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Review Article

Worldwide One-Year Dynamics Of COVID-19 Manifestations: A Systematic Review And Meta-Analysis

Samaneh Abiri[1], Aref Ghanaatpisheh[2], Mojtaba Sohrabpour[3], Mohammad Sadegh Sanie Jahromi[4], Seyed Reza Habibzadeh[5], Behzad Shahi[6], Mahdi Foroughian[5], Fatemeh Maleki[7], Arman Hakemi[5], Esmaeil Rayat Dost[1], Ali Kazeminezhad[8*]

1 Department of Emergency Medicine, Jahrom University of Medical sciences, Jahrom, Iran.
2 Student research committee, Jahrom University of Medical Sciences, Jahrom, Iran.
3 Assistant Professor of Otorhinolaryngology, Head and Neck Surgery, Fasa University of Medical Science, Fasa, Iran.
4 Anesthesiology, Critical care and pain management research center, Jahrom University of Medical Sciences, Jahrom, Iran.
5 Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical sciences, Mashhad, Iran.
6 Department of Emergency Medicine, Faculty of Medicine, Zahedan University of Medical Sciences, Mashhad, Iran.
7 Department of Emergency Medicine, Faculty of Medicine, Birjand University of Medical sciences, Birjand, Iran.
8 Department of Neurosurgery, Peymanieh Hospital, Jahrom University of Medical Sciences, Jahrom, Iran.

* **Correspondence**: Ali Kazeminezhad. Department of Neurosurgery, Peymanieh Hospital, Jahrom University of Medical Sciences, Jahrom, Iran. Email: kazemimd@msn.com

Abstract:

Objective: To evaluate if the pattern of COVID-19 symptoms prevalence change through the time or not.

Study design: Systematic review and meta-analysis based on the PRISMA statement (PROSPERO registration code: CRD42021296324).

Method: To assess the pooled prevalence of COVID-19 symptoms in various time intervals, COVID-19 cross sectional studies published in databases of MEDLINE, EMBASE, PubMed, Scopus, Science Direct, Embase, Cochrane, and Web of Science were queried with proper keywords. Sample size, prevalence of clinical signs, country and months of conducting study were extracted and quantitively evaluated in Comprehensive Meta-Analysis software.

Results: In this systematic review and meta-analysis, 57 studies were included. pooled prevalence of fever varied from 85.8% in first months of the COVID-19 pandemic to 34.2% in last months reported in literature. In case of the pooled prevalence of cough in January-February, it was estimated to be 83.4; while in later conducted studies it was significantly lower, about the 55.3%. Myalgia prevalence rate ranged from 53.2% in first months to 2.5% later. Headache rate varied from 61.4% to 17.6% passing the time of studies. Dyspnea rate ranged from 49.4% to 5.2% through the time.

Conclusion: While due to the possible effect of study region and sample differences on the prevalence of each symptom; our study showed a significant changing pattern of COVID-19 main symptoms through the time.

Keywords: COVID-19, Fever, Symptom, Meta-Analysis.

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Introduction

In February 1, 2020, the World Health Organization (WHO) declared COVID-19 as a public health emergency raising international concerns (1). At the beginning of the outbreak, the same symptoms of last coronavirus pandemics were reported, firstly described as pneumonia with unknown causes (2). Fever, cough, and shortness of breath are among the

most obvious symptoms experienced by people infected with the new coronavirus (2-7), but after a while other different symptom were also been observed in COVID-19 patients. Loss of smell (anosmia), headache, myalgia, fatigue, diarrhea, dizziness, loss of appetite, and diarrhea are also highlighted as the important symptoms of COVID-19 (9-10). While the pandemic; the most important and prominent point about the symptoms of COVID-19 disease has got prolonged, the changes and overlap of the symptoms with the common diseases in different seasons. In summer, due to the type of food consumption, the incidence of diarrhea and vomiting, acute infectious diarrhea or viral diarrhea, which can mainly be associated with fever and abdominal pain, is very common. These conditions may do not even require any special treatment (11-12). So, evaluating the issue of COVID-19 symptoms through the different time periods seems necessary to diagnose the disease.

Methods

In this study a systematic review and meta-analysis was conducted based on PRISMA (Preferred reporting items for systematic review and meta-analysis protocol) statement, to evaluate prevalence of COVID-19 symptoms in various time intervals. This study was registered at PROSPERO registration service (CRD42021296324). As COVID-19 cross sectional studies are being published from the first months of the disease, our aim was to evaluate possible patterns of the disease manifestation change worldwide. So, we reviewed studies published from October 2019 to September 2020.

Eligibility criteria

Eligible studies were various observational studies (Cross-sectional, retrospective and cohort), reporting initial symptoms of PCR confirmed SARS-Cov2 infection and the availability of their full text in English. To access to more information, reference list of reviewed articles was also Hand-search assessed for other articles. Studies on Preprint servers and Gray literature were not included.

Information sources

articles published in international databases of MEDLINE, EMBASE, PubMed, Scopus, Science Direct, Embase, Cochrane, and Web of Science were queried with keywords of SARS-CoV-2, COVID-19, 2019-nCoV and Coronaviruse, in combination of Cross-sectional, retrospective, symptoms, cough, fever, and dyspnea. In case of need to more information, a contact was made with study authors. Studies which had sample size of adult patients with no focus on a specific group of patients like elderly or various underlying medical condition were evaluated.

Search strategy

Initially, all articles' citation, provided in first step of search based on titles and abstracts, were evaluated for duplicated records. Duplicated records were removed and in next step, full text of studies was assessed for reports of information of patients' symptoms upon arrival at the hospital. Exclusion criteria include irrelevant items, case reports, interventional studies, and unclear methodologies. Studies not reporting the time of the study were excluded as well as cross-sectional studies in a specific group of patients. In order to reduce bias, the articles were searched independently by two researchers, and in case of disagreement about a study, the record was judged by the head of the group.

Studies that focus on a single special group of patients were excluded, as shown in figure 1.

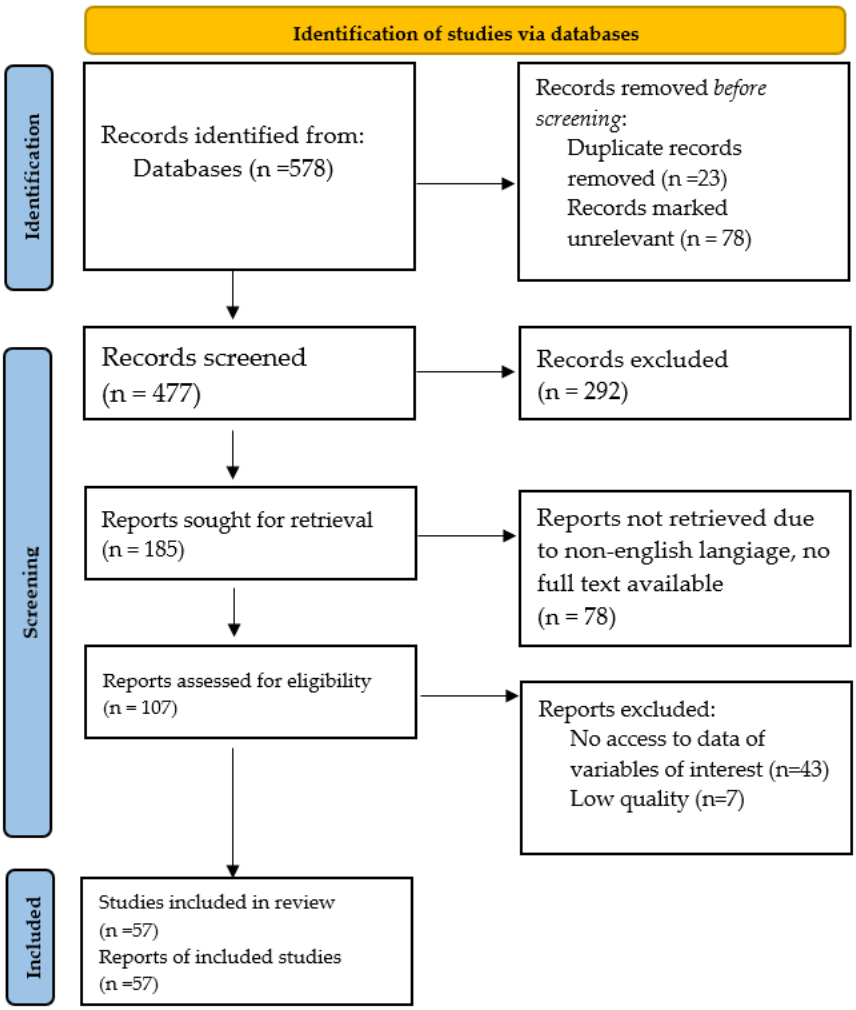

Figure 1. PRISMA flowchart of study

In the third stage, qualitative evaluation was conducted. Reporting disease symptoms data could be biased by self-reported bodily symptoms. Our study evaluated the possibility of study bias, based on the evaluation of symptoms methodology, and studies reporting data of medical exam and history taking by physicians were preferred for having low bias possibility.

Extracting the data:

All final papers obtained for the meta-analysis process were assessed by a checklist. Checklist included article title, first author name, year and month of publication, place of study, sample size, prevalence of clinical signs, and mean age.

Statistical analysis:

Data analysis using software Comprehensive Meta-Analysis (Version 2) was performed. To evaluate the heterogeneity of selected studies, I^2 index test and to evaluate the bias Egger's test and level significance of 0.05 as well as its corresponding Funnel plot.

Results

In current study, 57 (2-58) studies listed in table 1. were evaluated in meta-analysis. Most published studies were in China and in first months of the pandemic.

Table 1: Included studies characteristics

Study ID	Country	Time interval	Number of participants
Shi et al.	China	January 20 to February 10, 2020	24410
Xu a et al.	China	January and February 2020,	50
Yang et al.	China	January 17th to February 10th, 2020	149
Wang a et al.	China	January 21 to January 24, 2020	4
Zhang a et al.	China	January 16 to January 3, 2020	140
Chu et al.	China	January 7 and 11 January 2020	54
Guan et al.	China	January	1099
Deng et al.	China	January 1, 2020 to February	225
Wu a et al.	China	January to 14 February 2020	80
Huang et al.	China	December 2019 to January 2020	34
Liu et al.	China	December 30, 2019 to January 24, 2020	137
Mo et al.	China	January 1st to February	155
Ye et al.	China	January. 8 to February	5
Zhou et al.	China	January	191
Cheng et al.	China	January 19 February 6, 2020	11
Xu et al.	China	January 23 and February 18, 202	51
Wan et al.	China	23 January to 8 February 2020	135
Wang b et al.	China	16 January and 29 January 2020	69
Liu a et al.	China	January 1, 2020 to February 15, 2020	56
Huang a et al.	China	January	41
Xu b et al.	China	January	62
Chen et al.	China	January 20 to February 6, 2020	249
Luo et al.	China	January 1, 2020, to February 20	183
Song et al.	China	January 20, 2020, to January 27	51
Chen a et al.	China	January	99
Jin et al.	China	January to 8 February 2020	651
Zhang b et al.	China	January , 2020 to February	625
Zhu et al.	China	January , 2020 to February	32
Zhao et al.	China	January , 2020 to February	101
Wu b et al.	China	January , 2020 to February	201
Li et al.	China	January , 2020 to February	83
Nie et al.	China	January , 2020 to February	97
Goyal et al.	USA	3 March and 15 May 2020	1687
de et al.	France	March 18 to April 9, 2020	277
Rivera-Izquierdo et al.	Spain	March and 10 April	238
Tomasiewicz et al.	Poland	March 15 and April	28
Joseph et al.	USA	March 14, 2020 to April	326
Lagier et al.	France	March 3rd to April 27th	3737
Jalili et al.	Iran	20 February to 20 April 2020	259652
Cantini et al.	Italy	March 15th-May 5th, 2020.	191
Passamonti et al.	Italy	February 25 and May 18,	536
Mohamud et al.	Somalia	April 1 and April 20	60
Chen b et al.	China	January 20, 2020 to March	84
Asghar et al.	Pakistan	March and April 2020	100
Nguyen et al.	France	March 15th and April 14th	279
Javanian et al.	Iran	25 February 2020 to 12 March 2020.	100
Poncet-Megemont et al.	France	Feb 27th and April 15th,	139
Perez-Guzman et al.	UK	5th February 2020 and 5th April	614
Shah et al.	USA	February 3 and March 31,	33
Leonardi et al.	China	January 21 to June 27,	218
Argenziano et al.	USA	March 1 and April 5	1000

Arentz et al.	USA	February 20, 2020, and March 5, 2020,	21
Ciardullo et al.	Italy	22 February 2020 to 15 May	304
Alsofayan et al.	Saudi Arabia	March 2020 to 31st of March 2020	1519
Kong et al.	South Korea	January 2020 to February 14	28
Young et al.	Singapore	January 23 and February 3, 2020	18
COVID-19 National Incident Room	Australia	March 2020	71

Reviewing the pooled prevalence of fever in various months, 31 studies reported the prevalence of fever in January- February, with a prevalence rate of 0.858, while in the 8 studies reporting Fever in March-April, the prevalence rate was 0.342 and there were high heterogeneities in studies in both groups of March-April and January- February. In February-March, 5 studies were evaluated and showed 0.053 prevalence rate of fever with high heterogeneity (I2=99%). In case of the pooled prevalence of cough in various months, 31 studies reported the prevalence of cough in January- February, with a prevalence rate of 0.834, while in the 8 studies reporting Fever in March- April, the prevalence rate was 0.553 and there were high heterogenicities (table 2). In February-March, 5 studies were evaluated and showed 0.060 prevalence rate of cough with high heterogenicity (table 2). Myalgia was reported in 31 studies in January- February, with a pooled prevalence rate of 0.516, while in the 4 studies in March- April, its prevalence rate was 0.025 and there were high heterogenicities (table 2). In February- March, 5 studies showed 0.532 prevalence rate of myalgia with high heterogenicity (table 2).

Table 2. Meta-analysis of porportions of symptoms in different time intervals

	Fever					Cough					myalgia				
	Number of studies	Point estimate	Lower limmit	Upper limmit	I²	Number of studies	Point estimate	Lower limmit	Upper limmit	I²	Number of studies	Point estimate	Lower limmit	Upper limmit	I²
April	1	0.717	0.591	0.816	0.00	1	0.750	0.626	0.843	0.00	1	0.533	0.408	0.655	0.00
December2019-January	2	0.833	0.767	0.883	64.196	2	0.485	0.411	0.560	0.00	2	0.385	0.313	0.463	0.914
February- March	5	0.053	0.052	0.053	99.792	5	0.060	0.059	0.061	0.97	4	0.025	0.024	0.026	0.98
February- April	2	0.733	0.700	0.763	0.00	1	0.816	0.783	0.845	0.00	-	-	-	-	-
February- May	1	0.832	0.786	0.870	0.00	1	0.398	0.344	0.454	0.00	-	-	-	-	-
January- February	31	0.858	0.854	0.862	98.059	31	0.834	0.829	0.838	98.02	28	0.516	0.510	0.522	0.79
January- March	1	0.810	0.711	0.880	0.00	1	0.702	0.597	0.790	0.00	1	0.036	0.012	0.105	0.00
January- June	1	0.665	0.600	0.725	0.00	1	0.743	0.681	0.797	0.00	1	0.353	0.293	0.419	0.00
March	2	0.844	0.825	0.861	95.111	2	0.882	0.865	0.898	0.873	1	0.183	0.109	0.290	0.00
March- April	8	0.342	0.327	0.357	99.545	8	0.553	0.540	0.566	0.809	5	0.532	0.494	0.567	0.98
March- May	1	0.689	0.666	0.710	0.00	2	0.688	0.667	0.709	0.00	1	0.198	0.180	0.218	0.00
Overall	55	0.150	0.148	0.152	99.922	55	0.161	P.160	0.163	87	44	0.164	0.161	0.166	0.83

continue of Table 2.

	Headache					Diarrhea					Dyspnea				
	Number of studies	Point estimate	Lower limmit	Upper limmit	I^2	Number of studies	Point estimate	Lower limmit	Upper limmit	I^2	Number of studies	Point estimate	Lower limmit	Upper limmit	I^2
April	1	0.167	0.092	0.283	0.00	1	0.167	0.092	0.283	0.00	1	0.167	0.092	0.283	0.00
December2019- January	2	0.089	0.054	0.142	0.00	2	0.097	0.060	0.152	0.255	2	0.182	0.131	0.247	0.00
February- March	2	0.513	0.424	0.602	1.137	3	0.002	0.001	0.002	4.916	4	0.052	0.051	0.053	2.067
February- April	-	-	-	-	-	-	-	-	-	-	1	0.651	0.613	0.688	0.00
February- May	-	-	-	-	-	1	0.053	0.032	0.084	0.00	1	0.707	0.654	0.756	0.00
January- February	19	0.614	0.608	0.620	1.816	24	0.462	0.456	0.468	1.445	24	0.494	0.488	0.500	1.123
January- March	1	0.012	0.002	0.080	0.00	1	0.024	0.006	0.090	0.00	1	0.131	0.074	0.221	0.00
March	1	0.352	0.250	0.469	0.00	1	0.254	0.166	0.367	0.00	1	0.254	0.166	0.367	0.00
March- April	3	0.176	0.139	0.220	0.516	5	0.248	0.222	0.276	0.642	7	0.370	0.357	0.383	0.830
March- May	1	0.455	0.386	0.527	0.00	1	0.358	0.335	0.381	0.00	2	0.649	0.627	0.671	0.324
Overall	30	0.605	0.599	0.611	1.653	39	0.434	0.428	0.440	1.582	44	0.148	0.146	0.149	1.936

Headache was reported in 19 studies in January- February, with a pooled prevalence rate of 0.614, while in the 3 studies in March- April it was estimated to be 0.176 (table 2). Diarrhea pooled prevalence was estimated to be 0.462 in January- February and 0.248 on March- April. Dyspnea pooled prevalence was 0.052 in February- March based on 4 studies. On January- February it was estimated to be 0.494 based in 24 studies. In March- April, 7 studies were assessed and pooled prevalence was 0.370. The figure 2 shows the summarized schematic of the symptom prevalence in different months. There was low possibility of bias among the studies based on the eggers test ($P<0.05$) and asymmetry of funnel plots.

Figure 2. Summarized schematic symptom prevalence in different months

Due to high rate of heterogenicity and difference of studies area, an analysis in just studies in China was conducted. There were 33 studies from China in which 2 were cross-sectional studies performed in December2019- January, 29 performed in January- February, 1 in January- June and 1 in January-March, showing fever prevalence rate of 0.833, 0.859, 0.810, 0.665, Table 2.

Discussion:

In the early days of the virus spread in China, the common symptoms following the onset of the disease were limited symptoms such as fever, cough, and finally severe symptoms limited to the respiratory tract (15-19, 20,34). Over time, more extensive and severe symptoms were observed in patients.

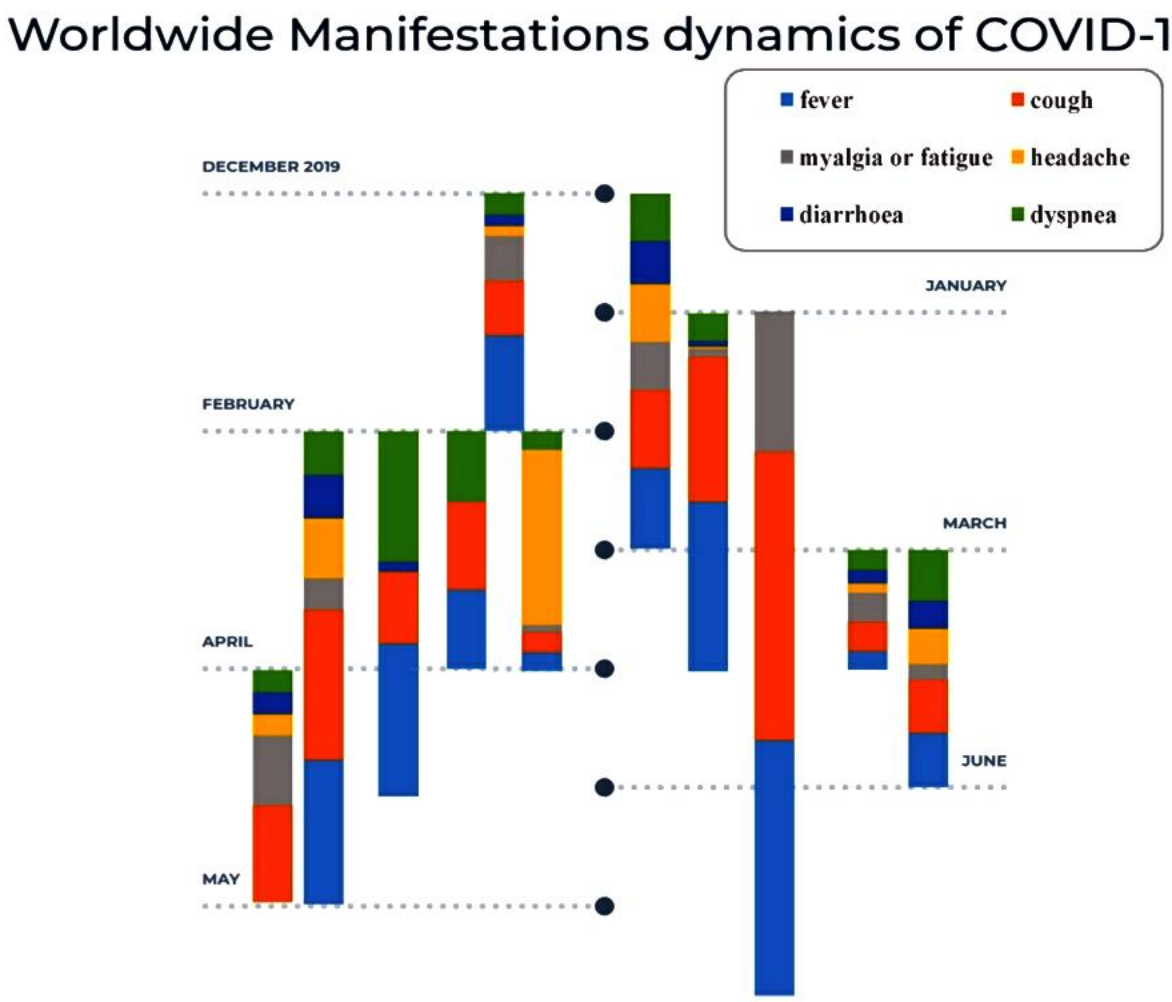

Figure 2. Summarized schematic symptom prevalence in different months

Symptoms such as body aches, headaches, dizziness, gastrointestinal symptoms, impaired renal function. To date, with the virus spreading across the globe, newer symptoms are being reported daily. In addition to heart, liver, kidney, eye, ear, throat, nose, and recently reported skin lesions, neurological symptoms are symptoms of COVID-19 (59-60). While most patients with COVID-19 have fever, cough, fatigue, and respiratory problems, some patients may appear to be nervous. Urticaria, hair loss, heart attack, kidney failure, liver involvement and jaundice, all may be symptoms of COVID-19. In the current situation of pandemic, many reports indicate the emergence of the COVID-19 in some patients with new manifestations. While these manifestations are rare, the main symptoms of COVID-19 are yet classic manifestations like fever, cough, dyspnea, and headache. Our study reviewed studies reporting patients with COVID-19 in various months after the disease initiation and we saw that symptoms of COVID-19 may tend to change dramatically since the disease was first reported on 2019. 57 articles were included in the systematic review and meta-analysis. The cumulative incidence of fever ranged from 85.8% during the first months of the COVID-19 pandemic to 34.2% in the literature published in recent months. It was reported to be 83.4 in the case of the pooled cough prevalence in January-February, although it was slightly lower in later studies, around 55.3 percent. Relevance of these findings is to key groups of healthcare providers

trying to actively identify positive cases of COVID-19 to stop spread of the disease.

Limitations:

The aim of our study was to investigate the variability and variation of COVID-19 symptoms in different times. While several limitations were Infront of us. First of all, most studies were conducted in China and in first months of disease spread. Reports from other countries were available for next months but there were not lots of eligible studies in each country. Our results may be biased by the study region as the different populations show different patterns of response to epidemic due to genetic, environmental, policies and many other known and unknown factors. Although the spread of the virus continues, the results of this study tried to identify patterns of changes in the symptoms and behavior of the virus from the beginning of the spread to the present day. to asses this hypothesis of bias possibility, we compared only studies within the china. our resulats had a similar conclusion that even in a specific region, rate of symptoms are being altered during the time. maybe the reason behind this could be the virus genomic chenges during the time.

Conclusion:

Although due to the potential impact of research region and sample variations on the prevalence of symptom, our research showed a substantial change in pattern of major symptoms of COVID-19 over time.

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Author contributions: SA, AG, and AK conceptulised the study topic. MS, MSSJ, SRH, BS performed the initial literature review. MF, FM, AH, and ER performed the data extraction. AK SA, and AG conducted the data analysis. manuscript was written by MS, MSSJ, and SRH. all authors contributed in revisions.

Competing interests: None.

Ethical approval: NA.

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