REVIEW ARTICLE

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Prevalence of neurological symptoms in patients with SARS-CoV-2: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: The novel coronavirus, dubbed SARS-CoV-2, which causes the COVID-19 disease, was detected on December 31, 2019, in Wuhan, China. **Objective:** To perform a systematic review with a meta-analysis about the prevalence of headache and myalgia in patients with SARS-CoV-2. **Methods:** High-sensitivity research was conducted on the main platforms (Medline by PubMed, Embase (Elsevier), and Cochrane Library). The entire versions of the manuscripts were analyzed by three independent researchers, and only observational studies describing the symptoms of the selected sample were included. **Results:** 1,782 studies were identified, which were submitted to exclusion criteria, remaining only 62 manuscripts to do qualitative synthesis and metanalysis. Of the 28,412 patients diagnosed with SARS-CoV-2, 12% (95% CI 9% - 16%) presented headache and 19% (95% CI 14% - 24%) presented myalgia, both with statistical significance and high heterogeneity (I2=97.0%, p<0.01 and I2=98.0%, p<0.01, respectively). **Conclusion:** It was noticed that headache and myalgia were the most ordinary neurological symptoms, but it is important to emphasize the prevalence of symptoms in different degrees of severity of the patients.

Keywords: Covid-19; neurology; Myalgia; Headache.

INTRODUCTION

In December 2019, a viral epidemic was established in Wuhan, China, and the disease agent was identified as a new coronavirus, named SARS-CoV-2. The virus quickly reached several countries around the world, and the World Health Organization (WHO) declared a pandemic in March 2020[1]. It is documented that the transmission was primarily in the Huanan seafood market, being later transmitted from person to person, symptomatic or asymptomatic, through aerosols[2,3].

Typically, its clinic consists of fever and respiratory symptoms such as dyspnea, cough, and fatigue[1,4]. It has a wide clinical spectrum, from asymptomatic patients to severe cases with respiratory failure[4]. Some populations are more prone to develop severe cases, such as the elderly and people with comorbidities (hypertension, chronic obstructive pulmonary disease, and diabetes)[1].

Other symptoms are attributed to the neuroinvasive capacity of the COVID-19 virus, although this capacity is little known[2]. This virus's ability to reach the individual's nervous system, although documentation is scarce, can generate mild neurological symptoms (anosmia, myalgia, headache, and hyposmia) and other important neurological symptoms (encephalopathy, Guillain-Barre syndrome, confusion, agitation, and cerebrovascular diseases)[1,4]. Of these neurological symptoms, is remarkable the prevalence of headache and myalgia among the patients who developed COVID-19 at different levels of severity[2,5,6].

Therefore, the objective of this study is to show the prevalence of headache and myalgia caused by SARS-CoV-2 by means of a systematic review and meta-analysis.

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METHODS

Search strategy

This study is presented as a systematic review with a meta-analysis of prevalence and is by the recommendations and criteria used in the report items for systematic reviews and meta-analyses (PRISMA) and Cochrane Handbook. The question was: what are the main neurological symptoms in patients with SARS-COV-2?

Data Sources

Potential studies were identified using a comprehensive strategy. Data collection was carried out between January 2020 and December 2021. The systematic review was performed in the databases: PubMed via Medline; EMBASE; Latin American and Caribbean Center on Health Sciences Information (Lilacs); and Cochrane Library (Central). The search strategy involved the crosschecking of keywords selected based on the Medical Subjects Headings (Mesh). There was language restriction for English, Spanish, and Portuguese. The following keywords were used: PubMed via Medline (coronavirus[MeSH Terms]) AND Myalgia; Headache OR coronavirus infections[MeSH Terms]) AND Myalgia; Headache OR "betacoronavirus"[MeSH Terms]) AND Myalgia; Headache OR "betacoronavirus 1"[MeSH Terms]) AND Myalgia; Headache OR (Coronaviruses OR “Coronavirus Infection” OR "COVID-19" OR “Coronavirus Infection Disease 2019” OR “2019 Novel Coronavirus Infection” OR “2019-nCoV Infection” OR “2019 nCoV Infection” OR “2019-nCoV Infections” OR Betacoronavirus* OR “Novel Coronavirus Pneumonia” OR “2019 novel coronavirus" OR “coronavirus disease 2019” OR “nCoV” OR COVID* OR “bat coronavirus”) AND Myalgia; Headache.

Embase (Elsevier) ('coronavirus infection'/exp OR 'coronavirus infection' OR 'betacoronavirus'/exp OR betacoronavirus OR 'coronavirus disease 2019'/exp OR 'coronavirus

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disease 2019') AND [article]/lim AND [humans]/lim AND [clinical study]/lim AND [embase]/lim AND Myalgia; Headache [article].

Latin American and Caribbean Center on Health Sciences Information (Lilacs) MH:("Coronavirus Infection") AND (Myalgia; Headache) OR ("Infecciones por Coronavirus") AND Myalgia; Headache OR ("Infecções por Coronavirus") AND (Myalgia; Headache) OR ("Coronavirus Infection") AND (Myalgia; Headache) OR ("Infection, Coronavirus") AND (Myalgia; Headache) OR ("Infections, Coronavirus") AND (Myalgia; Headache) OR "Coronavirus" AND (Myalgia; Headache) OR "Coronavirus" AND (Myalgia; Headache) OR "Coronavirus" AND (Myalgia; Headache) OR “bat coronavirus” AND (Myalgia; Headache) OR MH:C02.782.600.550.200$ OR MH:B04.820.504.540.150$.

Cochrane Central (MeSH descriptor: [Coronavirus AND Myalgia; Headache] explode all trees OR MeSH descriptor: [Betacoronavirus AND Myalgia; Headache] explode all trees OR MeSH descriptor: [Coronavirus Infections AND Myalgia; Headache] explode all trees OR Coronavirus* OR betacoronavirus* OR nCoV* OR novel coronavirus* OR novel coronavirus OR COVID* OR “bat coronavirus” AND Myalgia; Headache)After the selection of potentially relevant studies, the full-text versions were analyzed for methodological quality by two researchers independently and disagreement between reviewers was resolved by discussion or arbitration by the other researcher.

Types of studies and participants

The criteria adopted for the selection of the studies were: Cross-sectional studies; neurologic conditions to SARS COV outbreak. Editorials, letters to the editor, viewpoints, case presentations, or brief communication were excluded as they did not contain SARS-CoV-2 with other types of viruses, studies with demographic data only, did not perform symptom analysis, and incomplete manuscripts.

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Data extraction

The extensive material obtained by the search was exported to a Mendeley® paste and exposed in the PRISMA diagram (Figure 1). The first two screenings (selection by title and abstract) were conducted by three independent researchers (JR, NL, and CR), who performed a selection of potential manuscripts to be included in the systematic review. Regarding data extraction, the three independent researchers (JR, NL, and CR) used a Microsoft Excel® extraction file, to catalog: study data (authors, journal name, year of publication, country, and study setting), methodological information (study objective, design, total sample size, neurological symptoms, mean age, sex).

Quality Assessment

It was used the Newcastle–Ottawa scale to assess the quality of the included studies. Relevant organizational websites including the Joanna Briggs Institute publish a Reviewers' Manual, which is designed to support individuals who are performing systematic reviews following JBI methodologies and methods[7]. This checklist contains 9 questions, divided into 3 domains: participants (questions 1, 2, 4 and 9), outcome measurement (6 and 7), and statistics (3, 5 and 8). A study was rated with high quality when the methods were appropriate in all 3 domains. Quality assessment was also performed by 2 independent reviewers, and any uncertainties were resolved by consulting a third reviewer.

Data analysis

For the prevalence estimates of the included observational studies, a random-effects meta-analysis model was used with the Variance Estimator DerSimonian and Laird, assuming

that the effect of interest is the same in all studies and the differences observed between them are due only to sampling errors (variability within the studies). The Freeman-Tukey double sarcosine transformation was used to stabilize the variances[8]. The heterogeneity of the estimates of the sample size effect throughout these studies was quantified by the I2 statistic. The heterogeneity between the studies was assessed by Cochran's Q test and I2 statistics. The estimates of the headache and myalgia were presented in Forest Plot with 95% confidence intervals (95% CI) or Scatter Plots with point estimates and 95% CI. All analyses were performed using R statistical software version 4.0 (R Core Team, 2020), with meta package[9] version 4.11-0 z.

RESULTS

Selection and evaluation of studies

The initial search identified 1,846 studies with neurological symptoms related to the COVID-19 outbreak. Sixty-two duplicate studies were removed which resulted in a total of 1,784 studies. After title and abstract analysis, 1,687 ineligible studies were excluded based on inclusion criteria (Figure 1).

Included studies.

This systematic included a total of 62 studies[10-65] (Table 1). Among the included studies, 50 were from China, 4 from Italy, 3 from the USA, 1 from France, 1 from Germany, 1 from South Korea, 1 from Japan, and 1 from the UK. The total population corresponded to 25,117 participants, with 7,027 healthcare workers, 16,203 general population, and 1,887 patients with SARS-CoV-2. Most of the respondents had >18 years and approximately 7,789 were male (some studies were unclear).

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Prevalence of headache and myalgia

The Forest Plot in Figure 2 shows that the prevalence of headache was 12% (95% CI 9% - 16%) of the 28,412 patients diagnosed with SARS-CoV-2, with statistical significance and high heterogeneity (I2=97.0 %, p=0). The lowest prevalence of headaches was found in the study of Shi et al.[1], at 4%, and the highest in the study of Lechien et al.[2] at 70%.

Figure 3 shows the prevalence of myalgia in 19% (95% CI 14% - 24%) of the 28,256 individuals with SARS-VoC-2 investigated, with statistical significance and high heterogeneity (I2=98.0%, p<0.01). The study of Yang et al.[3], had the lowest prevalence of 2% and Yang et al.[5], had the highest prevalence (86%) of myalgia.

The methodological quality of the selected studies

The Newcastle-Ottawa Scale is graduated by a system with stars graduation that goes from 0 to 9 delimited into three domains: selection, comparability, and outcome. The analysis indicated the presence of 7 studies with a high score in this review; such studies demonstrated a defined methodology and high evidence. Considering a maximum score of 10 points, the selected manuscripts varied from 2 to 10 points on the Newcastle-Ottawa Scale (Table 2). Higher scores represent better quality.

The risk assessment of bias using "The Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies" was described in Table 3. It was observed that all studies measured the outcomes validly and reliably and described the study subjects in detail.

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DISCUSSION

The main findings of the study reveal the occurrence of neurological symptoms due to Coronavirus infection. In this systematic review with meta-analysis, it was found that 62 studies identified headache and myalgia as the most recurrent neurological manifestations.

Several exposure factors can interfere with the frequency and duration of such symptoms, some factors such as age, gender, and regular physical exercise can influence these characteristics. Patients who have comorbidities, such as diabetes mellitus, systemic arterial hypertension, and chronic obstructive pulmonary disease, are more susceptible to the appearance of symptoms such as headache and neuromuscular complications such as muscle atrophy, muscle pain, and muscle fatigue[66,67].

Although the analyzed studies show a great heterogeneity, because they involve sample sizes and populations with distinct socio-demographic characteristics, in general, the investigations that included health professionals in China and Europe, and the elderly, presented a higher frequency of myalgia and headache[2,4]. The symptoms disappeared in most of the participants within two weeks after the onset of the disease[4]. Furthermore, was observed the high number of health professionals infected, and a higher frequency of studies originating from China because of the pandemic beginning in this location.

In a European multicenter study, the prevalence of headache and myalgia varied significantly according to age and gender in the evaluation of mild to moderate cases, in which female participants showed a higher frequency of symptoms[2]. In the present review, the generalization of the data was difficult, considering the different investigated populations, sometimes including young patients with less comorbidity, and the exclusion of severe cases due to the impossibility of reporting the investigated symptoms, in some studies.

Such symptoms were listed and considered in the creation and assessment of an early warning model based on risk factors to infer disease severity. There were significant differences

in the analysis between mild and severe subgroups when in the presence of comorbidities such as diabetes, cardiovascular diseases, and Chronic Obstructive Pulmonary Disease, with myalgia being the most reported.

This systematic review with meta-analysis shows the simultaneous occurrence of headache and myalgia in 35 studies, 9 investigations with only headache, and 17 with only myalgia. In this regard, it was possible to observe the presence of neurological symptoms of the central nervous system (headache) and skeletal muscle symptoms (myalgia), in most of the studies that had the broader objective of describing the clinical characteristics of patients with COVID-19, according to the classification of mild and moderate.

In studies that included hospitalized patients with the classification of moderate, severe, or critically ill in China, according to the Guidance for Corona Virus Disease 2019 (6th edition) released by the National Health Commission of China, it was observed in the evaluation between recovered and deceased patients, which those who died, the myalgia was one of the least common symptoms, and the incidence of this symptom did not differ significantly among the groups. However, those classified as severe were among the deceased, and the moderate to mild patients were among the recovered[21].

Prospective studies, which monitored hospitalized individuals, revealed that myalgia was among the most common symptoms reported, and in some cases with also headache[48,51]. However, it is worth pointing out the presence of limitations resulting from selection bias due to the inclusion of only patients registered in the monitoring programs.

The clinical presentation of COVID-19 has variations in its stages, and the difficulty in finding predictors of disease severity is a constant. However, the elderly and patients with comorbidities can have a greater risk of developing the disease in severe form[52]. The presence of the symptoms investigated in this review is among the initial ones, mainly myalgia[12,22].

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Headache, anosmia, ageusia, and myalgia are among the most limiting symptoms resulting from COVID-19, most found in the acute phase, but which can persist during long COVID[68]. In general, headaches are bilateral and occur due to reduced cerebral tissue perfusion, the inflammatory process, and hypoxemia[69]. Another factor that can exacerbate the occurrence of this symptom is the intense inflammatory process that occurs due to the activation of P2X7 receptors, which are related to the worsening of brain diseases in general, such as Parkinson's, Alzheimer's, and depression[70]. Therefore, it is believed that inhibitors of this activation of P2X7 receptors are one of the possibilities to minimize the occurrence of neurological symptoms resulting from COVID-19.

One of the limitations in this review is the concentration of studies from China, and the shortage of research from other locations in the world, due to the periodical effect of the pandemic advancement to the other locations and is also reflected in the manuscript's origin. One of the limiting points is the great variability of studies, including different populations in the sample, with different ages, with or without comorbidities, and severe, moderate, and mild complications. The fact is that at the beginning of the COVID-19 pandemic, there was a great variability of studies, and this systematic review chose to select comprehensive studies and demonstrate a general overview of how these symptoms appeared.

The selected studies did not directly evaluate the prevalence and associations between neurological symptoms and COVID-19. However, the systematic review with meta-analysis of these findings was able to estimate the prevalence of symptoms in different localities and populations worldwide. It has relevance in raising interest in the investigation of these symptoms in the various stages of the infection by the new coronavirus.

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Conclusion

The results of this systematic review with meta-analysis demonstrate the existence of neurological manifestations among the individuals affected by the new coronavirus, the presence of headache and myalgia in different severity stages, and the diversity of the populations investigated. Therefore, it is suggested to deepen the findings in novel studies with the theme and to investigate the symptoms associated with the severity of the cases, as well as the stage after the disease.

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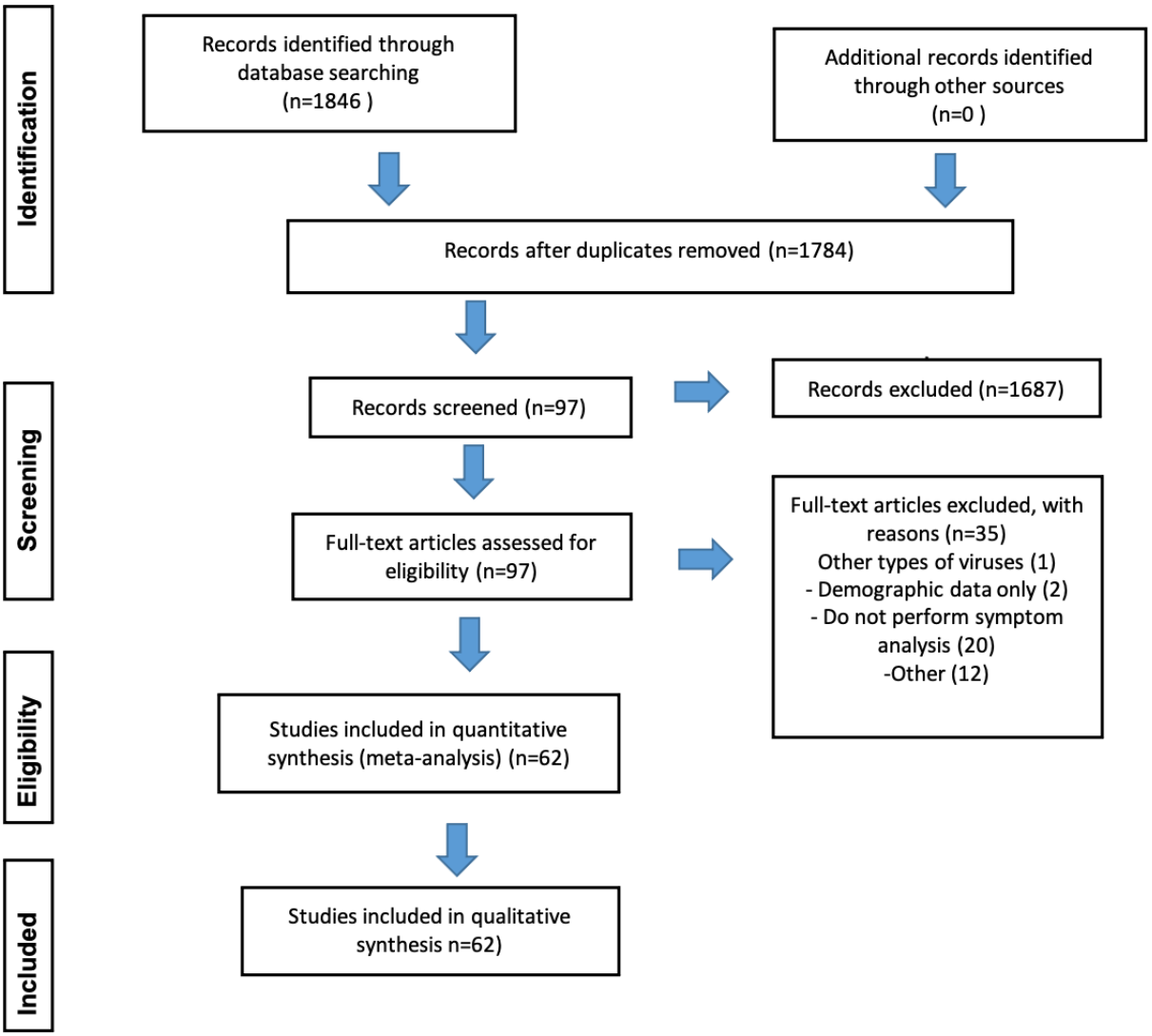
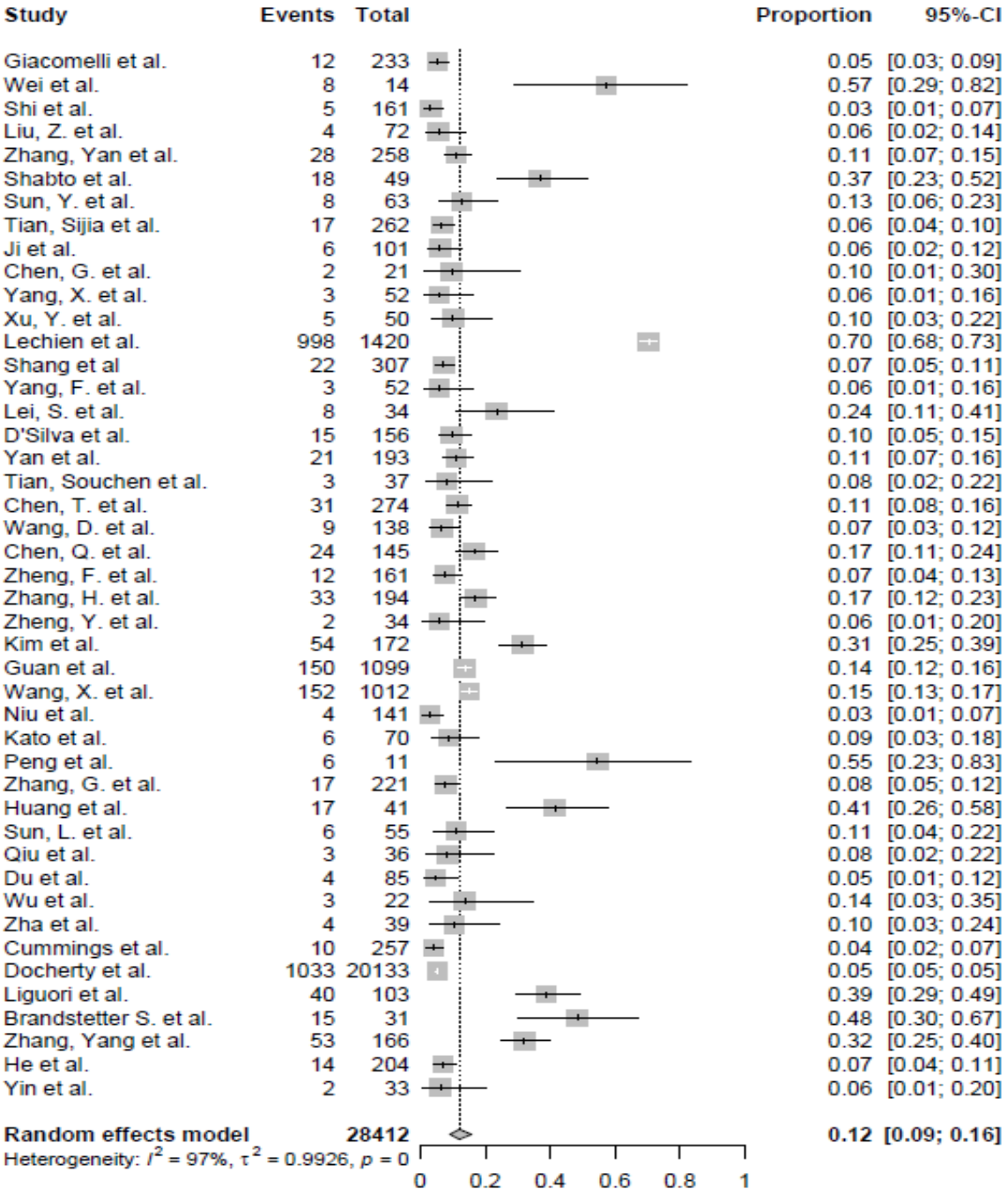
Figure 1: Study Flow Diagram - PRISMA 2009 Flow Diagram



https://doi.org/10.7322/abcshs.2023040.2299

Figure 2: Headache prevalence in the manuscripts that investigated the population with COVID-19.



https://doi.org/10.7322/abcshs.2023040.2299

Figure 3: Myalgia prevalence in the manuscripts that investigated the population with COVID-19.

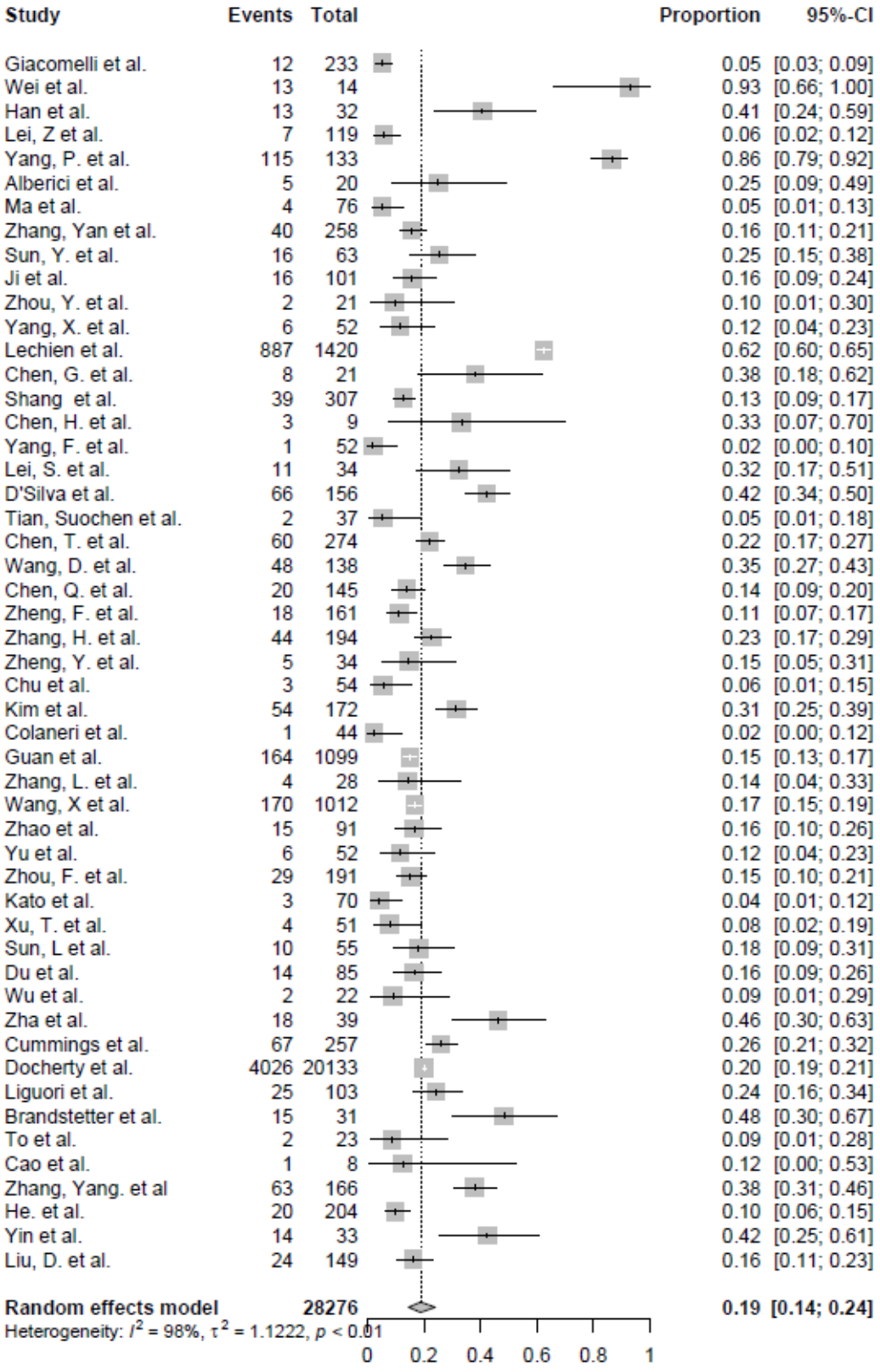


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Table 1: Study characteristics of studies included with country, age, sample, myalgia, and headache number of cases.

Authors	Country	Age	Sample Characteristics	Myalgia (n)	Headache (n)
Giacomelli et al.[10]	Italy	18-95	161 men (122 Sv-39 Mr) 72 women (63 Sv-9 Mr), 17 deaths	12	12
Wei et al.[4]	China	36±6	Health care workers	14	8
Han et al.[11]	China	0.2-70	Children (7) Adult (25)	13	n
Lei et al.[12]	China	21-82	Men (77) and Women (42); Admission to ICU (1)	18	n
Yang et al.[5]	China	41.22±17.549 vs 59.97±14.126	72 men (33 mild symptoms, 40 severe); 61 women (33 mild symptoms- 28 severe); Mild symptoms-smoking (58 men-7 women); severe symptoms (61 men-7 women)	115	124
Ma et al.[13]	China	<16	4 asymptomatic, 10 very mild, 108 mild, 4 severe	4	n
Shi et al.[1]	China	59.38± 16.54	104 (64.60%) males and 57 (35.40%) females	n	5
Liu et al.[14]	China	46.2 ± 15.9	39 men-33 women; No complication (3), mild (61), severe (8)	n	4
Zhang et al.[15]	China	56-70	138 men (38 with diabetes mellitus -100 without diabetes mellitus); 120 women (25 with diabetes mellitus; 95 without diabetes mellitus	40	28
Shabto et al.[16]	USA	30-94	Men (13)- Women (36)	n	18
Sun et al.[17]	China	47	8 patients had mild disease, 36 had moderate disease (57.1%), 10 were severe (15.9%), 9 were critically ill (14.3%)	16	8
Tian et al.[18]	China	47.5	Severe disease- 46, Common and mild- 216// 127 men and 135 women	n	17
Ji et.al.[19]	China	37–61	53 women, and 48 men//5 smokers	16	6
Zhou et al.[20]	China	66.10±;13.94	13 men, 8 women//8 (38.1%) severe and 13 (61.9%) critical; Never smoked (15) Smoker (6)	2	n
Lechien et.al.[2]	France	39.17± 12.09	Mild to moderate patients/ 436 health professionals	887	998
Chen et al.[21]	China	50.0–65.0	Moderate: 10; Severe: 11	8	2
Shang et al.[22]	China	46 ± 33.55	Patients with pneumonia by covid-19	39	22
Chen et al.[23]	China	26-40	Pregnant in the 3rd trimester, underwent cesarean, epidemiologically exposed to COVID-19	3	n
Yang et al.[9]	China	34-98	Cancer patients	1	3
Lei et al.[24]	China	43-63	COVID-19 Patients	11	8
D'Silva et al.[25]	USA	62.5	Patients with rheumatic disease: 52; Without rheumatic disease: 104	66	15
Yan et al.[26]	China	49-73	Patients with severe COVID-19	n	21
Tian et al.[27]	China	44.3± 1.67	37 patients (5 -mild, 30- moderate, 1 severe, 1 critically ill)	2	3
Chen et al.[6]	China	44-70	Patients	60	31
Wang et al.[28]	China	42-68	Hospitalized patients (40 health professionals)	48	9
Chen et al.[29]	China	47 ± 14.6	Severe patients: 43; no severe: 102	20	24
Zheng et al.[30]	China	33.5-57	Severe patients: 30; No severe: 131	18	12
Zhang et al.[31]	China	33-55	Mild patients: 116; moderates: 25; severe: 12	44	33
Zheng et al.[32]	China	58-73	Patients	5	2
Chu et al.[33]	China	26-7	Hospitalized health professionals. Common type of COVID-19: 11; Severe: 40; Critical: 3	3	n
Kim et al.[34]	South Korea	22-47	213 Patients (41-asymptomatic, 172-mild)	54	54
Colaneri et al.[35]	Italy	10-94)	Mild Patients: 27; severe: 17	1	n
Guan et al.[36]	China	0--65	No severe patients: 926; Severe Patients: 173; 39 Health Care	164	150
Zhang et al.[37]	China	56-70	Cancer patients	4	n
Wang et al.[38]	China	16-89	138 hospitalized patients	170	152
Niu et al.[39]	China	50-80	No severe patients: 93; Severe Patients: 48	n	4
Zhao et al.[40]	China	22-9	No Severe Patients: 61; Severe Patients: 30	15	n
Yang et al.[41]	China	59.7± 13.3	Severe Patients	6	3
Zhou et al.[42]	China	18-87	191 hospitalized patients	29	n
Kato et al.[43]	Japan	62-71	70 patients positive for SARS-CoV-2	3	6
Peng et al.[44]	China	51-69	No Severe Patients: 4; Severe Patients: 3; Critical patients: 3	N	6
Xu et al.[45]	China	35-53	COVID- 19 Patients	4	N
Zhang et al.[46]	China	39-65.5	No Severe Patients: 166; Severe Patients: 55	N	17
Huang et al.[47]	China	41-58	Patients outside the ICU: 28; Patients in the ICU: 13	N	17
Sun et al.[48]	China	34-56	No Severe Patients: 40; Severe Patients: 15	10	6
Liguori et al.[49]	Italy	55 ± 14.65	No Severe Patients	25	40
Brandstetter et al.[50]	Germany	18-65	Hospital staff	15	15
Cao et al.[51]	China	26-72	8 COVID-19 patients after discharge	1	n
Zhang et al.[52]	China	62.7 ± 14.2	Patients with moderate disease: 30; Patients with severe disease: 100; Patients with critical disease: 36	63	53
He et al.[53]	China	34-62	No Severe Patients: 135; Severe Patients: 69	20	14
Yin et al.[54]	China	27-78	COVID-19 Patients	14	2
Cummings et al.[55]	USA	≥18	257 patients, critically ill with acute hypoxemic respiratory failure	67	10
Docherty et al.[56]	UK	>90	Hospital inpatients with COVID-19	4026	1033
Du et al.[57]	China	0-65	85 fatal cases of COVID-19	14	4
Liu et al.[58]	China	36-56	COVID-19 pneumonia patients	24	n
To et al.[59]	China	37-75	COVID-19 Patients	2	n
Wu et al.[60]	China	46.9	COVID-19 Patients	2	n
Yu et al.[61]	China	65-88	4 Patients with COVID-19	6	3
Zha et al.[62]	China	32-54	31 patients infected with SARS-CoV-2	18	4
Qiu et al.[63]	China	1-16	Moderate children (19) and mild (17)	n	3
Alberici et al.[64]	Italy	51-64	20 Patients with pneumonia by SARS-CoV2	5	n
Xu et al.[65]	China	18-80	50 Patients (mild-9, common- 28, severe- 10, critically severe- 3)	n	5

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Table 2: Methodological quality of the studies by Newcastle-Ottawa Scale with data on representativeness of the sample, comparability, and outcome.

Representativeness of the sample (max 5 *)					Comparability (max 2 *)					Outcome (max 3 *)	
Authors	Representativeness of the sample (**)		Sample size (*)	Non-respondents (*)	Ascertainment of the exposure (risk factor) (***)		Confounding factors are controlled. (**)		Assessment of the outcome (*****)	Statistical test (*)	Total SCORE (OUT OF 10*)
Alberici et al.[64]		*		*	**		*		**		*******
Brandstetter et al.[50]		*			**		*	*	**	*	*********
Cao et al.[51]		*		*	**		*		**	*	********
Chen et al.[21]		*		*	**		*	*	**	*	*********
Chen et al.[23]		*		*		*	*		**		******
Chen et al.[6]	*		*	*	**		*	*	**	*	**********
Chen et al.[29]	*		*	*	**		*	*	**	*	**********
Chu et al.[33]		*		*	**		*		**	*	********
Colaneri et al.[35]		*		*		*	*		**		******
Cummings et al.[55]	*		*	*	**		*	*	**	*	**********
Docherty *et al.*[56]	*		*	*	**		*	*	**	*	**********
D'Silva et al.[25]		*		*	**		*		**	*	*********
Du et al.[57]		*		*	**		*		**		*******
Giacomelli et al.[10]		*	*	*	**		*		**	*	*********
Guan et al.[36]		*		*	**		*		**		*******
Han et al.[11]		*		*	**		*		**	*	********
He. et al. [53]	*		*	*	**		*	*	**	*	**********
Ji et al.[19]		*		*	**		*	*	**	*	*********
Kato et al.[43]		*		*	**		*		**	*	********
Kim et al.[34]		*			**		*		**		******
Lechien et al.[2]		*	*	*	**		*		**	*	*********
Lei et al.[12]		*	*	*	**		*	*	**	*	**********
Lei et al.[24]		*		*	**		*	*	**	*	*********
Liguori et al.[49]		*		*	**		*	*	**	*	*********
Liu et al.[14]		*		*	**		*		**	*	********
Ma et al.[13]	*		*	*	**		*		**	*	*********
Shang et al.[22]	*		*	*	**		*	*	**	*	**********
Sun et al.[17]		*	*	*	**		*		**	*	*********
Sun et al.[48]	*			*	**		*		**	*	********
Tian et al.[18]					**		*		**	*	******
Shabto et al.[16]					**		*		**	*	******
To et al.[59]		*	*		**		*			*	******
Wang et al.[28]		*		*		*	*		**	*	******
Wang et al.[38]	*		*		**		*		**	*	********
Wei et al.[4]		*	*		**		*		**	*	*********
Wu et al.[60]		*				*	*		**	*	******
Xu et al.[45]	*					*	*			*	**
Yang et al.[3]					**		*			*	****
Yang et al.[5]	*				**		*		**	*	*******
Yang et al.[41]	*			*	**		*	*	**	*	*********
Yin et al.[54]		*			**		*		**	*	*******
Yu et al.[61]	*	*				*			**	*	*****
Zha et al.[62]		*			**		*		**	*	*******
Zhang et al.[15]		*		*	**				**		******
Zhang et al.[31]	*	*	*		**		*		**	*	********
Zhang et al.[37]		*	*		**		*		**	*	********
Zhang et al.[46]	*			*			*		**	*	******
Zhao et al.[40]		*	*		**		*		**	*	*********
Zheng et al.[30]	*		*		**		*		**	*	********
Zheng et al.[32]		*		*	**		*		**	*	*******
Zhou et al.[42]		*	*	*	**		*		**	*	*********
Zhou et al.[20]		*			**				**	*	*******
Xu et al.[65]		*		*	**		*		**	*	*********
Huang et al.[47]		*	*		**		*		**	*	********
Zhang et al,[46]		*	*		**		*		**	*	********
Liu et al.[58]		*	*		**		*		**	*	********
Niu et al.[39]		*	*		**		*		**	*	********
Peng et al.[44]		*			**		*		**		******
Qiu et al.[63]		*			**		*		**	*	*******
Shabto et al.[16]		*			**		*		**		******
Shi et al.[1]		*			**		*		**	*	*******
Tian et al.[27]		*	*		**		*		**	*	********
Yan et al.[26]		*	*		**		*		**	*	*********

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Table 3: Study bias risk included according to JBI Critical Apprisal Checklist for Analytical Cross-Sectional Studies.

Authors	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured validly and reliably?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured validly and reliably?	Was appropriate statistical analysis used?
Alberici et al.[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Brandstetter et al.[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cao et al.[51]	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Chen et al.[21]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al.[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Chen et al.[6]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al.[29]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chu et al.[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Colaneri et al.[35]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Cummings et al.[55]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Docherty et al.[56]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D'Silva et al.[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Du et al.[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Giacomelli et al.[10]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Guan et al.[36]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han et al.[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
He et al.[53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ji et al.[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kato et al.[43]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al.[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Lechien et al.[2]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lei et al.[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lei et al.[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liguori et al.[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu et al.[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ma et al.[13]	yes	yes	Unclear	No	No	yes	yes	yes
Shang et al.[22]	Yes	yes	yes	yes	Unclear	yes	yes	yes
Sun et al.[17]	Unclear	yes	Unclear	yes	Not applicable	yes	yes	yes
Sun et al.[48]	yes	yes	yes	yes	yes	yes	yes	yes
Tian et al.[18]	yes	yes	yes	yes	Not applicable	yes	yes	yes
To et al.[16]	no	yes	yes	yes	Not applicable	yes	yes	yes
Wang et al.[59]	yes	yes	yes	yes	yes	yes	yes	yes
Wang et al.[28]	yes	yes	yes	yes	Not applicable	yes	yes	yes
Wei et al.[38]	yes	yes	yes	yes	Not applicable	yes	yes	yes
Wu et al.[4]	yes	yes	yes	yes	yes	yes	yes	yes
Xu et al.[60]	no	yes	yes	yes	yes	yes	yes	yes
Xu et al.[45]	yes	yes	yes	yes	Not applicable	yes	yes	yes
Yang et al.[3]	No	yes	yes	yes	Not applicable	yes	yes	yes
Yang et al.[5]	yes	yes	yes	yes	Not applicable	yes	yes	yes
Yang et al.[41]	yes	yes	yes	yes	Not applicable	yes	yes	yes
Yin et al.[54]	Unclear	yes	yes	yes	Not applicable	yes	yes	yes
Yu et al.[61]	unclear	yes	yes	yes	Not applicable	yes	yes	yes
Zha et al.[62]	unclear	yes	yes	yes	Not applicable	yes	yes	yes
Zhang et al.[15]	Unclear	yes	yes	yes	Not applicable	yes	yes	yes
Zhang et al.[31]	Unclear	yes	yes	yes	Not applicable	yes	yes	yes
Zhang et al.[37]	yes	yes	yes	yes	Not applicable	yes	yes	yes
Zhang et al.[46]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Zhao et al.[40]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Zheng et al.[30]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zheng et al.[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhou et al.[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhou et al.[20]	yes	yes	yes	yes	Yes	Yes	yes	yes
Huang et al.[65]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang et al.[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu et al.[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Niu et al.[39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peng et al.[44]	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes
Qiu et al.[63]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shabto et al.[16]	Unclear	Yes	Yes	Yes	Not applicable	Yes	Yes	Unclear
Shi et al.[1]	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes
Tian et al.[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yan et al.[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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