REVIEW

New-Onset Refractory Status Epilepticus Secondary to COVID-19 Infection in Adults: A Systematic Review

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Background: New-onset refractory status epilepticus (NORSE) has been reported in the scientific literature as a phenomenon associated with the COVID-19 infection. Given the resurgence of the newer variants of COVID-19 added with its multi-system manifestations, this project was conducted to study the clinical picture of NORSE secondary to COVID-19 infection.

Methods: Three electronic databases were searched using an extensive search strategy from November 2019 to December 2021. Patients reporting NORSE secondary to COVID-19 were included in this review. The status epilepticus severity score (STESS) was calculated by the study authors for individual patients. Statistical analysis was performed using SPSS version 26 with a p-value <0.05 as statistically significant.

Results: After screening, 12 patients were included in this study with a mean age of 61.6 ± 19.0-year olds. The most common type of status epilepticus reported in our study population was non-convulsive status epilepticus (NCSE) (7 out of 12 patients, 58.3%). The linear regression model revealed that STESS scores were significantly influenced by patients' age ($p = 0.004$) and intra-hospital occurrence (IHO) of status epilepticus ($p = 0.026$). Overall, 8 patients (66.7%) were discharged without complications.

Conclusion: Given the observed association of STESS with the aging population and IHO of status epilepticus, special attention is due to the caretakers of this population, while further studies are needed to further build upon this review.

Keywords: new-onset refractory status epilepticus, COVID-19, status epilepticus severity score, status epilepticus, NORSE, FIRES

Introduction

As of May 6, 2022, there are more than 513 million confirmed cases of COVID-19, in addition to estimated 6 million deaths worldwide, with many countries reporting a new surge in cases.[1] This pandemic has been known for its respiratory manifestations, but scientific literature has also reported neurological symptoms secondary to the COVID-19 infection. These include headache, meningitis, acute cerebrovascular disease, epileptic seizures, and status epilepticus (SE).[2,3] The ever-developing scientific information on COVID-19 infection has postulated the infection's neurological effects, taking its origins from transsynaptic spread or transfer across the blood–brain barrier. This, in turn, may contribute to hypoxia, vascular damage, and immune-mediated injury ("cytokine storm"), leading to the neurological manifestations of the COVID-19 infection.[4,5]

Status epilepticus (SE) and epileptic seizures have been reported conditions associated with the COVID-19 infection. Naureen Narula et al postulate three possible mechanisms by which the development of seizures can take place in an individual infected with the COVID-19.[6] These were categorized as (i) Direct mechanism (entry into the central nervous system (CNS) via targeting of angiotensin-converting-enzyme-2 (ACE-2) receptor cells, causing infection and subsequently seizures), (ii) Indirect mechanism (down-regulation of ACE-2 expression leading to overproduction of

angiotensin II which will subsequently cause brain degeneration, cytokine storm which causes uncontrolled inflammatory response causing organ damage, and hypoxia and hypoperfusion which may lead to seizures), and lastly (iii) Exacerbation of seizure in epileptic patients (COVID-19 is associated with factors, such as sepsis and fever, which provoke seizures).[6]

Given the mortality estimates for NORSE range from 10% to 20%, and the already dangerous condition accompanied by the modern age pandemic that has the potential to mutate and cause reinfections, a study was warranted.[7,8] In this regard, a detailed observation of the clinical features, treatment, and outcomes in patients reporting new-onset refractory status epilepticus (NORSE) secondary to COVID-19 infection was conducted.

Methods

This systematic review was conducted per the guidelines listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was registered in the PROSPERO international prospective register of systematic reviews (registration number CRD42022301280).

A comprehensive search of the following electronic databases: MEDLINE (accessed through PUBMED), CNKI, LILACS and Google Scholar, was conducted for the timeline from November 2019 to December 2021. The following search terms were used in devising the search strategies for all the databases; "NORSE", 'new-onset refractory status epileptics, "COVID-19", "SARS-CoV-2". There was no restriction on the type of studies or medium of language used. Additionally, reference lists of screened studies were scrutinized to ensure maximum coverage of relevant studies. The search date was updated to maximize the scope of this study which, however, did not yield any new studies. The search strategies for each database and the Quality Assessment of the included studies can be found in Supplemental Tables 1 and 2, respectively.

Two authors (AA and MAQ) screened the studies independently, while a third author (SST) was consulted when any disagreements were encountered. The inclusion criteria were set up for participants aged 18 or above who developed NORSE secondary to COVID-19. Any participant not fulfilling this criterion was excluded from our review. Diagnosis of NORSE is made if a patient without a history of seizures experienced either protracted or clusters of seizures without a recovery period and did not respond to at least two standard antiepileptic drugs. COVID-19 diagnosis was made based on a positive polymerase chain reaction (PCR) test before or during the emergence of symptoms of NORSE.

During the data extraction process, data on the author's names, date of publication, city, and country of origin, gender (male/female), underlying comorbidities, the severity of COVID-19 infection, symptoms, time of onset of symptoms in regard to covid infection, etiology (if reported), radiological and laboratory findings, description of treatment modalities, drug dosage, type of administration of the drug, drug form, frequency, and quantity of a drug, duration of treatment, treatment modalities that did not have the desired response, adverse effects and prognosis (recovery, complication, death) was extracted. In cases where there were missing data or not enough detailed descriptions, the corresponding author of the concerned study was contacted.

The study authors calculated the Status Epilepticus Severity Score (STESS) for individual patients. STESS scores were calculated using four variables which were given specific STESS scores.

- Level of consciousness: (Alert/somnolent/confused = 0, stuporous/comatose = 1),
- Worst seizure type (Simple (partial/complex partial, absence, myoclonic) = 0, generalized-convulsive = 1, non-convulsive status epilepticus in coma = 2),
- Age (≤65 years = 0, >65 years = 1),
- History of epilepsy (yes = 0, no/unknown=1).

The total score was categorized into two groups: a STESS score of 0–3 and 4–6.

The risk of bias for the included studies was accessed using the assessment tool for case series created by the National Heart, Lung, and Brain Institute (NHLBI).[9] The data analysis was performed using Microsoft Excel and SPSS version 26. Descriptive data were presented as frequency/percentages, while continuous data will be reported as mean complemented by standard deviation. Differences in the ages of discharged and deceased patients were accessed for any significant relationship using the Mann–Whitney U-test, while linear regression analysis was performed to describe any

relationship between clinical data and outcomes with STESS score. A further workup was performed on variables presented as statistically significant (that is a p-value less than 0.05) in our linear regression model using multivariate regression analysis with the STESS score as our variable of interest. The alpha level was set at 0.05 for statistical significance.

Results

A total of 89 studies were found eligible for the title and abstract screening, and 47 studies were assessed for full-text eligibility. Eleven studies were eventually included in this review, where all the studies were case reports/series. Thirty-six studies were excluded due to missing/lack of data (n-10) and not fulfilling criteria (n = 26). The PRISMA flow diagram of the included studies can be studied in Figure 1.[35] The risk of bias for the studies is depicted in Supplement Table 2.[21,25–34]

A total of 12 patients were included in this review, out of which males (6 out of 12 patients) accounted for 50% of the population. All the patients tested positive for the COVID-19 PCR test. The mean age of the study population was 61.6 ±

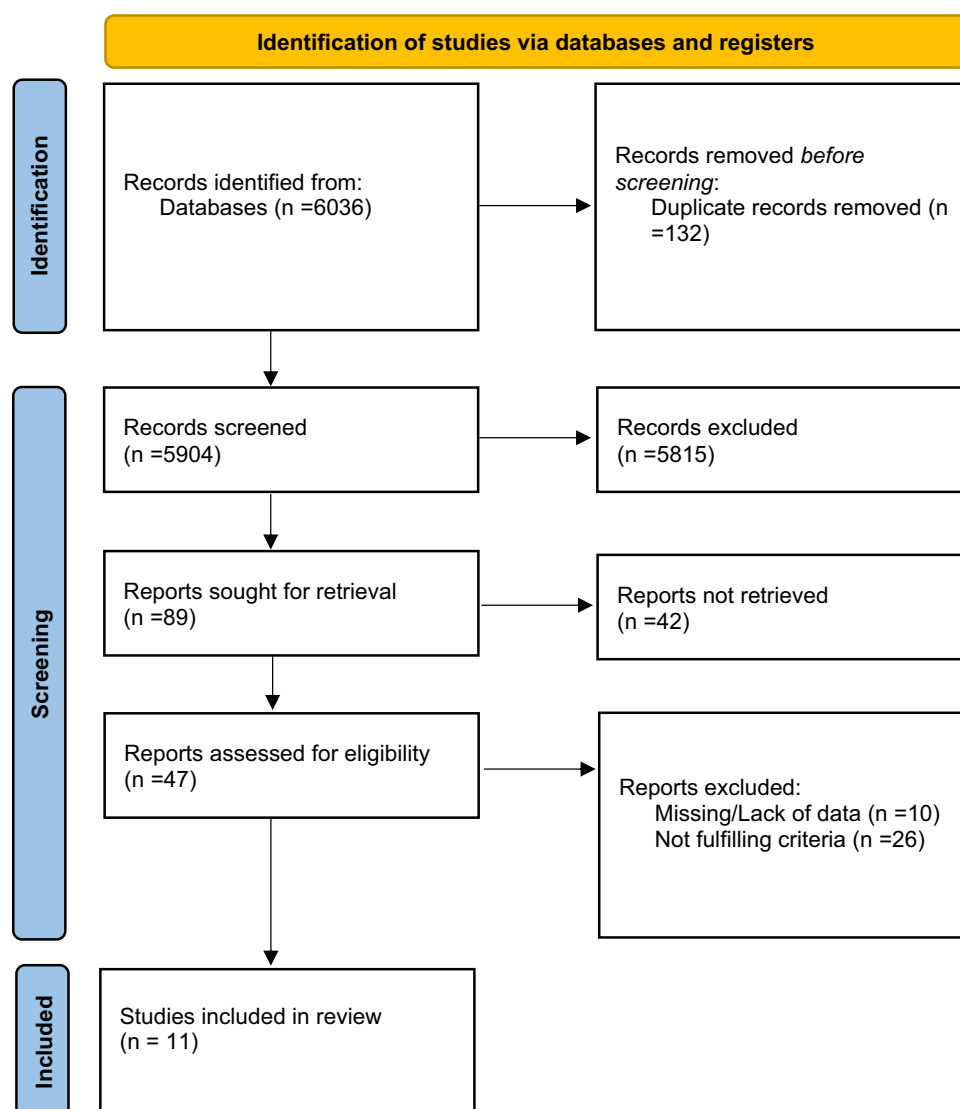**Figure 1** PRISMA flow diagram of included studies.
Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.[35]

19.0-year olds, ranging from 23 to 81-year old. Comorbidity was reported in 7 out of 12 patients (58.3%), with hypertension (5 out of 12 patients, 41.7%) being the commonest (Table 1). The most common symptom reported was that of the respiratory system (6 out of 12 patients, 50%), whereas 4 (33.3%) patients reported no typical symptoms of COVID-19. Other neurological symptoms reported include confusion (33.3%), altered mental status (25%), coma (16.7%), confabulation (8.3%), delirium (8.3%), dysphagia (8.3%), and Todd's paresis (8.3%). The most commonly used treatment for COVID-19 was antibiotics (6 out of 12 patients, 50%). Blood and cerebrospinal fluid laboratory findings can be studied in Table 1.

Table 1 Patient Demographics, COVID-19 Symptoms and Treatment, and Laboratory Findings

Characteristics		
Comorbidity Present	7/12 (58.3%)	
Diabetes	1/12 (8.3%)	
Hypertension	5/12 (41.7%)	
Chronic Kidney Disease	1/12 (8.3%)	
More than two comorbidities present	2/12 (16.7%)	
Respiratory symptoms	6/12 (50%)	
Dyspnea	3/12 (25%)	
Cough	3/12 (50%)	
Gastrointestinal symptoms	1/12 (8.3%)	
Diarrhea	1/12 (8.3%)	
Treatment for COVID-19		
Steroids	Yes	4/12 (33.3%)
	No	4/12 (33.3%)
Hydroxychloroquine	Yes	2/12 (16.7%)
	No	6/12 (50%)
Antibiotics	Yes	6/12 (50%)
	No	2/12 (16.7%)
LPV/r	Yes	1/12 (8.3%)
	No	7/12 (58.3%)
Acyclovir	Yes	1/12 (8.3%)
	No	7/12 (58.3%)
Remdesiver	Yes	1/12 (8.3%)
	No	7/12 (58.3%)
Anakinra	Yes	1/12 (8.3%)
	No	7/12 (58.3%)

(*Continued*)

Table 1 (Continued).

Characteristics		
Laboratory		
Blood work-up		
C-reactive protein	Normal	3/12 (25%)
	N/A	7/12 (58.3%)
D-dimer	Normal	1/12 (8.3%)
	N/A	9/12 (75%)
Procalcitonin	Normal	2/12 (16.7%)
	N/A	8/12 (66.7%)
Leukocytosis	Normal	1/12 (8.3%)
	N/A	10/12 (83.3%)
Antibodies detected	Anti Zic4	1
	Anti-amphiphysin	1
Cerebrospinal fluid work-up		
TCC	Normal	1/12 (8.3%)
	N/A	7/12 (58.3%)
Leukocytes	Normal	1/12 (8.3%)
	N/A	10/12 (83.3%)
WBC	Increased	2/12 (16.7%)
	N/A	9/12 (75%)
Protein level	Normal	6/12 (50%)
	N/A	5/12 (41.7%)
HSV PCR	Negative	7/12 (58.3%)
	N/A	3/12 (25%)
Gram stain culture	Negative	7/12 (58.3%)
	N/A	5/12 (41.7%)
Oligoclonal bands	Present	2/12 (16.7%)
	Absent	5/12 (41.7%)
	N/A	5/12 (41.7%)
COVID-19 PCR	Positive	1/12 (8.3%)
	Negative	5/12 (41.7%)
	N/A	6/12 (50%)

Abbreviations: PCR, polymerase chain reaction; N/A, not applicable; LPV/r, lopinavir/ritonavir; NORSE, new-onset refractory status epilepticus; TCC, terminal complement complex; WBC, white blood cells; HSV, herpes simplex virus.

Table 2 Status Epilepticus Features, Radiological Imaging Findings, and STESS Scores

Types of Status Epilepticus		
NCSE	7/12 (58.3%)	
FMS	1/12 (8.3%)	
MSE	1/12 (8.3%)	
GTCS	1/12 (8.3%)	
N/A	2/12 (16.7%)	
Super refractory	Yes	1/12 (8.3%)
	No	10/12 (83.3%)
Onset setting		
IHO	8/12 (66.7%)	
EHO	4/12 (33.3%)	
COVID-19 symptoms present before SE	Yes	7/12 (58.3%)
	None	4/12 (33.3%)
Fever before SE	Yes	6/12 (50%)
	No	6/12 (50%)
EEG pattern		
GPD	3/12 (25%)	
LPD	1/12 (8.3%)	
BILPDs	2/12 (16.7%)	
GRDA	2/12 (16.7%)	
N/A	4/12 (33.3%)	
STESS score		
0–3	4/12 (33.3%)	
4–6	6/12 (50%)	

Abbreviations: SE, status epilepticus; NCSE, non-convulsive status epilepticus; FMS, focal motor seizure; MSE, motor status epilepticus; GTCS, generalized tonic-clonic seizure; N/A, not applicable; IHO, intra hospital occurrence; EHO, extra hospital occurrence; EEG, electroencephalogram; GPD, generalized periodic discharges; LPD, lateralized periodic discharges; BILPDs, bilateral independent periodic discharges; GRDA, generalized rhythmic delta activity; STESS, status epilepticus severity score.

In this review, the most reported type of status epilepticus was non-convulsive status epilepticus (NCSE), reported in 7 out of 12 patients (58.3%) (Table 2). Five out of twelve patients (41.7%) presented as cryptogenic NORSE (Table 1). Febrile infection-related epilepsy syndrome (FIRES) was reported in 50% (6 out of 12 patients). The mean duration between the start of the status epilepticus and the point of no recurrence was reported in 3 studies as 35.0 ± 34.3 days, ranging from 8 to 90 days in length. Information regarding computerized tomography (CT) scans of the brain was reported to be non-significant in 7 out of 12 patients (58.3%). Calculated scores for status epilepticus severity score (STESS) revealed that half of the population had a score of ≥4. Further variables are shown in Table 2.

Table 3 gives an overview of the management and outcomes reported in the study population. Apart from the treatment mentioned, plasma exchange (2 out of 12 patients, 16.7%), tocilizumab (1 out of 12 patients, 8.3%),

Table 3 Treatment for Status Epilepticus and Outcomes

Treatment for Status Epilepticus		
Lorazepam	Yes	3/12 (25%)
	No	6/12 (50%)
Levetiracetam	Yes	9/12 (75%)
	No	1/12 (8.3%)
Lacosamide	Yes	6/12 (50%)
	No	3/12 (25%)
Phenytoin	Yes	5/12 (41.7%)
	No	5/12 (41.7%)
Diazepam	Yes	2/12 (16.7%)
	No	8/12 (66.7%)
Valproic acid/ Valproate	Yes	7/12 (58.3%)
	No	5/12 (41.7%)
Brivaracetam	Yes	2/12 (16.7%)
	No	9/12 (75%)
Phenobarbital	Yes	2/12 (16.7%)
	No	8/12 (66.7%)
Perampanel	Yes	3/12 (25%)
	No	8/12 (66.7%)
Zonisamide	Yes	1/12 (8.3%)
	No	10/12 (83.3%)
First AEM given		
Levetiracetam	2/12 (16.7%)	
Diazepam	2/12 (16.7%)	
Lorazepam	3/12 (25%)	
Valproic acid/ Valproate	2/12 (16.7%)	
Drugs used for sedation		
Diprivan	1/12 (8.3%)	
Propofol	4/12 (33.3%)	
Midazolam	6/12 (50%)	
Ketamine	1/12 (8.3%)	
Phenobarbital	1/12 (8.3%)	
Thiopentone	1/12 (8.3%)	

(*Continued*)

Table 3 (Continued).

Treatment for Status Epilepticus	
Outcomes	
Discharged	8/12 (66.7%)
Died	2/12 (16.7%)
Still admitted	1/12 (8.3%)

Abbreviation: ASM, antiepileptic medications.

cannabidiol (1 out of 12 patients, 8.3%), ketogenic diet (2 out of 12 patients, 16.7%) and IVIG (8 out of 12 patients, 66.7%) were also reported in the included studies. Duration of IVIG use was reported in 4 studies as 5 days, with 0.4 g/kg dosage administrated in most of the reporting studies (3 out of 12 patients, 25%). Steroids were administered for both COVID-19 and NORSE separately, accounting for 4 out of 12 patients (33.3%) and 6 out of 12 patients (50%), respectively. Overall, two deaths (16.7%) were reported, with eight patients (66.7%) being discharged without complications (Table 3).

A Mann–Whitney U-test for ages between discharged and deceased patients (p=0.114) showed no statistically significant association. Furthermore, the linear regression model showed that the severity of the STESS score was directly proportional to a relationship or positively influenced by the patients' age (p=0.004) and intra-hospital occurrence (IHO) of status epilepticus (p=0.026). At the same time, outcomes (p=0.404) and the total number of antiepileptic medicines used (p=0.071) had no significant influence. In the multiple regression model, the patients' age and IHO of status epilepticus were not statistically significant to the severity of the STESS score. A summary of all the included cases can be found in Supplemental Table 3.

Discussion

This systematic review highlights the data comprised of 11 articles on NORSE secondary to COVID-19 amongst patients, which were selected to review the significant clinical features, treatments, and outcomes. Patients' demographics show that the percentage of males was equal to females (50%); however, there has been proclaiming female predominance.[10] Mean age in all patients was 61.6 (± 19.0) years, where the youngest age was 23, and the oldest was 81. Several articles have proclaimed older age groups beyond 60 to be at high risk of NORSE.[10–12]

Unlike the literature, NCSE has been a common finding seen amongst 58.3% of patients, whereas in NORSE the most common type of seizure seen is FMS, which was present in just 1 (8.3%) patient from our cohort. NCSE is the absence of any prominent motor signs sparing the minor abnormal repetitive movements. Fever, which is present in as many as 2/3 of patients with NORSE,[13] was present in 6 (50%) of patients included in our study, which is in line with published literature. Further work can be done to consider the incidence of COVID-19 on worsened respiratory health. The patient outcome revealed the duration of initial diagnosis of status epilepticus to full recovery was 35.0 days (± 34.3 days). STESS scores are ≥4 in 50% of patients; whilst this is commonly recognized to lean more towards survival, many factors like age, medication, and in-hospital stay influence mortality.[14,15] CAT scanning had no significant findings seen in patients that showed neural structures had stability. Patient treatments were antibiotics, plasma exchange, and Intravenous Immunoglobulin (IVIG). IVIG was the most common method of treatment for NORSE (66.7%) reported to have comprised deficiency in immunity and prevent progression of clinical symptoms, as no specific treatment for NORSE exists. We have created an algorithm to depict the management and treatment plan for patients with NORSE (Figure 2). As many as half of the patients with NORSE have an underlying trigger, which could be infectious, autoimmune, or paraneoplastic in etiological nature, the consensus is to initiate immunotherapies at the earliest to prevent the progression of the illness.[16–19,22,23] It must be noted that 2 deaths occurred out of the 8 patients using IVIG as treatment, but these patients had underlying co-morbid, which could be a contributing factor to mortality.

STESS score severity was statically found to be influenced by age and intra-hospital occurrence (IHO) separately. Studies state old, aged patients are at high risk for epileptic seizures and other neurological complications due to
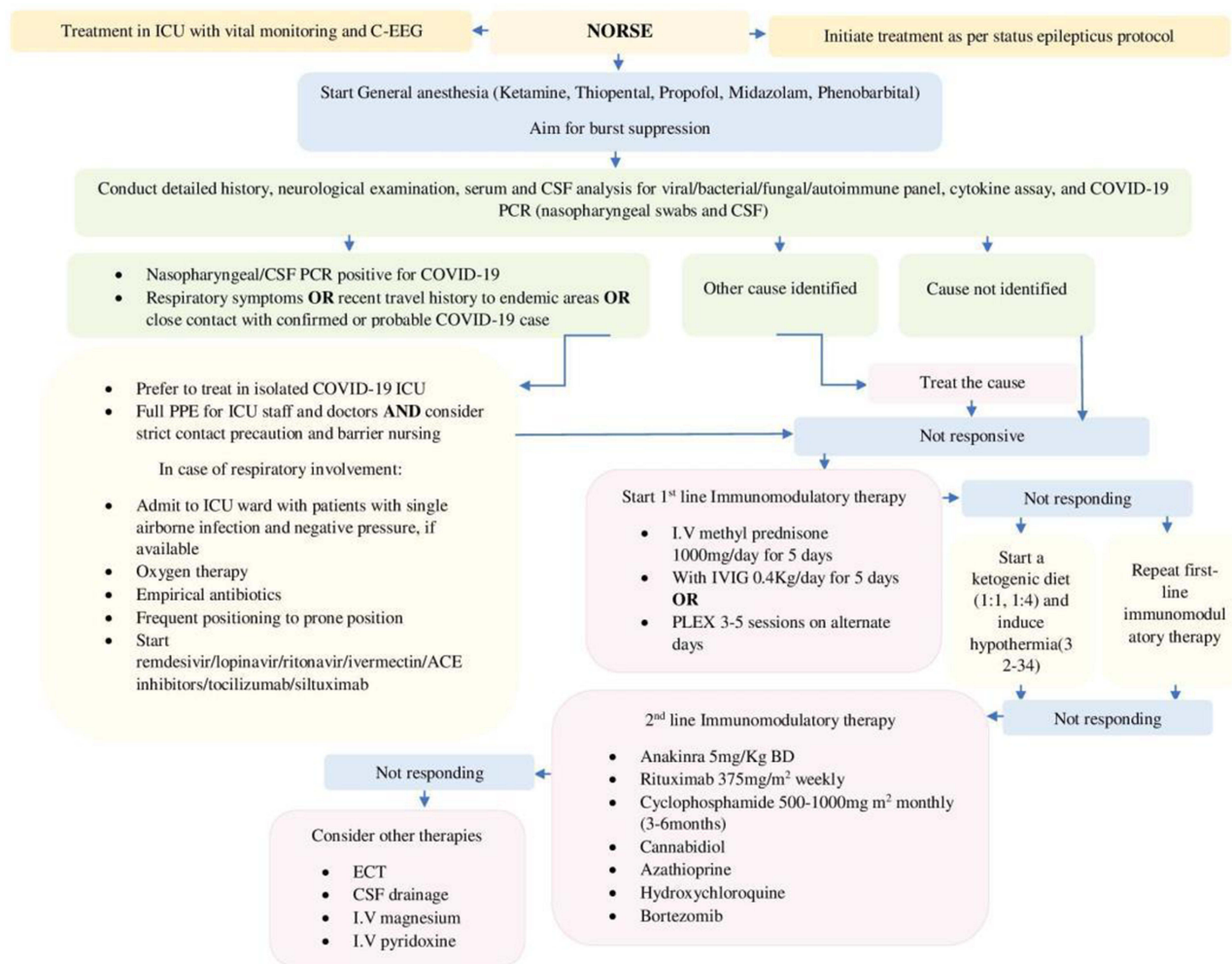
Figure 2 Algorithm for management for patients with NORSE secondary to COVID-19.

progressive neurodegenerative diseases, development of tumors, and are prone to shock and trauma injuries.[10,14,15,20,21] IHO can be explained as a factor that increases STESS score as exposure to the etiological causes of seizures, epilepsy, and NORSE are seen to be encephalitis and meningitis. Further lack of physical movement causes vascular complications and ischemic states, leading to irregularities in cerebral blood flow.[19,20,24,25]

Strengths and Limitations

The investigation of numerous huge databases using a comprehensive search method is one of the merits of this systematic study. The protocol was registered with PROSPERO, and PRISMA requirements were followed for methodological precision. Moreover, this systematic review synthesizes the most recent evidence of NORSE secondary to COVID-19 infection. We compiled and synthesized data on symptomatology, findings associated with the condition in laboratory and radiological tests, frequently used treatment modalities, and prognosis. The findings of this study make it an informative piece for healthcare professionals across the world, as it facilitates evidence-based healthcare and reduces variances in healthcare delivery during the COVID-19 pandemic.

Our study's limitations include a comparatively smaller sample size, which could be due to the difficulty in classifying a refractory status epilepticus as NORSE, as multiple detailed investigations are to be run to confirm no metabolic, toxic, or structural reason for RSE in the patient. Some cases included in this study were not published under the diagnosis of NORSE but fulfilled the criteria, which could signify a lack of awareness of this rare disease. In addition,

in most cases, the investigations performed were extremely variable due to which significant associations between findings were difficult to deduce. SARS-COV-2 PCR analysis on CSF and a CSF and serum autoimmune panel was not done in all cases, which prevented us from determining the underlying cause and perhaps led to an overestimation of the percentage of NORSE that is cryptogenic.

Conclusion

The findings of this systematic review include demographics, symptomatology, diagnostic procedures, and clinical outcomes of adult patients who acquired NORSE because of COVID-19 infection. Patients with and without respiratory symptoms were both subjected to NORSE. NCSE was the most prevalent kind of SE reported. Along with instances of cryptogenic NORSE, other possible etiologies have been documented. In every case, many ASM were tried, but immunomodulating medications proved to be the most effective in curing the patient to the point of no recurrence.

Data Sharing Statement

All relevant data are available within the article and the Supplemental Table files.

Ethical Approval

This study did not require any ethical approval being a systematic review of publicly available data.

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Disclosure

The authors report no conflicts of interest in this work.

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