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Clinical manifestations of COVID-19: An overview of 102 systematic reviews with evidence mapping

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) has rapidly spread worldwide, but there is so far no comprehensive analysis of all known symptoms of the disease. Our study aimed to present a comprehensive picture of the clinical symptoms of COVID-19 using an evidence map.

Methods: We systematically searched MEDLINE via PubMed, Web of Science, Embase, and Cochrane library from their inception to March 16, 2021. We included systematic reviews reporting the clinical manifestations of COVID-19 patients. We

Xufei Luo and Meng Lv contributed equally to the work.

followed the PRISMA guidelines, and the study selection, data extraction, and quality assessment were done by two individuals independently. We assessed the methodological quality of the studies using AMSTAR. We visually presented the clinical symptoms of COVID-19 and their prevalence.

Results: A total of 102 systematic reviews were included, of which, 68 studies (66.7%) were of high quality, 19 studies (18.6%) of medium quality, and 15 studies (14.7%) of low quality. We identified a total of 74 symptoms including 17 symptoms of the respiratory system, 21 symptoms of the neurological system, 10 symptoms of the gastrointestinal system, 16 cutaneous symptoms, and 10 ocular symptoms. The most common symptoms were fever (67 studies, ranging 16.3%–91.0%, pooled prevalence: 64.6%, 95%CI, 61.3%–67.9%), cough (68 studies, ranging 30.0%–72.2%, pooled prevalence: 53.6%, 95%CI, 52.1%–55.1%), muscle soreness (56 studies, ranging 3.0%–44.0%, pooled prevalence: 18.7%, 95%CI, 16.3%–21.3%), and fatigue (52 studies, ranging 3.3%-58.5%, pooled prevalence: 29.4%, 95%CI, 27.5%–31.3%). The prevalence estimates for COVID-19 symptoms were generally lower in neonates, children and adolescents, and pregnant women than in the general populations.

Conclusion: At least 74 different clinical manifestations are associated with COVID-19. Fever, cough, muscle soreness, and fatigue are the most common, but attention should also be paid to the rare symptoms that can help in the early diagnosis of the disease.

KEYWORDS
clinical manifestations, COVID-19, evidence map, SARS-CoV-2, systematic review

1 | INTRODUCTION

Human coronaviruses have in the past caused widespread outbreaks of serious diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[1] At the end of 2019, a novel coronavirus was identified as the etiology of a group of cases of pneumonia. The virus spread rapidly, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization (WHO) named the coronavirus disease 2019 (COVID-19).[2] The virus that causes COVID-19 has been given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On January 30, 2020, the WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC)[3] and on 11 March 2020, a pandemic.[4] As of August 10, 2021, the reported cumulative COVID-19 death toll surpassed four million lives, and the pace of deaths is accelerating. COVID-19 pandemic is becoming regular in our lives.[5]

Clinical symptoms are the external manifestations of the disease and are important for the diagnosis, treatment, and evaluation of the disease. Pneumonia is the most common manifestation in patients with COVID-19, characterized primarily by fever, fatigue, dry cough, dyspnea, and other similar symptoms.[6] Some patients also exhibit gastrointestinal symptoms, such as anorexia, nausea, vomiting, and diarrhea.[7] Ocular manifestations have also been reported in some COVID-19 patients.[8] Since the end of March 2020, skin manifestations and loss of sense of smell and taste have also been reported in patients with COVID-19.[9,10] As of April 20, 2021, several systematic reviews of the symptoms of COVID-19 have been published.[11–15] However, none of these have attempted to describe the full range of clinical manifestations of COVID-19.

Evidence mapping is a method to summarize the evidence. It consists of a comprehensive search of the relevant research, systematical summarization of the basic characteristics and results of various types of studies, and an accurate visual representation of the evidence, progress, and problems in the field, to provide a comprehensive picture of research in the field and improve the effectiveness and usefulness of research in the field.[16] This study aimed to summarize the existing knowledge on clinical manifestations of COVID-19 using evidence mapping to present a full picture of the clinical manifestations of COVID-19 patients to provide a basis for clinical practice.

2 | METHODS

2.1 | Registration and reporting guideline

This study has been prospectively registered in the PROSPERO, and the registration number is CRD42021251418. We conducted this

overview with an evidence mapping study following the guideline of Campbell Collaboration.[17] We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for reporting of methods and findings of this study[18] (Supplementary Material 1).

2.2 | Eligibility criteria and literature search

Systematic reviews were included if they met one of the following criteria: (1) systematic reviews with meta-analyses that pooled the incidence of different clinical manifestations of COVID-19; (2) systematic review with the proportions of different clinical manifestations of COVID-19. If the format of Population, Intervention, Comparison, Outcomes, and Study design (PICOS) is used to present our research questions, P is for COVID-19 patients, I and C are not applicable, and O is different clinical manifestations of COVID-19 patients, and S is systematic review.

We excluded studies on traditional Chinese medicine; studies focusing on other diseases in patients with COVID-19. We also excluded the systematic reviews that were not able to extract the incidence of COVID-19 symptoms and systematic reviews that were not able to access the full text after contacting the corresponding authors by email. The definition of the systematic review was determined according to the criteria of the Cochrane Handbook.

We searched MEDLINE via PubMed, Web of Science, Embase, and Cochrane library on March 16, 2021, with the terms ["2019-nCoV" OR "novel coronavirus" OR "COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus"] AND ["systematic review" OR "meta-analysis" OR "literature review"] AND ["characteristics" OR "features" OR "manifestations" OR "presentation" OR "symptoms"] published between January 1, 2020 and March 16, 2021 without any language restriction (see Supplementary Material 2 for details of search strategies). We also searched Google Scholar, the WHO database of publications on COVID-19 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov), and the reference lists of the included studies to find reports of additional studies. All searches were conducted independently by two separate reviewers (XL and XZ), and if the number of searches was inconsistent, the two reviewers searched together and determined the results.

2.3 | Study selection

Two reviewers (XL and ML) independently screened the titles, abstracts and full texts based on the inclusion and exclusion criteria. Before the screening, the two reviewers (XL and ML) performed a pretest extraction of 100 papers until an agreement on the screening process was reached. Disagreements were resolved by discussion with a third reviewer (YC). If the full text was not available, we contacted the authors to request the full text or further details. All screening was done using EndNote 20 software (Bld16742, Copyright © 1988–2021 Clarivate Analytics) except for full text.

2.4 | Data extraction and quality appraisal

Two groups of two reviewers (YL and ML, MR and LW) independently extracted the data. We extracted the following basic information: (1) title, (2) first author and his/her country, (3) journal, (4) the number of included studies, (5) study design of included studies, and (6) sample size; and the following information on the results: manifestations outcomes and related statistical indicators (prevalence, effect size, 95% confidence interval (CI), I^2, P). If essential information was missing, we contacted the author to get the data, or used data conversion to the largest possible extent. Data that could not be obtained were discarded.

We assessed the methodological quality of the included systematic reviews using the "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR) instrument.[19] The AMSTAR score has a total of 11 points, with studies scoring between 9 and 11 being of high quality, studies scoring between 6 and 8 of medium quality, and studies scoring between 0 and 5 of low quality. Quality assessments were done by two independent reviewers (XL and RL) and were determined by consulting a third reviewer (YC) in case of inconsistency.

2.5 | Data analysis

We presented the general characteristics of the included studies descriptively. We calculated the ranges for the proportion of COVID-19 patients having different symptoms. We presented the outcomes visually using a human anatomy diagram and a heat map. The heat map was prepared using Microsoft Excel 2016 software, and the human anatomy diagram was done using the Edraw Software (https://www.edrawsoft.com/). The clinical characteristics of COVID-19 patients were divided into five parts according to the different systems of the body: (1) respiratory symptoms; (2) neurological symptoms; (3) gastrointestinal symptoms; (4) cutaneous symptoms, and (5) ocular symptoms. We also divided the population into three categories, namely the general population, neonates, children and adolescents, and pregnant women. The pooled prevalence estimate (PPE) will be performed for each symptom using the Comprehensive Meta-analysis software, and if possible, we will examine the differences in prevalence by country, age, and gender.

3 | RESULTS

3.1 | Results of study selection

Our initial search revealed 2811 records, 759 of which were excluded as duplicates. After screening the titles and abstracts, 1897 of the remaining studies were excluded because of not related to COVID-19. We reviewed the full texts of the remaining 155 articles and excluded 53 irrelevant articles, 38 articles that did not pool clinical symptoms, and five articles that only reported on complications. Finally, we identified 102 systematic reviews related to the clinical symptoms of

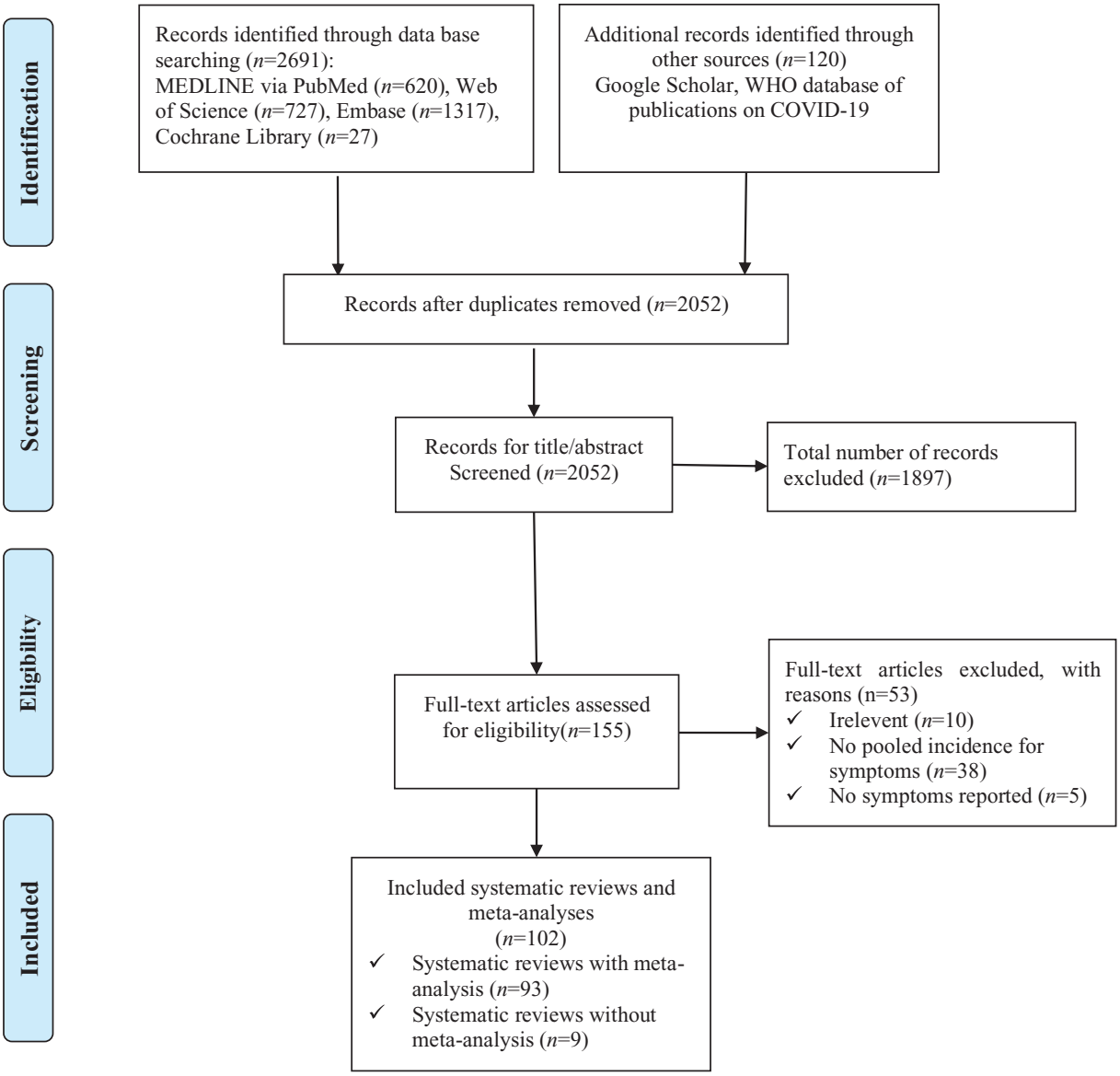

FIGURE 1 Flow chart of the literature search and selection

COVID-19. Figure 1 shows the flow of search and selection. Supplementary Material 3 presents a list of the inclusion and exclusion of systematic reviews.

3.2 | Characteristics of the included studies

Ninety-three (91.2%) of the 102 studies were systematic reviews with meta-analyses, the others have calculated percentages of different kinds of symptoms but no meta-analysis. They were published between March 11, 2020 and March 4, 2021, with 89 (87.3%) of them in 2020. One hundred and two studies were conducted mainly in 26 countries or regions, 28 (27.5%) of the studies were conducted in China; 16 (15.7%) in Iran; 8 (7.8%) in India; 7 (6.9%) in the United States; five (4.9%) in the United Kingdom; four (3.9%) each in Italy and Brazil; three (2.9%) each in Malaysia, Nigeria, and Republic of Korea; two (2.0%) each in Colombia, Nepal, Canada, Egypt, and France; and one (1.0%) each in Singapore, Indonesia, Philippines, Switzerland, Ethiopia, Turkey, Australia, Bangladesh, Peru, Kuwait, and the United Arab Emirates. Most included systematic reviews ($n = 74$, 72.5%) focused on the general populations of COVID-19, 15 (14.7%) systematic reviews focused on neonates, children, and adolescents, and 13 (12.8%) were pregnant women. The number of studies included in the systematic reviews varied from 5 to 349, and the sample size included varied from 33 to 280,000 COVID-19 patients, and the types of studies included were mainly case reports, case series, and other observational studies. Table 1 describes the characteristics of the included studies.

According to the AMSTAR scores, among the one hundred and two reviews included, 68 studies (66.7%) were of high quality, 19 studies (18.6%) of medium-quality, and 15 studies (14.7%) of low quality (Supplementary Material 4). The main reasons for low quality include lack

TABLE 1 Characteristics of the included systematic reviews and meta-analyses

Research ID	Published/ online date	Country/ region of First Author	Patients	Journal title abbreviations	Number of included primary studies	Number of participants	Age of participants (in years; range or mean)	Female
Hashan et al.	2021/3/1	Australia	General populations	EClinicalMedicine	49	25,567	Mean: 81.5 years	NA
Shehab et al.	2021/3/4	Kuwait	General populations	BMJ Open Gastroenterol	158	78,798	Mean: 66.6 years	45.20%
Soltani et al.	2021/1/12	Iran	General populations	Rev Neurosci	14	3148	Ranged from 19 to 95 years	NA
Kouhsari et al.	2020/11/4	Iran	General populations	Indian J Med Microbiol	50	8815	Mean: 46 years	46%
Soheili et al.	2021/2/18	Iran	Pregnant women	J Matern Fetal Neonatal Med	11	177	NA	100%
Irfan et al.	2021/2/16	Canada	Neonates, children and adolescents	Arch Dis Child	129	10,251	Mean: 7 years	44.50%
Zhong et al.	2021/2/5	China	General populations	Medicine	40	2459	NA	37.70%
Hassanipour et al.	2020/12/21	Iran	Pregnant women	Int J Reprod Biomed	10	135	Ranged from 22 to 42 years	100%
Xie et al.	2020/12/4	China	General populations	Ann Palliat Med	90	16,526	Ranged from 37 to 68 years	46.90%
Olumade et al.	2021/2/5	Nigeria	General populations	J Med Virol	7	4499	NA	31.20%
Nasiri et al.	2021/1/20	Iran	General populations	J Ophthalmic Vis Res	38	8219	NA	55.30%
Israfil et al.	2021/1/11	Bangladesh	General populations	Front Public Health	34	10,889	Mean 50.6 years	39.70%
Goel et al.	2021/1/27	India	General populations	Obstet Gynecol Sci	7	3231	Ranged from 47 to 62 years	44.85%
Lee et al.	2020/12/15	USA	General populations	Dermatol Online J	71	144	Mean: 45.9 years	46.50%
Nazari et al.	2021/1/9	Iran	General populations	Brain Behav	64	11,687	Mean 48.6 years	47.60%
Jafari et al.	2020/12/1	Iran	Pregnant women	Rev Med Virol	349	138,176	Mean age 51.2 (nonpregnant) Mean age 33 (pregnant)	100%
Khamis et al.	2020/12/3	United Arab Emirates	General populations	J Formos Med Assoc	35	10,972	NA	NA
Islam et al.	2020/11/27	Malaysia	General populations	Front Neurol	86	14,275	Ranged from 35.0 ± 8.0 to 70.7 ± 13.5 years	49.40%
Merola et al.	2020/10/12	Italy	General populations	Acta Gastroenterol Belg	33	4434	NA	NA
Saniasiaya et al.	2020/12/15	Malaysia	General populations	Otolaryngol Head Neck Surg	59	29,349	Ranged 28.0 ± 16.4 to 66.4 ± 14.9 years	64.40%
Ciaffi et al.	2020/10/28	Italy	General populations	BMC Rheumatol	88 (51 in meta)	NA	NA	NA
Silva et al.	2020/11/25	Brasil	General populations	Rev Soc Bras Med Trop	43	18,246	NA	NA

(Continues)

TABLE 1 (Continued)

Research ID	Published/ online date	Country/ region of First Author	Patients	Journal title abbreviations	Number of included primary studies	Number of participants	Age of participants (in years; range or mean)	Female
Wang et al.	2020/11/25	China	General populations	Medicine	25	4881	NA	NA
Li et al.	2020/11/2	China	Neonates, children and adolescents	Front Pediatr	96(54 in meta)	7004	NA	NA
Novoa et al.	2021/2/2	Peru	Pregnant women	Travel Med Infect Dis	37(4 in meta)	322	range 20–45	100%
Saniasiaya et al.	2020/12/5	Malaysia	General populations	Laryngoscope	83	27,492	NA	NA
Karabay et al.	2020/11/19	Turkey	Neonates, children and adolescents	J Matern Fetal Neonatal Med	35	NA	NA	NA
Aggarwal et al.	2020/11/5	India	General populations	PLoS One	16	2347	NA	NA
Alimohamadiÿ et al.	2020/10/6	Iran	General populations	J Prev Med Hyg	54	NA	NA	NA
Cagnazzo et al.	2020/10/30	France	General populations	J Neurol	39	68,361	Mean age 64.4	49%
Yee et al.	2020/10/22	Republic of Korea	General populations	Sci Rep	11	9370	NA	NA
Favas et al.	2020/12/1	India	General populations	Neurol Sci	212(74 in meta)	NA	NA	NA
Collantes et al.	2020/7/15	Philippines	General populations	Can J Neurol Sci	49	6335	NA	NA
Ibekwe et al.	2020/9/11	Nigeria	General populations	OTO Open	32	20,451	NA	NA
Amorim et al.	Feb-21	Brazil	General populations	J Dent Res	40	10,228	NA	NA
Panda et al.	2020/9/10	India	Neonates, children and adolescents	J Trop Pediatr	26	3707	Range: 0–18 years	NA
Allotey et al.	2020/9/1	UK	Pregnant women	BMJ	77	96,604	NA	100%
Ochoa et al.	2021/1/4	Colombia	General populations	Am J Epidemiol	97	230,398	40 (11) years	69.98%
Hasani et al.	2020/8/14	Iran	General populations	Biomed Res Int	30	3420	NA	NA
Khalil et al.	2020/8/25	UK	pregnant women	EClinicalMedicine	86	NA	NA	100%
Kaur et al.	2020/7/9	India	General populations	SN Compr Clin Med	50	6635	NA	NA
Jutzeler et al.	2020/7/27	Switzerland	General populations	Travel Med Infect Dis	148	12,149	Median age: 47 years	47.20%
Kumar et al.	Jun-20	India	General populations	Indian J Gastroenterol	62	8301	48.7(16.5)	46%
Gao et al.	2020/8/3	China	Pregnant women	BMC Infect Dis	14	236	NA	NA
Chen et al.	Feb-21	China	General populations	J Neurol	100	NA	NA	NA
Pormohammad et al.	Oct-20	Canada	General populations	Microb Pathog	80	61,742	NA	NA
Zarifian et al.	Jan-21	Iran	General populations	J Med Virol	67	13,251	NA	53.30%
Abdullahi et al.	2020/6/26	Nigeria	General populations	Front Neurol	60	11,069	NA	NA

(Continues)

TABLE 1 (Continued)

Research ID	Published/ online date	Country/ region of First Author	Patients	Journal title abbreviations	Number of included primary studies	Number of participants	Age of participants (in years; range or mean)	Female
Koh et al.	2020/6/11	Singapore	General populations	Front Med	29	578	NA	NA
Meena et al.	2020/9/15	India	Neonates, children and adolescents	Indian Pediatrics	27	4857	6.4 (3.4) years	43%
Tahvildari et al.	2020/5/15	Iran	General populations	Front Med	80	417	Mean: 49 years	NA
Grant et al.	2020/6/23	UK	General populations	Plos One	148	24,410	49 (11) years	45.50%
Wang et al.	2020/5/1	China	Neonates, children and adolescents	Ann Transl Med	49	1667	NA	42.70%
Ma et al.	2021/1/1	China	Neonates, children and adolescents	J Med Virol	15	486	NA	40.70%
Parasa et al.	2020/6/1	USA	General populations	JAMA Netw Open	29	4805	Mean 52.2 years	33.20%
Wan et al.	2020/7/1	China	General populations	Acad Radiol	14	1115	NA	NA
Park et al.	2020/5/1	Republic of Korea	General populations	Clin Exp Otorhinolaryngol	9	627	NA	45.00%
Sultan et al.	2020/7/1	USA	General populations	Gastroenterology	57	NA	NA	NA
Mao et al.	2020/7/1	China	General populations	Lancet Gastroenterol Hepatol	35	6686	NA	NA
Hu et al.	2020/6/1	China	General populations	J Clin Virol	21	47,344	NA	48.40%
Chang et al.	2020/5/1	Taiwan, China	Neonates, children and adolescents	J Formos Med Assoc	9	93	NA	48.40%
Zhu et al.	2020/10/1	China	General populations	J Med Virol	38	3062	NA	43.10%
Fu et al.	2020/6/1	China	General populations	J Infect	43	3600	Median: 41 years	43.50%
Cheung et al.	2020/7/1	HongKong, China	General populations	Gastroenterology	69	4875	Median: 45.1 years	42.70%
Cao et al.	2020/9/1	China	General populations	J Med Virol	31	46,959	Median: 46.62 years	44.40%
Morales et al.	2020/3/11	Colombia	General populations	Travel Med Infect Dis	58	NA	NA	NA
Li et al.	2020/6/1	China	General populations	J Med Virol	10	1994	NA	42.40%
Sun et al.	2020/6/1	China	General populations	J Med Virol	10	50,466	NA	48.00%
Daha et al.	2020/6/1	Nepal	General populations	Trop Biomed	40	2735	NA	45.20%
Elshazli et al.	2021/2/2	Egypt	General populations	J Med Virol	125	25,252	Mean 52.1 years	47.80%
Mansourian et al.	2021/1/9	Iran	Neonates, children and adolescents	Arch Pediatr	32	759	NA	47.40%
Badal et al.	2020/12/8	USA	Neonates, children and adolescents	J Clin Virol	20	1810	Median age 8	42.74%
Chi et al.	2021/2/1	China	General populations	Arch Gynecol Obstet	20	386	NA	NA
Sameni et al.	2020/10/29	Iran	General populations	Front Med	43	2621	NA	NA

(Continues)

TABLE 1 (Continued)

Research ID	Published/ online date	Country/ region of First Author	Patients	Journal title abbreviations	Number of included primary studies	Number of participants	Age of participants (in years; range or mean)	Female
Wong et al.	2020/11/13	Hong Kong, China	General populations	Sci Rep	76	11,028	NA	NA
Han et al.	2020/11/26	China	Pregnant women	J Perinat Med	36	1103	NA	100%
Sheleme et al.	2020/9/10	Ethiopia	General populations	Infect Dis (Auckl)	30	4829	Range: 0.25–94 years	47.40%
Bennett et al.	2020/9/23	UK	General populations	Int J Clin Pract	45	14,358	Average age 51 years	49%
Nasiri et al.	2020/7/21	Iran	General populations	Front Med	34	5057	NA	NA
Li et al.	Mar-21	China	General populations	J Med Virol	212	281,461	NA	NA
Yasuhara et al.	Oct-20	USA	Neonates, children and adolescents	Pediatr Pulmonol	46	114	Range: 0–16 years	NA
Ding et al.	2020/7/3	China	Neonates, children and adolescents	Front Pediatr	33	396	Range: 0–17 years	56.30%
Nepal et al.	2020/7/13	Nepal	General populations	Crit Care	37	NA	NA	NA
Matar et al.	2021/2/1	USA	Pregnant women	Clin Infect Dis	24	136	Range: 25–34	100%
Pinzon et al.	2020/5/29	Indonesia	General populations	Front Neurol	33	7559	NA	NA
Mantovani et al.	2020/6/17	Italy	Neonates, children and adolescents	Pediatr Res	19	2855	Mean age 6.9 ± 7.0 years	49.70%
Wang et al.	2020/10/1	China	General populations	J Neurol	41	NA	NA	NA
Kim et al.	2020/11/1	Republic of Korea	General populations	Eur Rev Med Pharmacol Sci	16	33	Median age 66	45.50%
Makvandiet al.	2020	Iran	Pregnant women	Gastroenterol Hepatol Bed Bench	43	374	NA	100%
Mesquita et al.	2020/11/26	Brasil	General populations	Wien Klin Wochenschr	152	41,409	NA	NA
Jindal et al.	2020/9/30	India	General populations	J Family Med Prim Care	44	458	NA	NA
Mirza et al.	2020/11/3	USA	Neonates, children and adolescents	Int J Dermatol	86	2560	NA	NA
Ibrahim et al.	2020/10/21	Egypt	General populations	CNS spectr	20	NA	NA	NA
Turan et al.	Oct-20	UK	Pregnant women	Int J Gynaecol Obstet	63	637	NA	100%
Zhao et al.	Nov-20	China	General populations	J Eur Acad Dermatol Venereol	44	507	NA	NA
Matar et al.	Nov-20	France	General populations	J Eur Acad Dermatol Venereol	56	1020	NA	NA
Tsai et al.	2020/5/19	Taiwan, China	General populations	Front Neurol	92	NA	NA	NA
Souza et al.	2020/8/1	Brazil	Neonates, children and adolescents	Pediatr Pulmonol	38	1124	NA	42.60%

(Continues)

TABLE 1 (Continued)

Research ID	Published/ online date	Country/ region of First Author	Patients	Journal title abbreviations	Number of included primary studies	Number of participants	Age of participants (in years; range or mean)	Female
Passarelli et al.	2020/6/1	Italy	General populations	Am J Dent	5	10,818	NA	NA
Kasraeian et al.	2020/5/19	Iran	Pregnant women	J Matern Fetal Neonatal Med	9	87	Median age: 30 years	100%
Yang et al.	2020/4/30	China	Pregnant women	J Matern Fetal Neonatal Med	18	114	NA	100%
Yang et al.	2020/5/1	China	General populations	Int J Infect Dis	7	1576	Median: 49.6 years	43.50%

References of Table 1 are listed in Supplementary Material 3.
NA, not available.

of prospective registration, failure to report on conflict of interests, and nonrepeatable data extraction and screening processes, etc.

3.3 | Respiratory symptoms

Seventeen different respiratory symptoms were reported in 71 systematic reviews and meta-analyses. Cough was reported in 40 systematic reviews in the general populations, 13 in neonates, children, and adolescents, and 15 in pregnant women; sore throat was reported in 29 systematic reviews in the general populations, 8 in neonates, children, and adolescents, and 10 in pregnant women; dyspnea was reported in 49 systematic reviews, of which, 9 related to neonates, children, and adolescents, 11 related to pregnant women, and the others were in the general populations. The remaining 14 symptoms are detailed in Figure 2A and Supplementary Material 5.

The most common symptoms of the respiratory system were cough (PPE = 53.6%, 95%CI, 52.1%–55.1%), sore throat (PPE = 12.4%, 95%CI, 9.8%–15.7%), dyspnea (PPE = 19.8%, 95%CI, 18.2%–21.6%), and expectoration (PPE = 23.4%, 95%CI, 21.6%–25.3%) (Figure 2A). Prevalence of cough was inconsistent across systematic reviews, ranging between 30.0% and 72.2%. The corresponding prevalence estimate for sore throat was 0.8%–32.0%, for dyspnea 1.0%–74.0% and for expectoration 1.5%–41.8%. The prevalence estimates for cough, sore throat, dyspnea and expectoration were lower in neonates, children and adolescents and pregnant women than in the general populations (Table 2, Supplementary Material 5 and 6).

3.4 | Neurological symptoms

Eighty-eight systematic reviews and meta-analyses covered a total of 21 different neurological symptoms: fever (67 studies), headache (58 studies), muscle soreness (56 studies), fatigue (52 studies), dizziness (28 studies), ageusia (23 studies), anosmia (20 studies), chillness (14 studies), confusion (10 studies), malaise (10 studies), arthralgia (8 studies), delirium (3 studies), rigor (3 studies), hypothermia (3 studies), dysacousis (1 study), back pain (1 study), drowsiness (1 study), numbness (1 study), otalgia (1 study), insomnia (1 study), and syncope (1 study) (Supplementary Material 5).

Fever (PPE = 64.6%, 95%CI, 9.8%–15.7%), fatigue (PPE = 29.4%, 95%CI, 27.5%–31.3%), headache (PPE = 11.1%, 95%CI, 9.0%–13.8%), and muscle soreness (PPE = 18.7%, 95%CI, 16.3%–21.3%) were the most common (Figure 2B). Prevalence of fever was above 80% in most studies, reaching up to 91.3%; the lowest reported value, 27.6%, was in a study on pregnant women. The prevalence of fatigue ranged between 3.3% and 58.5%, headache ranged between 0.1% and 67.0%, and the prevalence of muscle soreness between 3.0% and 44.0%; the lowest reported prevalence for both conditions was among pregnant women and neonates, children and adolescents. The prevalence of the remaining symptoms is detailed in Table 2 and Supplementary Material 5 and 6.

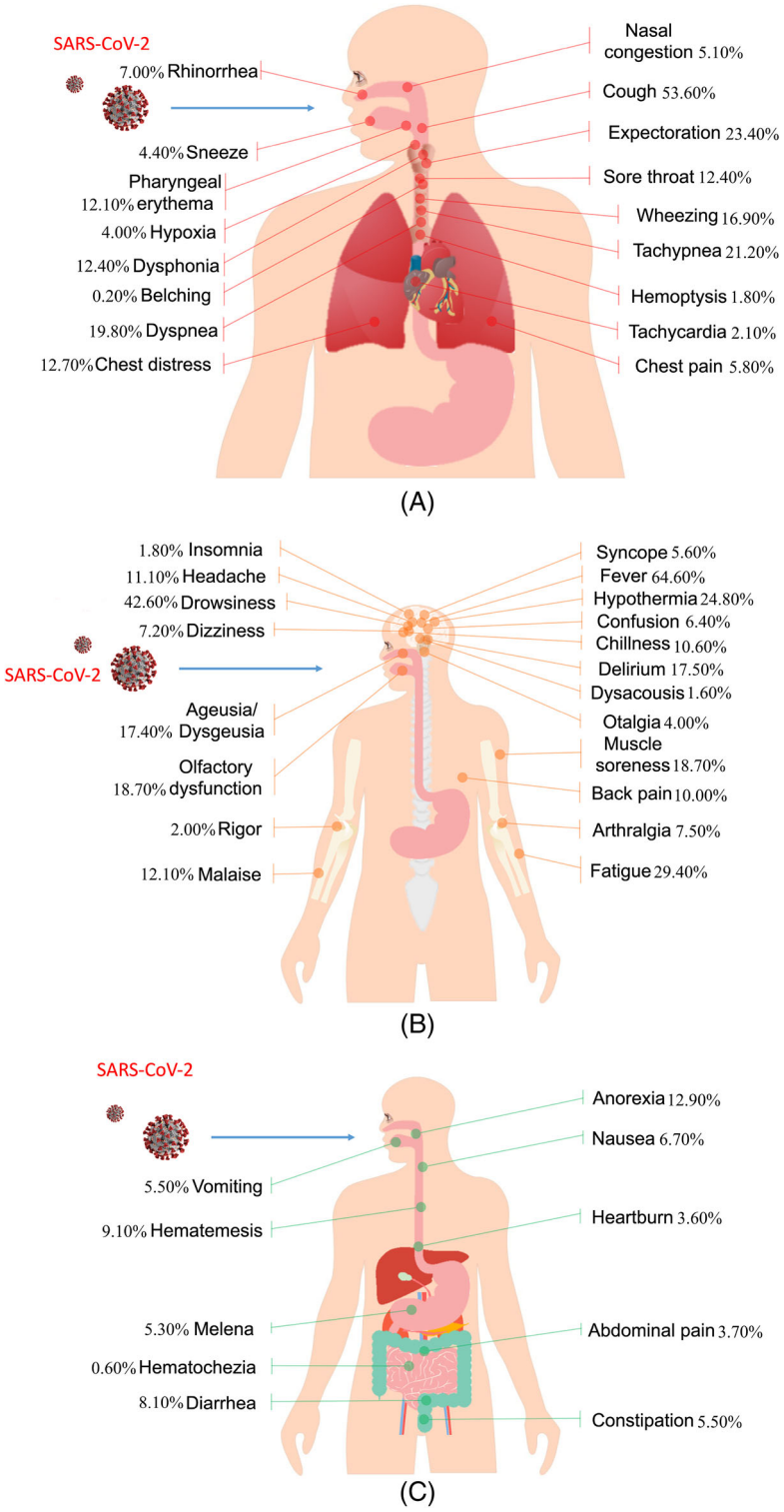

FIGURE 2 Human anatomy diagram of COVID-19 manifestations. (A) Respiratory symptoms; (B) neurological symptoms; and (C) gastrointestinal symptoms

3.5 | Gastrointestinal symptoms

A total of 10 gastrointestinal symptoms were reported in 67 systematic reviews and meta-analyses. Diarrhea was reported in 63 systematic reviews and meta-analyses (PPE = 8.1%, 95%CI, 7.3%–9.1%), vomiting in 42, nausea in 37, anorexia in 21, abdominal pain in 26, constipation in 3 studies, and 1 each in heartburn, hematemesis, melena, and hematochezia. The prevalence of diarrhea ranged between 0.1% and 19.6% (Figure 2C). Nausea (1.2%–27.0%) and vomiting (1.2%–20.0%) occurred often together. The prevalence of gastrointestinal symptoms is generally less than 20% and does not differ from the general population in neonates, children and adolescents, or pregnant women (Table 2

TABLE 2 Meta-analyses of symptoms of COVID-19

No.	Symptoms	Number of SRs	Pooled prevalence	LCI	UCI	*p* Value
1	Cough	68	53.60%	52.10%	55.10%	0.000
2	Fever	68	64.60%	61.30%	67.90%	0.000
3	Diarrhea	63	8.10%	7.30%	9.10%	0.000
4	Headache	58	11.10%	9.00%	13.80%	0.000
5	Muscle soreness	56	18.70%	16.30%	21.30%	0.000
6	Fatigue	52	29.40%	27.50%	31.30%	0.000
7	Dyspnea	50	19.80%	18.20%	21.60%	0.000
8	Sore throat	47	12.40%	9.80%	15.70%	0.000
9	Vomiting	42	5.50%	4.70%	6.30%	0.000
10	Nausea	37	6.70%	6.00%	7.40%	0.000
11	Expectoration	32	23.40%	21.60%	25.30%	0.000
12	Dizziness	28	7.20%	5.30%	9.70%	0.000
13	Tachypnea	26	21.20%	19.80%	22.60%	0.000
14	Abdominal pain	26	3.70%	2.80%	4.80%	0.000
15	Rhinorrhea	24	7.00%	6.10%	8.00%	0.000
16	Ageusia	23	17.40%	12.50%	23.80%	0.000
17	Anorexia	21	12.90%	10.00%	16.60%	0.000
18	Anosmia	20	18.70%	12.20%	27.40%	0.000
19	Nasal congestion	19	5.10%	3.90%	6.80%	0.000
20	Hemoptysis	18	1.80%	1.20%	2.80%	0.000
21	Chest pain	17	5.80%	4.60%	7.40%	0.000
22	Chest distress	14	12.70%	8.90%	17.90%	0.000
23	Chillness	14	10.60%	8.00%	13.90%	0.000
24	Malaise	10	12.10%	7.00%	19.90%	0.000
25	Confusion	10	6.40%	4.10%	9.90%	0.000
26	Arthralgia	8	7.50%	5.20%	10.80%	0.000
27	Rash	8	14.00%	6.80%	26.60%	0.000
28	Tachycardia	6	2.10%	1.70%	2.70%	0.000
29	Chilblains-like	5	24.60%	12.20%	43.30%	0.010
30	Livedo	5	4.60%	3.30%	6.50%	0.000
31	Conjunctivitis	5	5.50%	2.90%	10.20%	0.000
32	Pharyngeal erythema	4	12.10%	8.00%	17.80%	0.000
33	Hypoxia	4	4.00%	0.40%	29.50%	0.007
34	Urticaria	4	16.80%	14.30%	19.70%	0.000
35	Sneeze	3	4.40%	0.50%	29.60%	0.006
36	Rigor	3	2.00%	0.10%	37.80%	0.025
37	Hypothermia	3	24.80%	8.70%	53.20%	0.079
38	Delirium	3	17.50%	15.20%	20.10%	0.000
39	Constipation	3	5.50%	5.20%	5.80%	0.000
40	Papulosquamous	3	5.80%	1.70%	18.20%	0.000
41	Erythematous	3	33.90%	21.20%	49.40%	0.043
42	Pruritic	3	41.30%	17.20%	70.30%	0.569
43	Cyanosis	3	2.00%	0.30%	11.30%	0.000
44	Conjunctival congestion	3	3.80%	0.90%	13.90%	0.000

(Continues)

TABLE 2 (Continued)

No.	Symptoms	Number of SRs	Pooled prevalence	LCI	UCI	*p* Value
45	Eye pain	3	6.90%	1.90%	22.60%	0.000
46	Blurred vision	3	1.20%	0.00%	26.50%	0.011
47	Wheezing	2	16.90%	15.40%	18.60%	0.000
48	Chickenpox-like Vesicles	2	16.20%	13.50%	19.40%	0.000
49	Petechia	2	3.50%	0.90%	12.50%	0.000
50	Edematous	2	6.90%	3.70%	12.30%	0.000
51	Vesicular	2	11.80%	7.80%	17.40%	0.000
52	Dry eyes	2	14.50%	12.20%	17.20%	0.000
53	Eye itching	2	9.20%	4.80%	16.80%	0.000
54	Photophobia	2	4.80%	2.00%	11.00%	0.000
55	Chemosis	2	4.50%	3.90%	5.30%	0.000
56	Lid edema	2	1.60%	0.60%	4.20%	0.000
57	Dysphonia	1	12.40%	8.30%	18.10%	0.000
58	Belching	1	0.20%	0.10%	0.40%	0.000
59	Dysacousis	1	1.60%	0.00%	97.60%	0.301
60	Drowsiness	1	42.60%	32.70%	53.20%	0.169
61	Numbness	1	5.80%	0.20%	65.40%	0.110
62	Insomnia	1	1.80%	0.20%	12.00%	0.000
63	Syncope	1	5.60%	4.30%	7.20%	0.000
64	Back pain	1	10.00%	9.50%	10.60%	0.000
65	Otalgia	1	4.00%	1.20%	12.30%	0.000
66	Heartburn	1	3.60%	3.40%	3.80%	0.000
67	Hematemesis	1	9.10%	8.80%	9.50%	0.000
68	Melena	1	5.30%	5.00%	5.60%	0.000
69	Hematochezia	1	0.60%	0.50%	0.70%	0.000
70	Goosebumps	1	13.50%	11.70%	15.50%	0.000
71	Pustule	1	1.80%	0.20%	12.00%	0.000
72	Scales	1	7.40%	2.80%	18.10%	0.000
73	Ulcer	1	1.80%	0.20%	12.00%	0.000
74	Tearing	1	12.80%	10.80%	15.10%	0.000

SR, systematic review; LCI, lower 95% confidence intervals; UCI, upper 95% confidence intervals.

and Supplementary Material 5 and 6).

3.6 | Cutaneous and ocular symptoms

Thirteen systematic reviews and meta-analyses reported 16 cutaneous symptoms (Supplementary Material 5). Rash was the most common symptom reported in nine studies, and the prevalence of cutaneous symptoms according to those reviews was generally less than 20% (Figure 3B). The symptoms of the eyes were as low in incidence as those of the cutaneous. A total of 10 ocular symptoms were reported in 8 systematic reviews and meta-analyses (Figure 3A). The ocular symptoms were relatively rare in neonates, children and adolescents, and pregnant women, and the overall prevalence was low, between 5% and 20% (Table 2 and Supplementary Material 5).

4 | DISCUSSION

4.1 | Principal findings

Our study identified 74 different clinical manifestations of COVID-19 in 102 systematic reviews and meta-analyses. The most common respiratory symptoms were cough, sore throat, dyspnea, and expectoration, and the most common symptoms of neurological symptoms were fever, fatigue, headache, and muscle soreness. The gastrointestinal system

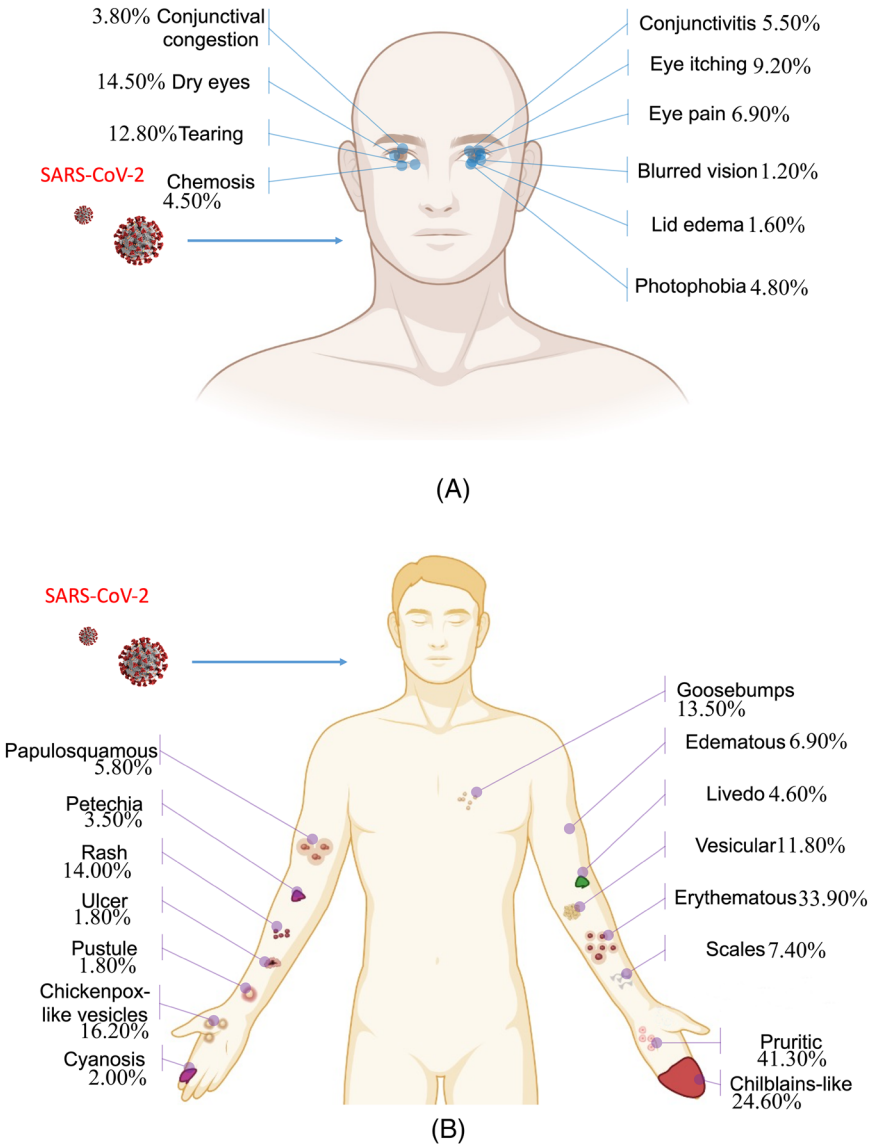

FIGURE 3 Human anatomy diagram of COVID-19 manifestations. (A) Ocular symptoms and (B) cutaneous symptoms

included diarrhea, nausea, and vomiting, and we also identified some other symptoms such as manifestations of the eyes or skin. The prevalence of the same condition tended to vary broadly across the different systematic reviews and population groups, and lower prevalence of symptoms in pregnant women and neonates, children and adolescents than in the general population.

Clinical symptoms are important for the diagnosis of a disease. There is no doubt that fever, cough, and fatigue are the three most prevalent symptoms of COVID-19 patients. Many studies have estimated the prevalence of different symptoms of SARS-CoV-2 infection. Like in the case of SARS-CoV and MERS-CoV, cough and fever are the most common symptoms, which can be caused also by many other causes, such as common flu.[20,21] An accurate diagnosis of COVID-19 therefore often requires a combination of clinical symptoms, laboratory tests and CT findings. Attention in the diagnosis should also be paid to the differentiation of clinical manifestations associated with comorbidities, such as hypertension, diabetes, and coronary heart disease.

The clinical symptoms of COVID-19 vary across population groups. One systematic review[22] suggested that children appear to have a less severe course and better prognosis than adults, and deaths in children are extremely rare. In addition, the multisystem inflammatory syndrome in children (MIS-C) should be given more attention when diagnosing children with COVID-19, in addition to symptoms similar to those of adults.[23] Studies have shown that pregnant women's symptoms are essentially the same as in the general population, but the prevalence was lower.[24,25] At the same time, gastrointestinal symptoms, eye symptoms and skin symptoms are relatively less common in pregnant women.[26]

The diagnosis of SARS-CoV-2 infection in asymptomatic patients requires special attention. Many asymptomatic patients have been reported worldwide. Nishiura et al.[27] estimated the proportion of asymptomatic patients was 30.8% (95% CI, 7.7%–53.8%). Hu et al. found that the course of illness was milder in asymptomatic cases than in other cases.[28] However, the asymptomatic carriers may be a challenge to containment for COVID-19 transmission.[29] Asymptomatic

people can transmit SARS-CoV-2 to others for a long time, perhaps more than 14 days.[30] Therefore, it is important to screen asymptomatic SARS-CoV-2 carrier populations, when resources are available, to minimize the chance of infection, although it may raise the treatment cost31.

Our study identified some unusual symptoms, such as skin (livedo, cyanosis, edematous, etc.) and eye manifestations (conjunctivitis, blurred vision, eye pain, etc.). However, because such symptoms were rarely reported during the pre-epidemic period, they can be easily overlooked. Patients with unusual symptoms are not easily screened and diagnosed; therefore, understanding and knowing these unusual symptoms, has important implications for the current improvement in the identification of SARS-CoV-2 infections. Besides, as the epidemic grows and some COVID-19 variant strains emerge, some specific symptoms may appear. However, there is no relevant systematic review yet, and further updating of associated symptoms regarding COVID-19 variant strains is needed in the future.

4.2 | Implications for future research and practice

As the second wave of the outbreak rages on, countries need again to pay attention to finding as many infected patients as early as possible to cut the transmission chains and avoid a new wave of the epidemic. This means that even rare symptoms can be important in the screen and diagnosis. Our study found that many systematic reviews and meta-analyses of different quality are being conducted for the same symptom, which may result in wasting research on COVID-19,[32] and before conducting systematic reviews of symptoms for researchers, we recommend retrieval to determine if a systematic review is already available on the PROSPERO website, and if not, it should be registered.

For patients with COVID-19 in the second wave of the epidemic, our study can provide a full picture of the symptoms map of COVID-19 to inform the screening and diagnosis of patients. Furthermore, in the context of a global COVID-19 epidemic, our study could help clinicians or stakeholders to identify COVID-19 through some rare symptoms.

4.3 | Strengths and limitations

To the best of our knowledge, this is the first evidence map to comprehensively review and summarize the clinical symptoms of COVID-19. We systematically searched the main databases and performed a detailed analysis of the included literature. However, this study also has some limitations. First, because of the substantial overlap between the studies included in the systematic reviews, we have limited confidence in the pooled results of the meta-analyses. Second, although we systematically searched the literature, there is a possibility that some studies were missed due to the constantly increasing number of COVID-19 studies. Third, given that the frequency of COVID-19 symptoms may be varied in different countries or territories due to different sources or genotypes of COVID-19, we did not perform a subgroup analysis of symptoms in different geographical locations. However, this can provide information for tracing the origin of the SARS-CoV-2 virus. To address the above limitations, we believe it is meaningful and necessary to conduct a living systematic review of the symptoms of COVID-19 patients.

4.4 | Conclusion

In conclusion, COVID-19 is associated with at least 74 different clinical manifestations, the most common of which are fever, cough, muscle soreness, and fatigue. In addition, some symptoms, despite being rare, may be useful in the early diagnosis of COVID-19 in patients who otherwise have no or only mild symptoms. Future research should pay particular attention to these rare symptoms to help treat the infected patients and control the epidemic.

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CONFLICT OF INTEREST

There are no relevant financial or nonfinancial competing interests to report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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