthese new clinical manifestations of the disease however, areyet to be established.

Conclusions

All age groups are susceptible to COVID-19, with 60 and above being the most common age group infected. There were a total of 20 clinical symptoms associated with COVID-19 were reported from Johns Hopkins University Repository Online Worldwide Database from 11th November 2019 until 18th March 2020. The most common symptoms were fever, non-productive cough and fatigue. There were also a range of less common symptoms such as chest discomfort, nasal congestion or conjunctivitis for COVID-19. Those presented with these symptoms should be evaluated thoroughly for any possibility of COVID-19. Results from this review may also prove useful to facilitate more accurate risk-prediction model for screening and surveillance strategies especially in cases where resources for mass population diagnostic testing are limited.

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Conflict of interest: None.

Authors' contribution:

All authors were involved in ideas generation and data gathering of the study. MSI and NMH prepared the initial writing. All authors contributed with editing and approved the final draft. The manuscript was completed and submitted by MSI and SI.

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