Neurological manifestations in adult and pediatric patients with COVID-19: A systematic review and meta-analysis

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Abstract

Background and aim: In light of evidence for the possible long-term effects of Covid-19 on the nervous system, the aim of present study was to evaluate the Neurological manifestations in adult and pediatric patients with COVID-19.

Method: The present study is based on PRISMA guidelines, which includes all articles published in international databases such as PubMed, Scopus, Science Direct and Embase between January 2019 and May 2022. 95% confidence interval was done with fixed effect model and inverse variance method. Analysis of data collected from selected studies was done using STATA.V16 software.

Result: In the initial review, the abstracts of 730 studies were reviewed, the full text of 249 studies was reviewed by two authors and finally, 16 studies were selected. Proportions of headache, Myalgia and Dizziness associated with COVID-19 infection was 12% (effect size: 0.12; 95% CI, -0.16 to 0.40), 20% (effect size: 0.20; 95% CI, -0.06 to 0.46) and 9% (effect size: 0.9; 95% CI, -0.40 to 0.48).

Conclusion: The meta-analysis of the present study shows that the incidence of neurological symptoms such as headache and myalgia in Covid-19 patients is higher than other neurological symptoms.

Key words: Neurological manifestations, COVID-19, SARS-CoV-2

Introduction

Coronaviruses are a group of viruses that can cause disease in humans or animals. To date, several types of coronavirus have been identified associated with respiratory problems(1). The latest example of this type of virus is SARS-CoV-2, which causes Covid-19 disease(2). SARS- CoV-2 was unknown before the December 2019 epidemic in Wuhan, China(3). The highest rate of death in Covid-19 is related to people who have a history of underlying diseases such as high blood pressure, diabetes, cancer, cardiovascular diseases or chronic respiratory disease (3). SARS-CoV-2 is a positive single-stranded RNA virus that can be transmitted from one infected person to another through small nasal or oral respiratory droplets when exhaling, sneezing, or coughing. The beginning of the pathogenesis of SARS-CoV-2 is by binding to one of its surface structural proteins called Spike (S), to the type 2 enzyme converted to angiotensin: angiotensin-converting enzyme 2 (ACE2) as its receptor (5). Pathology of Covid-19 with a wide range of symptoms; It is accompanied by fever, cough, shortness of breath, sore throat, headache, fatigue, digestive complications such as diarrhea and vomiting, loss of sense of smell and taste, and hearing disorders (6).Because acute respiratory syndrome is a hallmark of Covid-19 disease, most early studies have focused on Covid-19 and its effect on the respiratory system. However, there is ample evidence that SARS-CoV-2 infects other organs as well and can affect different parts of the body; including the nervous system(7). Central Nervous System (CNS) involvement in Covid-19 infection is of great importance because it may affect disease severity, clinical manifestations, and frequency of symptoms; in particular, CNS involvement may affect the respiratory status of patients with SARS-CoV-2 . Exacerbating the neurologic involvement of SARS-CoV-2 may explain why some patients have respiratory failure, while others

do not (8). On the other hand, human and animal studies, the ability of SARS-CoV-2 to infect the brain; In particular, they have shown the brain stem. Therefore, some coronaviruses can spread to the brainstem through the axons of mechanoreceptors and chemoreceptors in the lungs and lower respiratory tract.(9). Preliminary clinical studies show that intraoral or intraocular injection of coronaviruses into non-human mammals leads to the detection of RNA or antigen of these viruses in the cerebrospinal fluid (CSF)(10). Human coronavirus OC43 is also associated with fatal encephalitis in pediatric(11). In addition, the severe systemic inflammatory response associated with viral infection can lead to breakdown of the blood-brain barrier-BBB, which in turn allows access of peripheral cytokines to the CNS.(12). Preliminary research shows that 36 percent of 214 patients with Covid-19 in China have complications of SARS-CoV-2 on the nervous system, including impaired sense of smell and taste, nerve pain to seizures and stroke. The virus can also enter the CNS through the olfactory bulb and cause inflammation and demyelination: therefore, it is common for coronavirus infections to be associated with neurological manifestations (such as mood swings, encephalitis, and cerebrovascular problems). According to the above evidence about the possible long-term effects of covid-19 on the nervous system, the aim of the current study was to investigate neurological manifestations in adult patients and children with covid-19.

Method

Search strategy

The present study was based on the PRISMA guidelines (13) and searches were conducted between January 2019 and May 2022 in PubMed, Scopus, Science Direct, Embase databases using (``COVID-19" [Mesh] OR ``SARS-CoV." Keywords include 2[Mesh]) AND ("Models, Neurological" [Mesh] OR "Diagnostic Techniques, Neurological" [Mesh] OR "Neurological Manifestations" [Mesh] OR "Neurosurgeons" [Mesh]) OR "Headache" [mesh]) or "Headache Disorders"[mesh]) or "Myalgia" [mesh]) or ("Myalgia/Complications"[mesh] or "Myalgia/Statistics and Numerical Data[mesh])) or ("dizziness" [mesh] or "dizziness" [mesh])) or "dizziness" [mesh]) or "nausea" [mesh]) or "vomiting" [mesh]) or "neuralgia" [mesh]) or "disorders It was a vision.In the present study, an attempt was made to investigate the neurological manifestations associated with Covid-19 disease. The data of the selected studies were extracted after the study, which included demographic information (sample size, gender, age) and the main findings of the studies.

Criteria for inclusion in the present study were articles that were retrospective, prospective and RCT; the association between neurological manifestations and Covid-19 disease was investigated; the full text of the article was available and published in English. Studies such as case study, case series, and review, letter to the editor, laboratory and animal studies were excluded from the study.

The Newcastle-Ottawa Scale (NOS) (14) used for non-randomized studies was used to assess the risk of bias in selected studies. The instrument is scored according to Table 2, and scores between 1-3 indicate a high bias risk, 4 to 6 indicate a moderate bias risk, and 7 to 9 indicate a low bias risk.

Data analysis using STATA.V16 software and for meta-analysis used effect size (95% confidence interval) with fixed effect modal and inverse-variance method. I^2 index test was used to evaluate the level of heterogeneity (I^2< 50% = low levels, 50<I^2< 75% = moderate and I^2>75% = high levels).

Result

In the first search in international databases using keywords related to the research topic, 794 articles were found. After removing 64 duplicate articles, abstracts of 730 articles were reviewed and studies that did not match the current study and criteria were excluded from the study (481). In the next step, the full text of 249 studies was reviewed and 233 articles that had exclusion criteria and did not have the purpose of the study were removed, and finally 16 studies were selected and reviewed.

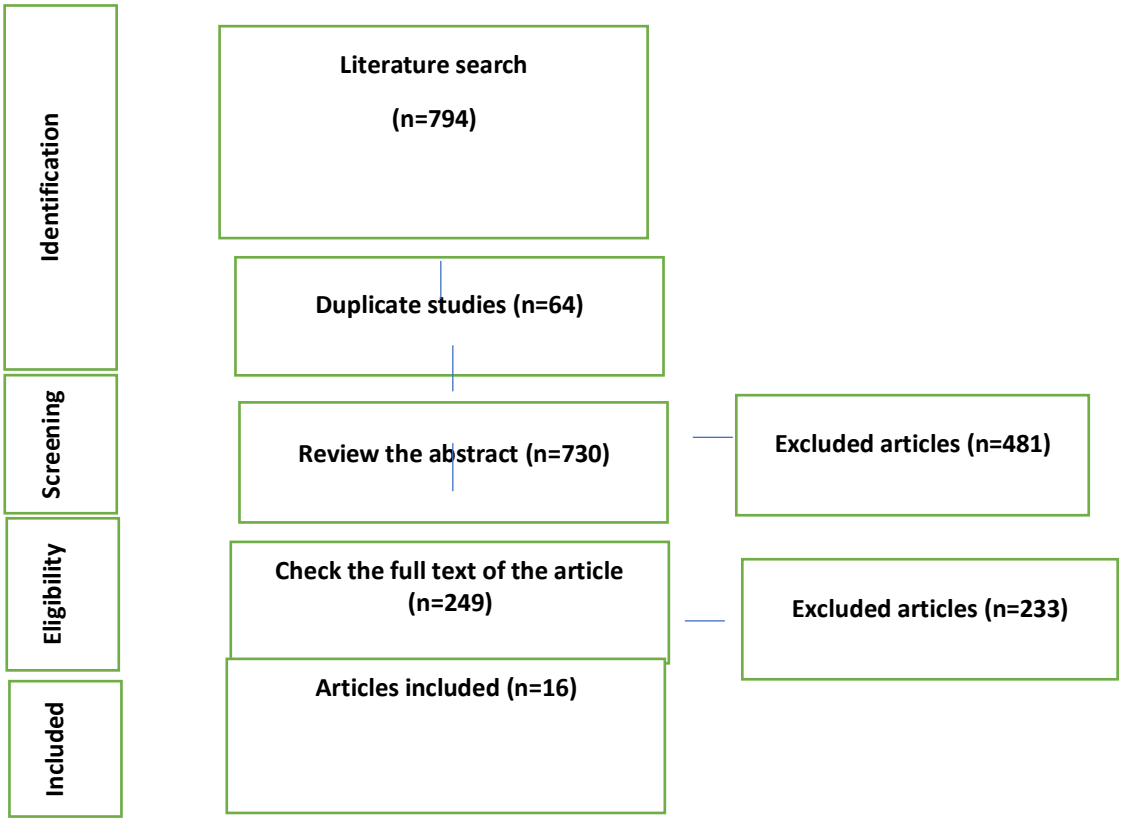

Figure 1. PRISMA flowcharts

Participants Characteristics

In the present study, 15 selected studies were retrospective and one study was prospective; after reviewing and summarizing the data, 3718 patients with a mean age of 51.36 years with Covid-19 were included in the study, of which 2071 male and 1647 female.

Bias assessment

According to the NOS instrument, the risk of bias was high in 8 studies, 2 moderate and 6 low.

Table 1. Summary of demographic data and main findings of selected studies

Study. Years	Study type	Number of patients		Age Mean (years)	Outcome
		male	female		
Huang et al., 2020 (15)	Retrospective	30	11	49.4	Mya and H
Kim et al., 2020 (16)	Retrospective	15	13	43	H and Mya
Li et al., 2020 (17)	Retrospective	279	269	60.3	Mya, H, di, vomiting, and co
Mao et al., 2020 (18)	Retrospective	87	127	53	Di, H, nerve pain, impairment of vision, and skeletal muscle injury
Chang et al., 2020 (19)	Retrospective	10	3	34	H and Mya
Chen et al., 2020 (20)	Retrospective	67	32	56	Ma, co, H, nausea, and vomiting
Chen et al., 2020 (21)	Retrospective	171	103	54.3	Mya, H, di, nausea, and vomiting
Chung et al., 2020 (22)	Retrospective	108	95	51.2	Ms, H, and nausea
Du et al., 2020 (23)	Prospective	97	82	58	Mya and H
Feng et al., 2020 (24)	Retrospective	271	205	53.2	Mya and NS
Guan et al., 2020 (25)	Retrospective	640	459	47.3	Mya, H, and nausea/ vomiting
Yang et al., 2020 (26)	Retrospective	35	17	60	Mya, H, and vomiting
Zheng et al., 2020 (27)	Retrospective	80	81	46	Mylagia, H, and nausea
Zhou et al., 2020 (28)	Retrospective	119	72	57	Mya, nausea, and vomiting

Pan et al., 2020 (29)	Retrospective	6	15	49.1	Mya
Shen et al., 2020 (30)	Retrospective	56	63	50	H, nausea, and vomiting

H: Headache; Mya: Myalgia; Ma: Muscle ache; di: dizziness; co: confusion; Ms: Muscle soreness; NS: neurological symptom

Table 2. Bias assessment (NOS tool)

study	Selection (5 score)				Comparability (2 score)	Outcome (2 score)		Total score
	representative sample	Sample size	Non respondents	Ascertainment of the exposure	Based on design and analysis	Assessment of outcome	Statistical test	
Huang et al., 2020 (15)	*	*	-	*	*	-	-	4
Kim et al., 2020 (16)	*	*	*	*	*	-	-	4
Li et al., 2020 (17)	*	*	*	*	-	-	*	5
Mao et al., 2020 (18)	*	*	*	*	*	-	*	6
Chang et al., 2020 (19)	*	*	*	*	*	*	*	7
Chen et al., 2020 (20)	*	*	*	*	*	-	-	4
Chen et al., 2020 (21)	*	*	*	*	*	-	-	4
Chung et al., 2020 (22)	*	*	*	*	*	-	-	4
Du et al., 2020 (23)	*	*	*	*	**	*	*	8
Feng et al., 2020 (24)	*	*	*	**	**	*	*	9
Guan et al., 2020 (25)	*	*	-	*	*	-	-	4
Yang et al., 2020 (26)	*	*	-	*	*	-	-	4
Zheng et al., 2020 (27)	*	*	*	*	*	*	*	7
Zhou et al., 2020 (28)	*	*	-	-	*	-	-	3
Pan et al., 2020 (29)	*	*	*	*	*	*	*	7
Shen et al., 2020 (30)	*	*	*	*	*	*	*	7

Neurological symptoms associated with COVID-19 infection

Headache

Proportions of headache associated with COVID-19 infection was 12% (effect size: 0.12; 95% CI, -0.16 to 0.40) among twelve studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=1.00) (Figure 2).

Myalgia

Proportions of myalgia associated with COVID-19 infection was 20% (effect size: 0.20; 95% CI, -0.06 to 0.46) among fourteen studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=1.00) (Figure 3).

Dizziness

Proportions of dizziness associated with COVID-19 infection was 9% (effect size: 0.9; 95% CI, -0.40 to 0.48) among four studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=1.00) (Figure 4).

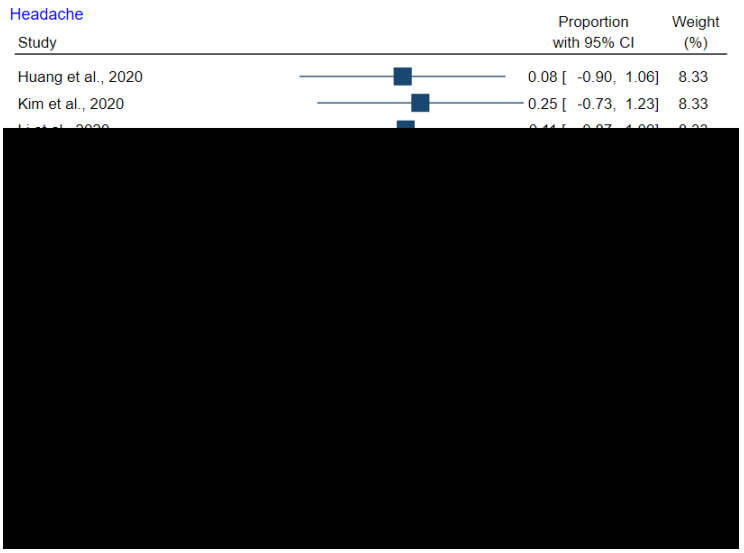

Figure 2. Forest plot showed Proportions of headache associated with COVID-19 infection

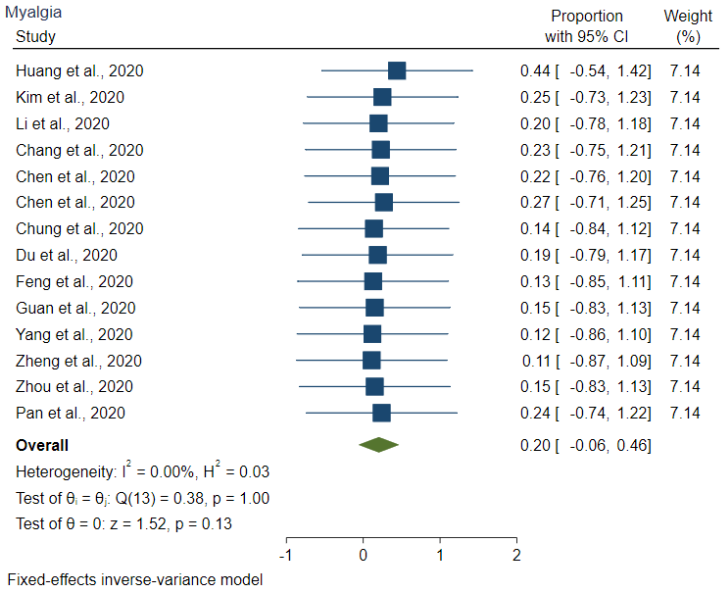

Figure 3. Forest plot showed Proportions of Myalgia associated with COVID-19 infection

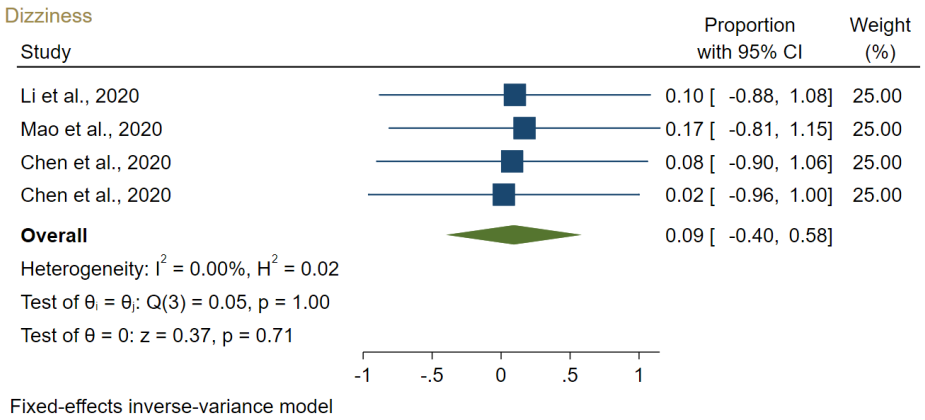

Figure 4. Forest plot showed Proportions of Dizziness associated with COVID-19 infection

Confusion

Proportions of Confusion associated with COVID-19 infection was 6% (effect size: 0.6; 95% CI, -0.63 to 0.75) among two studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=0.93) (Figure 5).

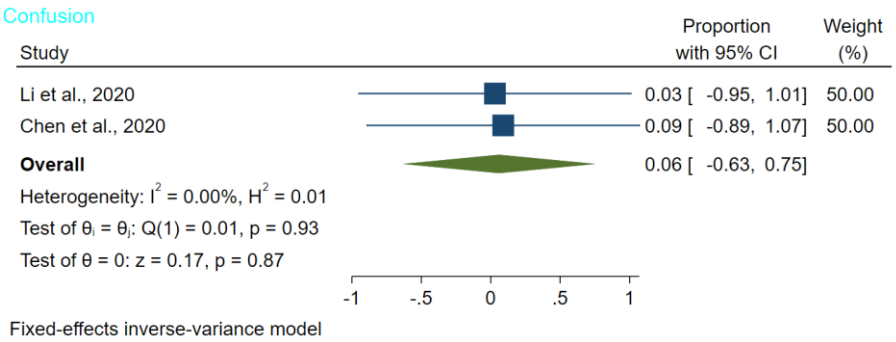

Figure 5. Forest plot showed Proportions of Confusion associated with COVID-19 infection

Nausea and vomiting

Proportions of nausea associated with COVID-19 infection was 6% (effect size: 0.6; 95% CI, -0.51to 0.63) among three studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=1.00) (Figure 6).

Proportions of vomiting associated with COVID-19 infection was 5% (effect size: 0.5; 95% CI, -0.44 to 0.54) among four studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=1.00) (Figure 7).

Proportions of Nausea and vomiting associated with COVID-19 infection was 3% (effect size: 0.3; 95% CI, -0.46 to 0.52) among four studies that reported this variable; According to I^2, which is zero percent, low heterogeneity was observed (p=1.00) (Figure 8).

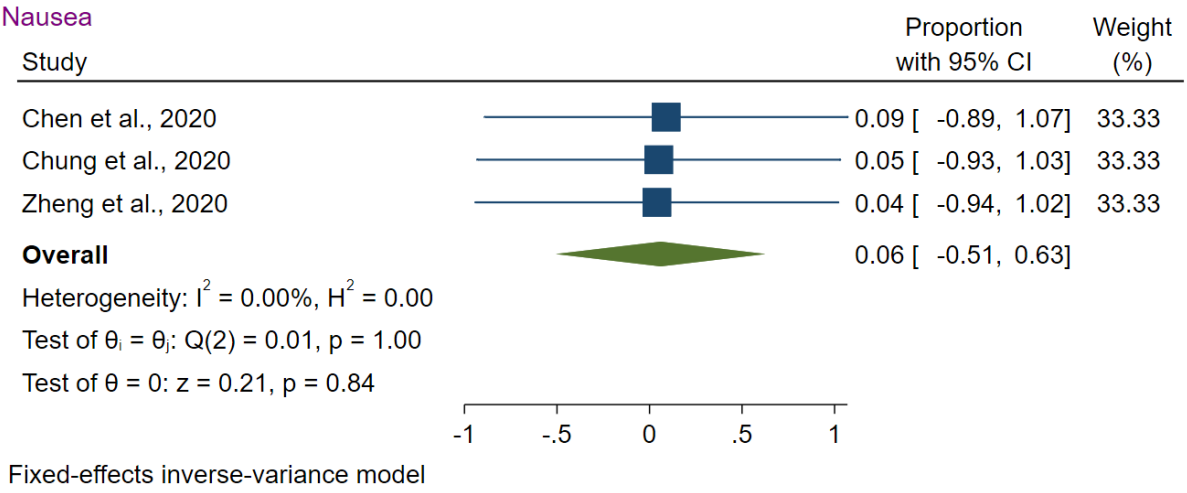

Figure 6. Forest plot showed Proportions of Nausea associated with COVID-19 infection

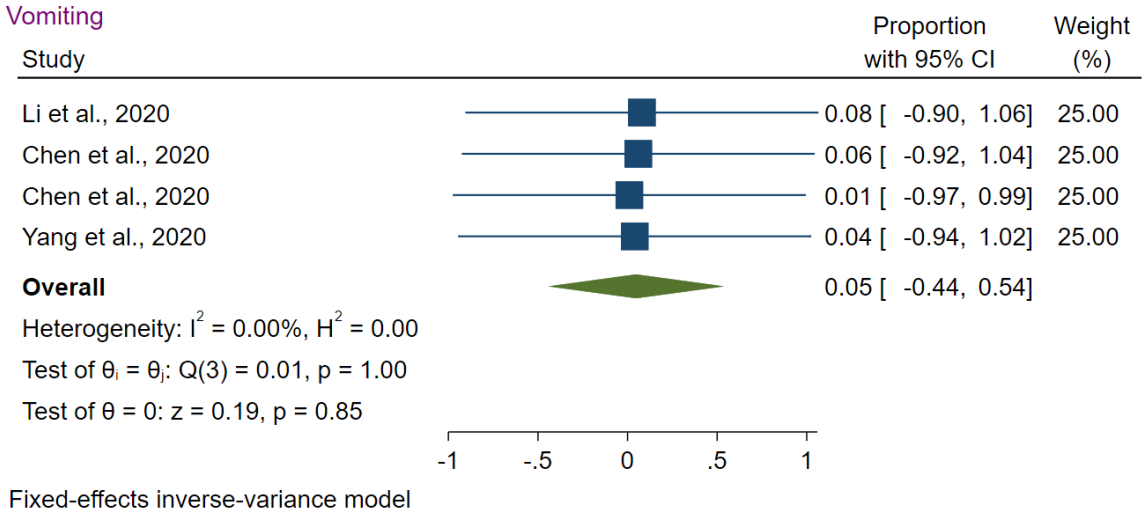

Figure 7. Forest plot showed Proportions of vomiting associated with COVID-19 infection

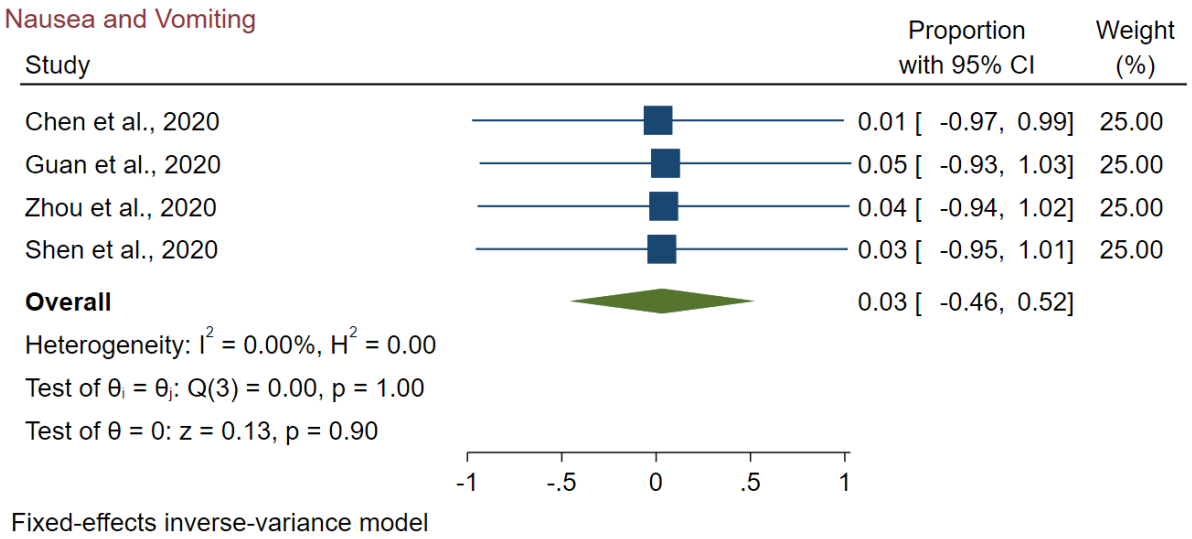

Figure 8. Forest plot showed Proportions of Nausea and vomiting associated with COVID-19 infection

Discussion

In the present study, 3718 patients with covid-19 who had neurological symptoms were examined. The proportion of men was more than women and the average age of the patients was 51.36 years. According to studies, myalgia and headache are more common than other neurological symptoms associated with Covid-19. According to the findings of the meta-analysis of the present study, almost 50% of patients who are hospitalized due to covid-19 have neurological symptoms.

Other neurologic complications associated with Covid-19 that were not included in the meta-analysis due to high heterogeneity between studies included cerebrovascular disorders presenting as acute cerebral infarction or bleeding or cerebral sinus venous thrombosis with relatively high prevalence. The best way to diagnose neurological complications is through a clinical examination followed by brain imaging, which can show evidence of a heart attack or hemorrhage in suspected patients. Evidence shows that viruses can migrate, reach tissues and multiply by infecting motor or sensory nerves through neurotransmission. In relation to the SARS-CoV-2 virus, they can multiply in lung tissue cells and cause CNS hypoxia and increased anaerobic metabolism in the brain. It has also been reported that this virus can infect macrophages, microglia and astrocytes and can cause a pro-inflammatory disease.

Studies have shown that SARS-CoV-2 spike protein can interact with ACE2 expressed in capillary endothelium, possibly damaging the blood-brain barrier and invading the CNS by reaching the vasculature (31–33).

In the present study, there were only two pediatric patients in whom neurological manifestations were evaluated. Due to small sample size, age range was not included in the meta-analysis. But it can be said that neurological symptoms are reported more in elderly patients and the cause can be underlying diseases.

Very little heterogeneity was observed between study findings in relation to any neurological complication. As a result, the findings of this study can provide sufficient evidence. However, the quality of most studies is low and the poor methodological design needs to be improved in future studies. The results of the present study can be confirmed. Other limitations of the present study clinical heterogeneity between studies were the fact that only English studies were reviewed.

Conclusion

The meta-analysis of the present study shows that the incidence of neurological symptoms such as headache and myalgia in Covid-19 patients is higher than other neurological symptoms. Also, the most common neurological complication associated with Covid-10 was cerebrovascular disease for which no meta-analysis was performed. Therefore, according to the findings of the present study, in order to diagnose and treat neurological complications early, all reported symptoms should be examined and a complete neurological referral should be performed.

Since only prospective and retrospective studies were reviewed, it is necessary to perform RCT studies in this regard, as well as to consider the sample size of higher studies and to review and record the complications and consequences in the full course of the disease.

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