Clinical symptoms, diagnosis, treatment, and outcome of COVID-19-associated encephalitis: A systematic review of case reports and case series

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Abstract
Introduction: Since COVID-19 outbreak, various studies mentioned the occurrence of neurological disorders. Of these, encephalitis is known as a critical neurological complication in COVID-19 patients. Numerous case reports and case series have found encephalitis in relation to COVID-19, which have not been systematically reviewed. This study aims to evaluate the clinical symptoms, diagnosis, treatment, and outcome of COVID-19-associated encephalitis.

Methods: We used the Pubmed/Medline, Embase, and Web of Science databases to search for reports on COVID-19-associated encephalitis from January 1, 2019, to March 7, 2021. The irrelevant studies were excluded based on screening and further evaluation. Then, the information relating diagnosis, treatment, clinical manifestations, comorbidities, and outcome was extracted and evaluated.

Results: From 4455 initial studies, 45 articles met our criteria and were selected for further evaluation. Included publications reported an overall number of 53 COVID-19-related encephalitis cases. MRI showed hyperintensity of brain regions including white matter (44.68%), temporal lobe (17.02%), and thalamus (12.76%). Also, brain CT scan revealed the hypodensity of the white matter (17.14%) and cerebral hemorrhages/hemorrhagic foci (11.42%) as the most frequent findings. The IV methylprednisolone/oral prednisone (36.11%), IV immunoglobulin (27.77%), and acyclovir (16.66%) were more preferred for COVID-19 patients with encephalitis. From the 46 patients, 13 (28.26%) patients were died in the hospital.

Conclusion: In this systematic review, characteristics of COVID-19-associated encephalitis including clinical symptoms, diagnosis, treatment, and outcome were described. COVID-19-associated encephalitis can accompany with other neurological symptoms and involve different brain. Although majority of encephalitis condition are
1 | INTRODUCTION

Humans have been struggling with the COVID-19 epidemic for nearly 2 years. As of early August 2020, more than 17.5 million cases of COVID-19 were identified in 188 countries, including 680,000 deaths. The disease that often has respiratory symptoms but sometimes also has extrapulmonary manifestations such as neurological symptoms. On average, neurological symptoms appear three weeks after respiratory symptoms. Less common clinical manifestations of COVID-19 include headache, brain status alteration, chest pain, abdominal pain, diarrhea, and nausea. Nervous manifestations can range from a mild nervous agitation to severe encephalitis. The roll of central nervous system in SARS-CoV-2 epidemic has been determined. Ischemic stroke, central nervous system (CNS) inflammation, encephalopathy, and myelitis are common clinical manifestations of the CNS in COVID-19 patients. Encephalitis means inflammation of the brain, which is mainly caused by the autoimmune process and/or the viral infection. Encephalitis is one of the main and devastating complications associated with CNS. In previous epidemics, MERS-CoV and SARS-CoV viruses have caused brain complications such as polyneuropathy, ischemic stroke, encephalitis, and brain status change in patients with Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus. Several case reports and case series have reported the patients with COVID-19-associated encephalitis, which in some cases have been fatal. The pooled mortality rate from COVID-19-associated encephalitis is reported to be 13.4%. In a multicenter study by Pilotto et al. in Italy, 25 out of 45 people with encephalitis tested positive for SARS-CoV-2. They found that there is a wide range of clinical manifestations in patients and the response to treatment depends on the specific CNS manifestations. Due to the importance of encephalitis in COVID-19 patients and the risk of death for them, it is necessary to conduct a detailed systematic review on this study. Therefore, the aim of this study was to evaluate the clinical symptoms, diagnosis, treatment, and outcome of COVID-19-associated encephalitis.

2 | MATERIALS AND METHODS

This systematic review was performed according to “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement.

2.1 Search strategy

We used Pubmed/Medline, Embase, and Web of Science databases for this literature. The articles included were only those published in English from January 1, 2019, to March 7, 2021. The search keywords used were “encephalitis,” “brain,” “neurologic,” “COVID-19,” “severe acute respiratory syndrome coronavirus 2,” “SARS-CoV-2,” “2019-nCoV,” “nCoV disease,” “coronavirus disease-19,” “2019 novel coronavirus,” and “Wuhan pneumonia.”

2.2 Inclusion/exclusion criteria

Case reports and case series reporting encephalitis in patients with COVID-19 were included. These studies met the following inclusion criteria: (i) COVID-19 patients were confirmed and diagnosed with RT-PCR as suggested by WHO; (ii) the raw data for clinical symptoms, diagnosis, treatment, and outcome of COVID-19-associated encephalitis were addressed. Studies without enough data, review article, modelling study, commentary, correspondence, editorial, guideline, and news were excluded. All potentially relevant articles were then screened for eligibility. Two reviewers independently screened the records by title, abstract, and full texts to exclude those not related to the current study.

2.3 Data collection

The extracted data included first author name; country where the study was conducted; year of publication; type of study; number of patients investigated; distribution of age and sex in the population; diagnosis methods; data for clinical, radiological, and laboratory findings; therapy, and the patient outcome.

2.4 Quality assessment

We used the case reports/case series appraisal checklist supplied by the Joanna Briggs Institute (JBI) to evaluate the quality of the studies.

3 | RESULTS

3.1 Study selection and general characteristics

As shown in Figure 1, at the first screening, 4455 papers were retrieved. In the second phase, after removing duplicates, 2171 papers remained. These papers were screened by title and abstract, and 119 were selected for detailed full-text evaluation. Applying the criteria to the full-text documents, 45 articles were eligible for inclusion.
in the systematic review. The results of various studies including participants’ clinical manifestations, comorbidities, diagnosis, treatment, and outcome are reported in Tables 1 and 2. Moreover, a summary of the case report and case series findings are reported in Table 3.

3.2 | Study population

From a total of 45 studies, 53 patients with COVID-19-associated encephalitis were enrolled from 18 countries. Forty-one (93.18%) studies were case reports and 4 (6.82%) were case series. The most significant number of studies was conducted in the USA (n = 10), followed by Italy (n = 6) and Iran (n = 5).

3.3 | Demographic data

Demographic information of the individuals with COVID-19-associated encephalitis can be found in Tables 1 and 2. The patients were 21 female and 32 male with mean age of 52.12 years ranged between 9 months and 89 years. The highest incidence of COVID-19-associated encephalitis was observed in people over 50 years of age (54.72%).

3.4 | Diagnostic methods

COVID-19 was most often diagnosed by RT-PCR (92.45%) and chest CT (37.73%). In addition, serological tests (11.32%) and simplex assay (1.88%) were used to detect SARS-CoV-2 virus (Table 3). Brain MRI (81.48%), CSF analysis (46.29%), electroencephalography (42.59%), and head CT (37.03%) were the most frequently used methods to diagnose encephalitis (Table 3). The most common brain MRI patterns were hyperintensity in the white matter (44.68%), hyperintensity in the temporal lobe (17.02%), and hyperintensity of the thalamus (12.76%). In addition, hypodensity of the white matter (17.14%) and cerebral hemorrhages/hemorrhagic foci (11.42%) were the most common head CT scan patterns.

3.5 | Clinical manifestations

Clinical manifestations were reported in five categories including (A) neurological manifestations such as altered mental status (53.70%), decreased consciousness/unconsciousness (33.33%), and seizure (29.62%); (B) psychiatric symptoms (14.81%); (C) general symptoms such as fever (70.37%), headache (20.37%), weakness/asthenia (18.51%), and drowsiness (16.66%); (D) neuromuscular symptoms such as myalgia (7.40%), myoclonus (5.55%); and (E) other clinical
manifestation such as respiratory symptoms (68.51%), renal dysfunction (18.51%), and visual impairment (7.40%).

### 3.6 | Comorbidities

The most common comorbidities were hypertension (29.16%), diabetes mellitus (14.58%), obesity (12.50%), and neurologic disorders (10.41%). The less common comorbidities were anemia (2.08%), hypercholesterolemia (2.08%), hypothyroidism (2.08%), vitiligo (2.08%), and asthma (2.08%).

### 3.7 | Treatment options

A wide range of treatment options was used to treat COVID-19. The most common of which were hydroxychloroquine (50%), acyclovir (20%), and ritonavir/lopinavir (16.66%), respectively.

Common encephalitis treatment modalities included IV methylprednisolone/oral prednisone (36.11%), IV immunoglobulin (27.77%), acyclovir (16.66%). In Table 3, we summarize all of the drugs used.

### 3.8 | Outcomes

In total, 58.69% of the patients with COVID-19-associated encephalitis discharged and 13.05% of them were still hospitalized. The pooled mortality rate of these patients was 28.26%.

### 3.9 | Risk of bias assessment

The results of the critical appraisal (JBI checklist) of included studies are summarized in Table S1. Overall, 45 articles were identified as having a low risk of bias (quality assessment score >7).
4 | DISCUSSION

Encephalitis is one of the specific neurological manifestations of COVID-19 that can cause severe damage to the patient. In this study, we reviewed case series and case reports to evaluate the clinical symptoms, diagnosis, treatment, and outcome of COVID-19-associated encephalitis.

The patients with COVID-19-associated encephalitis can show encephalitis weeks after the onset of symptoms of COVID-19 or to have symptoms of COVID-19 and encephalitis at the same time. Our study indicated that the clinical manifestations in patients with COVID-19-associated encephalitis can be both central nervous system symptoms (i.e., headache, dizziness, and impaired consciousness) and peripheral nervous system symptoms (i.e., hypogeusia, hyposmia, etc.). The most common symptoms were related to altered mental status (53.7%), decreased consciousness/unconsciousness (33.3%), and seizure (29.6%).

These results were consistent with a systematic review performed by Siow et al. They also reported that decreased level of consciousness (77.1%), alter in mental state (72.3%), and seizures (38.2%) were the most common symptoms in patients with COVID-19-associated encephalitis.

Correia et al. conducted a systematic review on the neurological manifestations of patients with COVID-19. The rate of altered consciousness in their study was reported to be 11.2%. The difference in the results of their study with us could be due to differences in the time frame of each study and the number of patients admitted.

Furthermore, headache (20.37%) and weakness/asthenia (18.51%) were other clinical symptoms of COVID-19-associated encephalitis in the present study. Correia et al. and Siow et al. reported headache rates of 16.8% and 27.3%, respectively.

In this study, myalgia (7.4%) was the most frequent neuromuscular symptom. The prevalence of myalgia in a meta-analysis done by Li et al. was 35.8%.
| First author | Country       | Published time | Age (years) | Sex | Encephalitis diagnosis method          | CT results                                                                 | MRI results                                                                 |
|--------------|---------------|----------------|-------------|-----|----------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Kumar N      | India         | October 2020   | 35          | M   | Head CT                                | Hypodensities in both thalami and left caudate nucleus                      | NP                                                                         |
| Novi G       | Italy         | September 2020 | 64          | F   | Brain and spine MRI, CSF analysis      | NP                                                                         | Multiple enhancing lesions of the brain, bilateral optic nerve enhancement  |
| Ayuso LL     | Spain         | September 2020 | 72          | F   | Brain MRI, immunoblot analysis        | NP                                                                         | Hyperintensity in cerebellum, contrast enhancement on the floor of the fourth ventricle |
| Khan Z       | USA           | November 2020  | 30          | M   | Head CT                                | Opacifications of paranasal sinuses, hypodensity of the white matter        | Hyperintensity in the white matter of cerebral hemispheres                  |
| Westhoff TH  | Germany       | July 2020      | 69          | M   | Brain MRI, CSF analysis               | NP                                                                         | Linear meningeal enhancement / hyperintensity in the white matter           |
| Kamal YM     | United Arab Emirate | September 2020 | 31          | M   | CSF analysis, head CT, brain MRI      | Bilateral hypodensities in the external capsules, the insular cortex and white matter of the frontal lobes | Bilateral diffusion restriction in the temporal and frontal lobes / bilateral hyperintensity in the temporal lobe cortex |
| Rebeiz T     | USA           | September 2020 | NM          | M   | CSF analysis, brain MRI               | Subarachnoid hemorrhage within the mesial parietal region / nonspecific hypo- attenuation in the splenium of the corpus callosum | Diffusion restriction and hyperintensity of the corpus callosum, left thalamus and frontal cortex |
| Zoghi A      | Iran          | June 2020      | 21          | M   | CSF analysis, brain and cervical MRI  | NP                                                                         | Hyperintensity in the internal capsule, cerebral peduncles, pons and the corpus callosum |
| Moriguchi T  | Japan         | May 2020       | 24          | M   | Brain MRI                              | NP                                                                         | Hyperintensity along the wall of right lateral ventricle, right temporal lobe and hippocampus, slight hippocampus atrophy |
| First author Country | Published time | Age (years) | Sex | Encephalitis diagnosis | SARS-CoV-2 diagnosis method | Clinical manifestations | SARS-CoV-2 diagnosis in CSF sample | Comorbidities | Outcomes |
|----------------------|----------------|-------------|-----|------------------------|----------------------------|------------------------|-------------------------------|---------------|----------|
| Kumar N              | India          | 36          | M   | Head CT                | RT-PCR                     | Fever, vomiting, DC    | NP                            | Invasive meningioma | Death    |
| Novel G              | Italy          | 37          | F   | Brain and spine MRI, CSF analysis | RT-PCR, antibody testing | RS, anosmia, ageusia, visual impairment, behavioral changes, headache, hyperreflexia | Positive | Vitiligo, hypertension, monoclonal gammopathy | Discharged |
| Ayuso LL             | Spain          | 38          | F   | Brain MRI, immunoblot analysis | RT-PCR                     | Psychiatric symptoms, fever, AMS, dizziness, visual impairment, unsteadiness, cerebellar signs | NP | Hypertension, hyperlipidemia, smoking, depression | Discharged |
| Khan Z               | USA            | 39          | M   | Head CT                | Acyclovir RT-PCR, chest CT | Seizure, DC, behavioral changes, myoclonus, AMS, psychiatric symptoms | NP | Obesity | Still hospitalized |
| Westhoff TH          | Germany        | 40          | M   | Brain MRI, CSF analysis | RT-PCR, chest CT | Fever, RS, diarrhea, pancreas and kidney allograft dysfunction, seizure, hemi-neglect, fatigue | Positive | Immunosuppression | Discharged |
| Kamal YM             | United Arab Emirate | 41     | M   | CSF analysis, head CT, brain MRI | Acyclovir RT-PCR, chest CT | Behavioral changes, AMS, agitation, drowsiness | Positive | None | Discharged |
| Rebeiz T             | USA            | 21          | M   | CSF analysis, brain MRI | Acyclovir RT-PCR, chest CT | Behavioral changes, fever, AMS, psychiatric symptoms | NP | None | Death |
| Zoghi A              | Iran           | 42          | M   | CSF analysis, brain and cervical MRI | IV vancomycin, meropenem, acyclovir | Anorexia, vomiting, food intolerance, malaise, lower limbs paralysis, weakness, urinary retention, drowsiness | Negative | None | NM |
| Moriguchi T          | Japan          | 24          | M   | Brain MRI | Acyclovir RT-PCR, chest CT | Fatigue, fever, headache, RS, seizure, unconsciousness | Positive | NM | Still hospitalized |
| First author | Country | Published time | Age (years) | Sex | Encephalitis diagnosis method | CT results | MRI results |
|--------------|---------|----------------|-------------|-----|-------------------------------|------------|-------------|
| Haqiqi A | United Kingdom | January 2021 | 56 | M | Head CT, brain MRI, CSF analysis | Diffuse hypodensity of the white matter/multiple bilateral white matter hemorrhagic foci involving the corpus callosum | Hyperintensity of the white matter/diffuse hemosiderin staining throughout the white matter and the corpus callosum/some cystic hemorrhagic areas within both cerebral hemispheres |
| Pizzanelli C | Italy | January 2021 | 74 | F | Brain MRI, total body PET/TC | Unremarkable | Hyperintensity in the temporal lobes, mild hippocampal thickening |
| Al Mazrouei SS | United Arab Emirates | September 2020 | 43 | M | Head CT, brain MRI | Hypodensity of bilateral thalami | Hyperintensity in the frontal lobes, insula, thalamus and globus pallidus |
| Sirous R | USA | August 2020 | 50 | M | MRI, magnetic resonance angiography, magnetic resonance venography | Mild cerebral generalized parenchymal volume loss with sulcal enlargement | Cerebral edema with mass effect, downward cerebellar tonsillar herniation/compression and displacement of the brainstem and 4th ventricle |
| Mardani M | Iran | July 2020 | 64 | F | CSF analysis | Unremarkable | NP |
| Vandervorst F | Belgium | July 2020 | 29 | M | Brain MRI | Unremarkable | Hyperintensity of the left temporal cortex/mild gyral expansion |
| Freire-Álvarez E | Spain | October 2020 | 39 | M | Brain MRI | Unremarkable | Hyperintensity at the cortical and subcortical right frontal regions, right thalamus and mammillary body, temporal lobes and cerebral peduncles |
| Parsons T | Germany | May 2020 | 51 | F | Brain MRI, EEG | NP | Hyperintensities in the white matter |
| Al-olama M | United Arab Emirates | May 2020 | 36 | M | Brain CT, CT angiography | Hematoma in the right frontal lobe with surrounding edema/extracerebral hemorrhage/cortical swelling/bilateral supratentorial leptomeningeal increased enhancement | NP |
| First author | Country | Published time | Age | Sex | Encephalitis diagnosis method | COVID-19 treatment | Clinical manifestations | Comorbidities | Outcomes |
|--------------|---------|----------------|-----|-----|-------------------------------|-------------------|------------------------|---------------|----------|
| Haqiqi       | A       | United Kingdom | January 2021 | 56   | M                             | CT, brain MRI, CSF analysis | Diffuse hypodensity of the white matter/multiple bilateral white matter hemorrhagic foci involving the corpus callosum | Hypertension, chronic kidney disease, hypercholesterolemia, asthma, obesity | Discharged |
| Pizzanelli   | C       | Italy          | January 2021 | 74   | F                             | Brain MRI, total body PET/TC | Unremarkable Hyperintensity in the temporal lobes, mild hippocampal thickening | None | Discharged |
| Al Mazrouei  | SS      | United Arab Emirates | September 2020 | 43   | M                             | CT, brain MRI | Hypodensity of bilateral thalami | Diabetes mellitus type2 | Death |
| Sirous       | R       | USA            | August 2020  | 50   | M                             | MRI, magnetic resonance angiography, magnetic resonance venography | Mild cerebral generalized parenchymal volume loss with sulcal enlargement Cerebral edema with mass effect, downward cerebellar tonsillar herniation/compression and displacement of the brainstem and 4th ventricle | None | Death |
| Mardani      | M       | Iran           | July 2020    | 64   | F                             | CSF analysis | Unremarkable | None | Discharged |
| Vandervorst  | F       | Belgium        | July 2020    | 29   | M                             | Brain MRI | Unremarkable Hyperintensity of the left temporal cortex/mild gyral expansion | None | Discharged |
| Freire-Alvarez | E    | Spain          | October 2020 | 39   | M                             | Brain MRI | Unremarkable Hyperintensity at the cortical and subcortical right frontal regions, right thalamus and mammillary body, temporal lobes and cerebral peduncles | None | Discharged |
| Parsons      | T       | Germany        | May 2020     | 51   | F                             | Brain MRI, EEG | NP | Hyperintensities in the white matter | None | Clinical improvement, Still hospitalized |
| Al-tolama    | M       | United Arab Emirates | May 2020    | 36   | M                             | Brain CT, CT angiography | Hematoma in the right frontal lobe with surrounding edema/extracerebral hemorrhage/cortical swelling/bilateral supratentorial leptomeningeal increased enhancement | None | Still hospitalized |

**TABLE 2 (Continued)**

- **IV methyl-prednisolone, oral prednisolone**
- **NM**
- **IV hydroxychloroquine**
- **NM**
- **IV acyclovir, hydroxychloroquine**
- **IV immunoglobulin, tocilizumab**
- **Methylprednisolone, IV Immunoglobulin**
- **NM**
- **PCR**

(Continues)
| First author      | Country | Published time | Age (years) | Sex | Encephalitis diagnosis method | CT results                      | MRI results                                                  |
|------------------|---------|----------------|-------------|-----|------------------------------|--------------------------------|-------------------------------------------------------------|
| Goodloe TB       | Alabama | January, 2021  | 52          | M   | Bead CT, EEG                 | Unremarkable                   | Unremarkable                                                 |
| Sattar SBA       | USA     | September 2020 | 44          | M   | Brain MRI, head CT, CSF      | Few scattered foci of white matter hypo-attenuation | Abnormal medial cortical signals in the bilateral frontal lobes |
| Haider A         | USA     | March 2020     | 66          | M   | EEG, brain MRI               | Unremarkable                   | Small lacunar infarcts and a patchy area of bright signals in the cortical and lateral periventricular regions |
| Cariddi LP       | Italy   | June, 2020     | 64          | F   | Head CT, brain MRI           | Bilateral hypodensity of the white matter/a small left occipital parenchymal hemorrhage | Bilateral edema with bilateral occipital foci of subacute hemorrhage |
| Sofijanova A     | Republic of Macedonia | November 2020 | 9 month  | NM  | Head CT, biochemical blood test | Enlargement of the lateral ventricles, with intraventricular masses, internal hydrocephalus | NP |
| Ghosh R          | India   | August 2020    | 44          | F   | Brain MRI, CSF analysis      | NP                             | T2-weighted hyperintensity in the parietal lobes with peri-lesional edema |
| Pilotto A        | Italy   | August, 2020   | 60          | M   | EEG, brain MRI, CSF analysis | Unremarkable                   | Unremarkable                                                 |
| Azab MA          | Egypt   | February, 2021 | 89          | M   | MRI, post-mortem biopsy      | NP                             | Hyperintensity near the basal ganglia and thalami            |
| Abdi S          | Iran    | June, 2020     | 58          | M   | Brain MRI, CSF analysis      | NP                             | Hyperintensity of the white matter/ involvement of cortical and deep gray matter and midbrain |
| Dharsandiya M    | India   | August, 2020   | 68          | M   | Head CT, blood test, CSF     | Age-related cortical atrophy (unremarkable) | NP |
| Babar A          | USA     | October, 2020  | 20          | F   | Brain MRI, CSF analysis, EEG | Unremarkable                   | Unremarkable                                                 |
| Special encephalitis treatment | SARS-CoV-2 diagnosis method | COVID-19 treatment | Clinical manifestations | SARS-CoV-2 diagnosis in CSF sample | Comorbidities | Outcomes |
|-------------------------------|-----------------------------|--------------------|------------------------|-----------------------------------|---------------|----------|
| Vancomycin, ceftriaxone, azithromycin, acyclovir | RT-PCR | NM | AMS, agitation, fever | NP | Hypertension, diabetes mellitus type2, end-stage renal disease, coronary artery disease | Discharged |
| Tocilizumab, IV immunoglobulin, rituximab | RT-PCR, chest CT | Hydroxychloroquine, azithromycin | Fever, RS, seizure, AMS, unresponsiveness | Positive | None | Discharged |
| NM | RT-PCR | Hydroxychloroquine, darunavir/cobicistat | Fever, RS, visual impairment, AMS, drowsiness, reduced tendon reflexes | Negative | Hypertension, gastrointestinal reflux disease, hyperuricemia, dyslipidemia, obstructive sleep apnea, atrial fibrillation | Partial recovery |
| Anti-edematous therapy | NM | Cephalosporin, aminoglycoside, antiviral drug | RS, convulsive status, fever, DC, vomiting, seizure | NP | NM | Transferred to another hospital |
| IV methylprednisolone | RT-PCR | Ceftriaxone, vancomycin, azithromycin | Myalgia, RS, hypogeusia, hyposmia, AMS, seizure, unconsciousness, reduced tendon reflexes, loss of sphincter control | NP | None | Death |
| Methylprednisolone | RT-PCR, chest CT | Ritonavir/lopinavir, hydroxychloroquine | Fever, RS, cognitive fluctuations, DC, AMS, behavioral changes, asthenia | Negative | None | Discharged |
| NM | Serological test | Acyclovir, acetaminophen | Rash, seizure, tremors, RS, cerebellar signs, fever, headache, dizziness, myalgia | NP | NM | Death |
| IV dexamethasone | RT-PCR, chest CT | NM | Drowsiness, gait disturbance, DC | Negative | NM | Death |
| Methylprednisolone, tocilizumab | RT-PCR, chest CT | Azithromycin, hydroxychloroquine, gamma globulin | Fever, RS, renal failure, viral sepsis, autonomic disturbance, AMS, seizure | NP | Diabetes, hypertension | Death |
| Methylprednisolone | RT-PCR | Levofoxacin, acyclovir | RS, ageusia, insomnia, Fever, AMS, psychiatric symptoms | Negative | Obesity, anxiety | Discharged |
TABLE 2 (Continued)

| First author | Country   | Published time | Age (years) | Sex | Encephalitis diagnosis method | CT results                                                                 | MRI results                                                                 |
|--------------|-----------|----------------|-------------|-----|-----------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Virhammar J  | Sweden    | June, 2020     | 55          | F   | Head CT, CSF analysis, EEG, brain MRI | Hypodensities in the thalami and midbrain | Hyperintensity in subinsular regions, thalami, and brainstem/involvement of temporal lobes, hippocampi, and cerebral peduncles |
| Farhadian S  | USA       | June, 2020     | 78          | F   | Brain MRI, EEG, CSF analysis | NP                                                                         | Generalized atrophy/hyperintensity in white matter |
| de Miranda Henriches-Souza AM | Brazil October, 2020 | 12          | F   | Brain and spine MRI, CSF analysis | NP                                                                         | Bilateral restricted diffusion in the white matter/hyperintensity of the corpus callosum |
| Afshar H     | Iran      | August, 2020   | 39          | F   | Brain MRI                  | NP                                                                         | Hyperintensities in bilateral thalami, temporal lobes and pons              |
| Crosta F     | Italy     | December, 2020 | 79          | M   | EEG, brain MRI             | Unremarkable                                                             | Hyperintensity of the left temporal cortex, with mild gyril expansion     |
| Sangare A    | France    | November, 2020 | 56          | M   | EEG, brain MRI             | NP                                                                         | Hemorrhagic lesions in the pontine tegmentum and subinsular regions, including corpus callosum |
| El-Zein RS   | USA       | September, 2020 | 40          | M   | EEG, blood tests, CSF analysis | Unremarkable                                                             | Unremarkable                                                               |
| Etemadifar M | Iran      | September, 2020 | 51          | M   | Head CT, brain MRI         | Generalized brain edema/signs of brain herniation                        | Generalized brain edema, downward herniation of cerebellar tonsils and brainstem, hyperintensities in bilateral cerebral cortices and corpus striatum |
| Peng LV      | China     | February, 2021 | 90          | F   | CSF analysis, physical and neurological examination | Unremarkable                                                             | NP                                                                         |
| Hayashi M    | Japan     | August, 2020   | 75          | M   | Neurological examination, brain MRI | NP                                                                         | Hyperintensity in the splenium of corpus callosum                         |
| Kumar A      | USA       | November, 2020 | 35          | F   | Brain MRI, EEG, CSF analysis | Unremarkable                                                             | Hyperintensity in the white matter involving bilateral cerebral peduncles |
| Muccioli L   | Italy     | September, 2020 | 47          | F   | EEG, brain MRI             | NP                                                                         | Hyperintensity in the white matter                                        |
| Special encephalitis treatment | SARS-CoV-2 diagnosis method | COVID-19 treatment | Clinical manifestations | SARS-CoV-2 diagnosis in CSF sample | Comorbidities | Outcomes |
|-------------------------------|-------------------------------|-------------------|------------------------|-----------------------------------|---------------|----------|
| IV immunoglobulin            | RT-PCR, chest CT            | Acyclovir, plasma exchange | Fever, myalgia, impaired brain stem reflexes, myoclonus, lethargy, DC | Positive          | None          | Discharged to rehabilitation |
| NM                            | RT-PCR, chest CT            | Hydroxychloroquine  | Seizure like activity, RS, fever, AMS | Negative          | Immunosuppression due to kidney transplantation  | Discharged   |
| Methylprednisolone           | RT-PCR                     | NM                 | Tetraplegia, fever, deep areflexia, skin rash, headache, RS, acute motor weakness, numbness | Negative          | None          | Discharged   |
| IV immunoglobulin, IV methyl- | Chest CT                   | Meropen, levofloxacin, linezolide, hydroxychloroquine, atazanavir, IV immunoglobulin | Fever, myalgia, anorexia, drowsiness, RS, DC, headache, seizure | Negative          | None          | Discharged   |
| NM                            | RT-PCR                     | Clarithromycin, dexamethasone | Fever, AMS, anosmia, RS, ageusia, DC, short-term memory deficits, psychiatric symptoms | NP                 | Hypertension, diabetes, chronic heart failure | Discharged   |
| IV methylprednisolone, plasma exchange with albumin | RT-PCR, chest CT | Cephalosporin linezolide, trimethoprim-sulfamethoxazole, meropenem aminosid | Fever, RS, reversible acute kidney failure, visual impairment, unresponsiveness | Negative          | Hypertension | Discharged   |
| IV immunoglobulin            | Simplex SARS-CoV-2 assay    | Hydroxychloroquine | Fever, fatigue, AMS, RS, psychiatric symptoms, increased agitation | Negative          | None          | Discharged   |
| NM                            | RT-PCR                     | Hydroxychloroquine, lopinavir/ritonavir, IV acyclovir, IV dexamethasone | Headache, drowsiness, nausea, vomiting, RS, seizure, cardiac arrest, impaired brain stem reflexes | NP                 | Hypothyroidism migraine | Death        |
| Mannitol and anti-viral therapy (Ganciclovir) | RT-PCR, Chest CT | NM | Fever, RS, fatigue, unconsciousness, unresponsiveness, increased muscle tension | Negative          | Cerebral lacunar infarction with no neurological deficits- live in a healthcare unit | Death (irrelevant cause) |
| Corticosteroid pulse, meropenem | RT-PCR                     | Favipiravir, corticosteroid pulse | Urinary incontinence, diarrhea, DC, cerebellar signs, fever, AMS, tremor, gait disturbance | NP                 | Mild Alzheimer's disease | Death        |
| Methylprednisolone, IV immunoglobulin, plasma exchange | RT-PCR, serological tests | NM | Anosmia, ageusia, gait disturbance, neuropathy, weakness, drowsiness, lethargy | Negative          | Gastric bypass surgery, anemia | Discharged to a long-term care facility |
| Tocilizumab                  | Chest CT, RT-PCR           | NM                 | Asthenia, RS, ageusia, hyposmia, language disturbance, pain in the extremities, fever, AMS, headache, agitation | Negative          | None          | Discharged   |
**TABLE 3** Summary of the case reports and case series findings

| Variables          | No. of studies | n/N   | %   |
|--------------------|----------------|-------|-----|
| **Gender**         |                |       |     |
| Male               | 29             | 32/53 | 60.38 |
| Female             | 19             | 21/53 | 39.62 |
| **Age**            |                |       |     |
| <30 (years old)    | 6              | 6/53  | 11.32 |
| 31–50 (years old)  | 16             | 18/53 | 33.96 |
| >51 (years old)    | 25             | 29/53 | 54.72 |
| **Age/sex**        |                |       |     |
| <30 (years old)    | 4              | 4/6   | 66.67 |
| Male               | 2              | 2/6   | 33.33 |
| Female             | 2              | 2/6   | 33.33 |
| 31–50 (years old)  | 11             | 12/18 | 66.67 |
| Male               | 6              | 6/18  | 33.33 |
| Female             | 5              | 5/18  | 27.78 |
| >51 (years old)    | 15             | 16/29 | 55.17 |
| Male               | 12             | 13/29 | 44.83 |
| **Clinical manifestation** |            |       |     |
| **Neurological manifestations** |      |       |     |
| Decreased consciousness/unconsciousness | 17 | 18/54 | 33.33 |
| Behavioral changes | 6             | 6/54  | 11.11 |
| Altered mental status | 24 | 29/54 | 53.70 |
| Cerebellar signs   | 4              | 5/54  | 9.25  |
| Seizure            | 15             | 16/54 | 29.62 |
| Agitation          | 5              | 6/54  | 11.11 |
| Headache           | 11             | 11/54 | 20.37 |
| Memory deficits    | 2              | 2/54  | 3.70  |
| Unresponsiveness   | 4              | 4/54  | 7.40  |
| Convulsive status  | 2              | 2/54  | 3.70  |
| Cognitive impairment | 2  | 5/54  | 9.26  |
| Language disturbance | 2  | 2/54  | 3.70  |
| Paraphasia         | 1              | 1/54  | 1.85  |
| Tremors            | 2              | 2/54  | 3.70  |
| Lower limbs paralysis | 2   | 2/54  | 3.70  |
| Gait disturbance   | 3              | 3/54  | 5.55  |
| Unsteadiness       | 1              | 1/54  | 1.85  |
| Hemi-neglect       | 1              | 1/54  | 1.85  |
| Impaired brain stem reflexes | 2 | 2/54  | 3.70  |
| Pain               | 3              | 3/54  | 5.55  |
| Coma               | 1              | 1/54  | 1.85  |
| Apraxia            | 1              | 1/54  | 1.85  |
| Dysexecutive syndrome | 1 | 1/54  | 1.85  |
| Psychomotor slowing | 1  | 1/54  | 1.85  |
| Ideo-motor slowing | 1              | 1/54  | 1.85  |
| **Psychiatric symptoms** |        |       |     |
| Oral automatism    | 1              | 1/54  | 1.85  |
| Neuropathy         | 1              | 1/54  | 1.85  |
| Reduced tendon reflexes | 2 | 2/54  | 3.70  |
| Loss of sphincter control | 1 | 1/54  | 1.85  |
| Deep areflexia     | 1              | 1/54  | 1.85  |
| **Psychometric symptoms** |      |       |     |
| Fever              | 32             | 38/54 | 70.37 |
| Nausea             | 3              | 3/54  | 5.55  |
| Diarrhea           | 4              | 4/54  | 7.40  |
| Anosmia/hyposmia   | 7              | 8/54  | 14.81 |
| Ageusia/dysgeusia  | 8              | 8/54  | 14.81 |
| Dizziness          | 2              | 2/54  | 3.70  |
| Malaise            | 3              | 3/54  | 5.55  |
| Fatigue            | 8              | 9/54  | 16.66 |
| Drowsiness         | 9              | 9/54  | 16.66 |
| Weakness/asthenia  | 10             | 10/54 | 18.51 |
| Lethargy           | 3              | 3/54  | 5.55  |
| Chills             | 2              | 3/54  | 5.55  |
| Anorexia           | 3              | 3/54  | 5.55  |
| Food intolerance   | 1              | 1/54  | 1.85  |
| Insomnia           | 1              | 1/54  | 1.85  |
| Numbness           | 1              | 1/54  | 1.85  |
| **Neuromuscular symptoms** |        |       |     |
| Myalgia            | 4              | 4/54  | 7.40  |
| Hyperreflexia      | 1              | 1/54  | 1.85  |
| Myoclonus          | 3              | 3/54  | 5.55  |
| Neck stiffness     | 1              | 1/54  | 1.85  |
| Flaccid muscles    | 1              | 1/54  | 1.85  |
| Tetraplegia        | 1              | 1/54  | 1.85  |
| Increased muscle tension | 1 | 1/54  | 1.85  |
| **Other**          |                |       |     |
| Respiratory symptoms | 30 | 37/54 | 68.51 |
| Visual impairment  | 4              | 4/54  | 7.40  |
| Renal dysfunction  | 8              | 10/54 | 18.51 |
| Cardiac dysfunction| 2              | 4/54  | 7.40  |
| Rash               | 2              | 2/54  | 3.70  |
| Viral sepsis       | 1              | 1/54  | 1.85  |
| Delayed awakening after sedation | 1 | 2/54  | 3.70  |
| Autonomic disturbances | 1 | 1/54  | 1.85  |
| **Comorbidities**  |                |       |     |
| Hypertension       | 13             | 14/48 | 29.16 |
| Diabetes mellitus  | 7              | 7/48  | 14.58 |
| Variables                        | No. of studies | n/N | %     |
|---------------------------------|---------------|-----|-------|
| Obesity                         | 6             | 6/48| 12.50 |
| Neurologic disorders            | 5             | 5/48| 10.41 |
| Cardiologic disorder            | 4             | 4/48| 8.33  |
| Dyslipidemia                    | 2             | 2/48| 4.16  |
| Anemia                          | 1             | 1/48| 2.08  |
| Psychiatric disorders           | 2             | 2/48| 4.16  |
| Renal dysfunction               | 3             | 3/48| 6.25  |
| Immunosuppressive state         | 2             | 2/48| 4.16  |
| Smoking                         | 2             | 2/48| 4.16  |
| Hypercholesterolemia            | 1             | 1/48| 2.08  |
| Hypothyroidism                  | 1             | 1/48| 2.08  |
| Vitiligo                        | 1             | 1/48| 2.08  |
| Monoclonal gammopathy           | 1             | 1/48| 2.08  |
| Asthma                          | 1             | 1/48| 2.08  |
| Colorectal cancer               | 1             | 1/48| 2.08  |
| Fatty liver disease             | 1             | 1/48| 2.08  |
| Gastroesophageal reflux disease | 1             | 1/48| 2.08  |
| Hyperuricemia                   | 1             | 1/48| 2.08  |
| Obstructive sleep apnea         | 1             | 1/48| 2.08  |
| Benign prostatic hypertrophy    | 1             | 1/28| 3.57  |
| Gestation                       | 1             | 1/20| 5.00  |
| No comorbidities                | 15            | 15/48|31.25 |

**Presence of SARS-CoV-2 RNA in the CSF sample**

| Presence          | No. of studies | n/N | %     |
|-------------------|---------------|-----|-------|
| Positive          | 7             | 7/34| 20.58 |
| Negative          | 21            | 27/34|79.41 |

**SARS-CoV-2 diagnosis method**

| Method                              | No. of studies | n/N | %     |
|-------------------------------------|---------------|-----|-------|
| RT-PCR                              | 40            | 49/53|92.45 |
| Chest CT                            | 20            | 20/53|37.73 |
| Serological testing (anti-SARS-CoV-2 antibody) | 5             | 6/53|11.32 |
| Simplexa SARS-CoV-2 assay           | 1             | 1/53|1.88  |

**Encephalitis diagnosis method**

| Method                                      | No. of studies | n/N | %     |
|---------------------------------------------|---------------|-----|-------|
| Brain MRI                                   | 36            | 44/54|81.48 |
| Head CT scan                                | 15            | 20/54|37.03 |
| CSF analysis                                | 21            | 25/54|46.29 |
| Electroencephalogram                        | 15            | 23/54|42.59 |
| Total body PET/TC                           | 1             | 1/54|1.85  |
| FDG-PET/CT imaging                          | 1             | 4/54|7.40  |
| CT angiogram                                | 1             | 1/54|1.85  |
| Magnetic resonance angiography and venography | 1             | 1/54|1.85  |
| Biochemical blood tests                     | 3             | 3/54|5.55  |
| Post-mortem biopsy                          | 1             | 1/54|1.85  |
| Physical and neurological examination        | 2             | 2/54|3.70  |

**Immunoblot analysis**

| No. of studies | n/N | %     |
|---------------|-----|-------|
| 1             | 1/54|1.85  |

**Brain tomography**

| No. of studies | n/N | %     |
|---------------|-----|-------|
| 1             | 1/54|1.85  |

**Special encephalitis treatment**

| Method                                      | No. of studies | n/N | %     |
|---------------------------------------------|---------------|-----|-------|
| Dexamethasone                               | 2             | 3/36|8.33  |
| Plasma exchange                             | 3             | 3/36|8.33  |
| IV methylprednisolone/oral prednisone       | 13            | 13/36|36.11 |
| IV immunoglobulin                           | 8             | 10/36|27.77 |
| Corticosteroids                             | 2             | 4/36|11.11 |
| Steroids                                    | 1             | 1/36|2.77  |
| Propofol infusion                           | 1             | 1/36|2.77  |
| Mannitol                                    | 2             | 2/36|5.55  |
| Acyclovir                                   | 6             | 6/36|16.66 |
| Ceftriaxone                                 | 3             | 3/36|8.33  |
| Vancomycin                                  | 4             | 4/36|11.11 |
| Meropenem                                   | 2             | 2/36|5.55  |
| Tocilizumab                                 | 4             | 4/36|11.11 |
| Azithromycin                                | 1             | 1/36|2.77  |
| Rituximab                                   | 1             | 1/36|2.77  |
| Anti-edematous therapy                      | 1             | 1/36|2.77  |

**COVID-19 treatment**

| Method                                      | No. of studies | n/N | %     |
|---------------------------------------------|---------------|-----|-------|
| Hydroxychloroquine                          | 15            | 15/30|50.00 |
| Chloroquine                                 | 1             | 1/30|3.33  |
| Azithromycin                                | 4             | 4/30|13.33 |
| IV amoxicillin-clavulanic acid              | 1             | 1/30|3.33  |
| IV immunoglobulin                           | 2             | 2/30|6.66  |
| Ceftriaxone                                 | 3             | 3/30|10.00 |
| Dexamethasone                               | 3             | 3/30|10.00 |
| Favipiravir                                 | 2             | 2/30|6.66  |
| Ritonavir/lopinavir                         | 5             | 5/30|16.66 |
| Plasma exchange                             | 2             | 2/30|6.66  |
| Remdesivir                                  | 1             | 1/30|3.33  |
| Clarithromycin                              | 1             | 1/30|3.33  |
| Corticosteroid pulse                        | 1             | 1/30|3.33  |
| Clindamycin                                 | 1             | 1/30|3.33  |
| Interferon beta-1b                          | 1             | 1/30|3.33  |
| Darunavir/cobicistat                        | 1             | 1/30|3.33  |
| Cefalosporin                                | 2             | 2/30|6.66  |
| Aminoglycoside                              | 1             | 1/30|3.33  |
| Vancomycin                                  | 1             | 1/30|3.33  |
| Linezolide                                  | 2             | 2/30|6.66  |
| Acyclovir                                   | 6             | 6/30|20.00 |
| Acetaminophen                               | 1             | 1/30|3.33  |
| Gamma globulin                              | 1             | 1/30|3.33  |
| Levofloxacin                                | 2             | 2/30|6.66  |
| Meropenone                                  | 1             | 1/30|3.33  |

(Continues)
Fever (70.37%) and respiratory failure (68.51%) were the most common symptoms of COVID-19 in our evaluation. Heidary et al.\textsuperscript{19} achieved the same results in their study. They reported that clinical symptoms of COVID-19 included coughing (81.3%), fever (62.8%), and dyspnea (60%). Also, Koupaei et al.\textsuperscript{20} demonstrated that the COVID-19 patients mostly suffered from fever (78.8%), cough (63.7%), and respiratory distress (22.6%).

So far, several cases of COVID-19-associated encephalitis have been reported in people who did not have symptoms of COVID-19. The presence of asymptomatic people with encephalitis recommends that performing the diagnostic tests is necessary to prevent the spread of the disease.\textsuperscript{21,22}

On the contrary, CNS involvement is similar in the SARS-CoV-2, SARS-CoV, and MERS-CoV viruses.

\begin{table}[h]
\centering
\caption{Variables}
\begin{tabular}{|l|l|l|l|}
\hline
Variables & No. of studies & n/N & \% \\
\hline
Atazanavir & 1 & 1/30 & 3.33 \\
Trimethoprim-sulfamethoxazole & 1 & 1/30 & 3.33 \\
Meropenem aminosid & 1 & 1/30 & 3.33 \\
\hline
Outcome & & & \\
Death & 13 & 13/46 & 28.26 \\
Discharged & 20 & 23/46 & 50.00 \\
Discharged to rehabilitation/partial recovery & 4 & 4/46 & 8.69 \\
Still hospitalized & 4 & 4/46 & 8.69 \\
Transferred to another hospital & 2 & 2/46 & 4.34 \\
\hline
Brain MRI pattern & & & \\
Unremarkable & 6 & 6/47 & 12.76 \\
Hyperintensity in the white matter & 15 & 21/47 & 44.68 \\
Hyperintensity in the corpus callosum & 5 & 6/47 & 12.76 \\
Hyperintensity in the cerebellum & 3 & 3/47 & 6.38 \\
Hyperintensity of the thalamus & 6 & 6/47 & 12.76 \\
Hyperintensity in the temporal lobe & 8 & 8/47 & 17.02 \\
Hyperintensity in the frontal lobe & 5 & 5/47 & 10.63 \\
Hyperintensity in the brainstem & 3 & 3/47 & 6.38 \\
Hyperintensity in the parietal lobe & 2 & 2/47 & 4.25 \\
Hyperintensity along the wall of lateral ventricle & 1 & 1/47 & 2.12 \\
Hemorrhagic/microhemorrhagic areas & 4 & 5/47 & 10.63 \\
Signs of brain edema & 4 & 4/47 & 8.51 \\
Confluent diffusion restriction in the white matter & 2 & 4/47 & 8.51 \\
Compression and displacement of the brainstem and fourth ventricle & 1 & 1/47 & 2.12 \\
Downward cerebellar tonsillar herniation & 2 & 2/47 & 4.25 \\
Mild gyral expansion & 2 & 2/47 & 4.25 \\
Involvement of cortical and deep gray matter and midbrain & 1 & 1/47 & 2.12 \\
Diffuse hemosiderin staining throughout the white matter and corpus callosum & 1 & 1/47 & 2.12 \\
\end{tabular}
\end{table}
Thus, it is recommended that more sensitive and specific tests be performed.\textsuperscript{23}

In this study, the most common methods used to diagnoseencephalitis were MRI (81.48%), CSF analysis (46.29%), electroencephalogram (42.59%), and head CT scan (37.03%). Among the analysis performed on CSF, only 79.41% were positive and showed the presence of viral RNA. This may be due to the mechanism of encephalitis that the virus has not entered CSF and cannot be detected. Moreover, in the early stages of the disease, CSF may have a normal level and cause a false-negative result.\textsuperscript{5}

The most common MRI findings included hyperintensity in the white matter, hyperintensity in the temporal lobe, and hyperintensity in the corpus callosum, respectively. Although the CT findings of patients with COVID-19-associated encephalitis usually are not remarkable,\textsuperscript{24} our study showed that the most findings are hypodensity of the white matter (17.14%) and cerebral hemorrhages/hemorrhagic foci (11.42%).

Probably, some of the signs in the imaging are related to the subcortical white matter hyperintensities and microbleeds in the deep gray nuclei caused by underlying diseases.\textsuperscript{12}

The association between underlying diseases such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cerebrovascular disease has been identified with COVID-19. People with the above underlying diseases are more likely than others to develop COVID-19 and the severity of the disease.\textsuperscript{25} In the present study, patients with COVID-19-associated encephalitis had a higher percentage of hypertension (29.16%) and diabetes mellitus (14.58%).

Angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, is abundant in various organs.\textsuperscript{3} Diabetes can increase the serum ACE2. Thus, it is not surprising that diabetes is a common comorbidity in patients with COVID-19-associated encephalitis.\textsuperscript{26}

In this study, COVID-19-associated encephalitis was more common in people over 50 years of age (54.72%). It seems that elderly people with several underlying diseases are less able to physiological rearrangement, which makes them more prone to encephalitis.\textsuperscript{27}

Although various treatments have been used to treat COVID-19-associated encephalitis, none of them can be used with certainty. At the time of the COVID-19 epidemic, physicians should suspect SARS-CoV-2 as a differentiating factor when certain diseases and neurological symptoms occur.\textsuperscript{21} Our survey showed that IV methylprednisolone/oral prednisone (36.11%), IV immunoglobulin (27.77%), and acyclovir (16.66%) were the common treatment options to treat encephalitis. The healing role of IV immunoglobulin in severe cases of COVID-19 has been confirmed in several studies.\textsuperscript{28–31}

There are some limitations in this study. First, only case reports and case series were enrolled in this systematic review. Thus, the existence of publication bias should be considered. Second, since our search was limited to articles published in English, some relevant articles in other languages have missed. Third, some studies lacked sufficient data.

5 | CONCLUSION

In this systematic review, various aspects of COVID-19-associated encephalitis including clinical symptoms, diagnosis, treatment, and outcome were studied. COVID-19-associated encephalitis is one of the complications of SARS-CoV-2, which may accompany with other neurological symptoms and make the patient’s condition worse. It usually occur in severe cases and can increase the mortality rate. Thus, it is recommended to pay special attention to neurological symptoms during the COVID-19 epidemic. Lack of proper attention causes problems such as delay in COVID-19 diagnosis, virus transmission, and increased mortality. Therefore, further studies on COVID-19-associated encephalitis are suggested.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTION

Maryam Koupaei, Negar Shadabmehr, Mohamad Hosein Mohamadi, Arezoo Asadi, Sajjad Abasi Moghadam, Amirhossein Shekartabar, Mohsen Heidary, and Fazlollah Shokri contributed in revising and final approval of the version to be published. All the authors agreed and confirmed the study for publication.

DATA AVAILABILITY STATEMENT

All the data in this review are included in the study.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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