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Research Article

New-Onset Refractory Status Epilepticus Caused by Autoimmune Encephalitis May Have a Better Prognosis than when due to Other Causes

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Objective. To explore whether the new-onset refractory status epilepticus caused by autoimmune encephalitis has a better prognosis. *Methods*. This retrospective observational study enrolled patients with NORSE who were admitted from January 2015 to February 2024. The clinical data and clinical outcomes of the patients were collected and analyzed, and the primary outcome was seizures still at follow-up. Statistical analyses were performed using SPSS software V.22.0. *Results*. Among the 42 patients with NORSE, 15 (35.7%) had autoimmune encephalitis (AE), 3 (7.1%) patients had central nervous system infections, 24 (57.1%) patients had an unknown etiology, and 4 (9.5%) patients died in the hospital. Modified Rankin scale (MRS) scores at discharge of NORSE patients in the autoimmune encephalitis group and non-AE group were compared ($P = 0.339$). After 4 years of follow-up, analysis of patients who still had seizures showed that the only risk factor was etiology and that patients with nonautoimmune encephalitis etiology were more prone to later epilepsy ($P = 0.030$ (OR = 16.767, 95% CI: 1.454-213.395)). The MRS scores of the AE group and non-AE group were compared ($P \leq 0.001$), with the autoimmune group having a better functional outcome. *Significance*. The overall prognosis of patients with autoimmune encephalitis may be better than that of patients with other etiologies, and later epilepsy is more likely in patients with nonautoimmune encephalitis. However, this result requires further validation in larger studies with more data.

1. Introduction

New-onset refractory status epilepticus (NORSE) describes refractory status epilepticus (RSE) in patients with no history of seizure [1]. Febrile infection-related epilepsy syndrome (FIRES) is considered a subcategory of NORSE rather than a separate entity, as previously stated. The diagnosis of FIRES requires RSE with a history of fever between 2 weeks and 24 hours before onset (with or without fever at the onset of status epilepticus) [2]. NORSE refers to an unexplained clinical manifestation or syndrome, rather than a specific disease diagnosis, occurring in inactive epilepsy or prerelated neurological disorders without a clear acute or active structural, toxic, or metabolic cause [3]. However, specific viral infections (e.g., herpes simplex virus-1) and new-onset autoimmune syndromes should be considered [4]. The incidence of NORSE is approximately 6–12 per 1,000,000 people per year, and it can occur at all ages, but mainly in adulthood. In adult cases, there are more females, but in children, males are more common [5]. NORSE is a severe neurologic emergency condition characterized by high morbidity and mortality, poor functional outcomes, and high hospitalization costs [6].

NORSE usually has a history of febrile infection before the onset of symptoms and presents with persistent seizure activity with confusion, cognitive impairment, and focal neurological signs [7]. NORSE is a clinical syndrome with more than 20 different etiologies, up to 52% remain cryptogenic

[8]. The most commonly identified etiologies include autoimmune (19%), paraneoplastic encephalitis (18%), or those associated with infection (8%) [9]. Antibodies directed against neuronal cell surface antigens are directly pathogenic, and they include antibodies against the N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1), and γ-aminobutyric acid B receptor (GABABR) [2]. Antithyroid peroxidase, myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, acute disseminated encephalomyelitis, and encephalitis associated with systemic lupus erythematosus can also cause the development of NORSE [2]. Genetic and congenital disorders can also have a causative role in NORSE [2]. A previous study found that cases of cryptogenic NORSE persisted longer than those with established etiology [10]. Postinfection cytokine-mediated disorders may be determined by a genetic trait, but there is still a lack of corresponding mechanisms that can explain all manifestations [11].

NORSE is a relatively uncommon disorder, and these patients typically require long-term intensive care, often remain functionally disabled, including long-term chronic care, and are at significant risk of death [12]. However, some patients have good outcomes, even after prolonged status epilepticus, so patients need prompt examination and treatment [13]. Current mainstays of treatment include sedatives and antiseizure medications combined with other treatment modalities, including a ketogenic diet [14]. Although the evidence is limited, early attempts to alter the putative underlying pathogenesis through immune modulation are appropriate, and recent studies have found that interleukin inhibitors can be used [15].

At present, there are few studies on NORSE studying case characteristics and prognosis in more detail. The purpose of this study was to collect relevant cases of NORSE and analyze their characteristics and responses to treatment to help guide medical staff's diagnosis and treatment decisions.

2. Methods

We first retrospectively reviewed the clinical information of 320 patients with status epilepticus (SE) at West China Hospital and Chengdu Shang Jin Nan Fu Hospital between January 2015 and February 2024. Then, the patients were screened according to the characteristics of their onset time and whether they had a first onset. This study included a total of 42 patients with NORSE who presented clinical data, including the mode of onset of symptoms, clinical presentation (e.g., fever, headache, or psychobehavioral alterations before the onset of seizure or SE), neurological assessments, and conventional tests including brain MRI, electroencephalography (EEG), and cerebrospinal fluid (CSF) examination. This study was approved by the Research Ethics Committee of the West China Hospital of Sichuan University; the approval number is 2019 (936). Written informed consent was obtained from all participants or their direct relatives.

All patients were diagnosed according to the International League Against Epilepsy's (ILAE) most recent diagnostic criteria for status epilepticus [16]. NORSE may be considered as a separate subtype of RSE and SRSE [12]. We identified NORSE patients using the First International NORSE and FIRES symposium criteria: "a clinical presentation in a patient without active epilepsy or other preexisting relevant neurologic disorder, with new onset of refractory SE, without a clear acute or active structural, toxic, or metabolic cause" [12]. FIRES is "a subset of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to the onset of refractory status epilepticus, with or without fever at the onset of SE" [12].

The primary outcome was seizures still at follow-up, and the follow-up period was 0.5-7 years. Later epilepsy is defined as persistent seizures after a patient is treated with adequate immunotherapy and other causes and has no significant evidence of inflammatory activity [17, 18]. Secondary outcomes were MRS scores at hospital discharge and follow-up. The results were obtained through regular telephone follow-up and outpatient follow-up, and some patients need to be readmitted to the hospital. The following seizure outcomes were collected: presence, timing, duration, number, and EEG pattern of seizures and presence, location (focal, multifocal, lateralised, or generalized), and pattern of interictal paroxysmal and nonparoxysmal EEG anomalies. Patients' follow-up had an EEG review semiannually.

All investigators were trained and certified to assess the MRS. Neurological deficit was assessed by a neurologist according to scores on the MRS at enrollment and discharge, 1 month, and 3 months, and the outcome was graded according to the MRS. Functional outcome was assessed on the MRS (MRS score range 0–6, with 0 indicating no symptoms and 6 indicating death) at 3 months by a face-to-face interview conducted by a neurologist and at 6 and 12 months by a standardized and validated telephone interview conducted. Good or better outcomes were defined as MRS 0-3, and poor outcomes were defined as MRS 4-6.

The inclusion criteria were as follows: (1) patients were included in this study if they met the definition of NORSE, (2) age 14 years or older, and (3) SE refractory to appropriate doses of 2 lines of antiseizure treatment.

Exclusion criteria were RSE by the study investigator to be secondary to trauma, vascular malformation, ischaemic stroke, electrolyte disturbances, or tumor; current use of antiseizure drugs or history of epilepsy; pregnancy or breastfeeding; previous history of severe depression or psychotic disorder; and known terminal illness.

Based on the etiologies, patients with NORSE were divided into two groups: the autoimmune encephalitis (AE) group and the non-AE group. The diagnostic criteria for all autoimmune encephalitis patients were performed in a Chinese expert consensus on the diagnosis and management of AE (2022 edition) [19]. The diagnosis of AE requires a comprehensive analysis of the clinical findings, cerebrospinal fluid examination, neuroimaging and electroencephalography, and the exclusion of other etiologies. (A) Clinical manifestations are acute or subacute onset (<3 months) with 1 or more neurological and psychiatric symptoms, including recent memory loss, seizures, and mental behavior abnormalities; (B) neuroimaging or EEG abnormalities; (C) CSF or serum was positive for antineuronal antibodies, including NMDAR, LGI1, $GABA_BR$, CASPR2, IgLON5, AMPAR,

DPPX, $GABA_AR$, mGLluR5, GAD, AK5, Hu, CV2, and Ma2; and (D) reasonable exclusion of other causes. The clinical features were compared between the two groups, including sex, age, symptoms preceding the onset of NORSE (e.g., fever, headache, psychobehavioral, or memory alterations), mechanical ventilatory support, CSF finding, brain MRI pattern, presence of tumor, cost, and MRS. Psychobehavioral or memory alterations or fever that developed after the onset of NORSE was not included in the clinical features. In this study, we focused on the etiology of the acute stage of NORSE; thus, we did not assess the response to conventional immunotherapy or long-term outcomes.

All AE patients received immunotherapy treatment, including methylprednisolone (1000 mg ×5 d), or intravenous immunoglobulin (IVIg, 0.4 g/kg/d ×5 d), or immunosuppressants, or both.

Statistical analyses were performed using SPSS software version 22.0. Data were expressed as medians with interquartile range (IQR) or as proportions. Fisher's exact test was performed for comparison of categorical variables, and the Mann–Whitney test was used for continuous variables. P values < 0.05 were considered statistically significant. Risk factor screening for NORSE patients still having seizures (later epilepsy) was performed using the Pearson χ^2 test by univariate analysis, and $P < 0.05$ was statistically significant. Multivariable analyses were performed with a binary logistic regression model in which each variable with a P value of < 0.05 (based on the univariate analysis) was entered into the model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The significance level α was set to 5%. Hence, P values < 0.05 were regarded as statistically significant. The treatment effect on the MRS score at discharge and at follow-up was evaluated for the two groups using multivariable ordinal regression analysis. The reported OR expresses the odds of having a better outcome (i.e., a lower MRS score).

3. Results

The clinical features of 42 patients with NORSE are shown in Table 1. The etiology of 15 (35.7%) of these patients was autoimmune encephalitis, 3 (7.1%) patients had central nervous system (CNS) infections, and 24 (57.1%) patients had an unknown etiology. Three (7.1%) acute CNS infections included 2 (4.8%) herpes simplex virus infections and 1 (2.4%) cytomegalovirus infection. Among the 42 NORSE patients, 19 (45.2%) were female, with an average age of 38.24 ± 20.83 years, an average hospital stay of 36.71 ± 63.53 days, and an average total cost of 217.85 ± 131.67 thousand yuan. Of the 42 NORSE patients, 3 (7.1%) had tumors (1 had oophoroma, 2 had lung cancer), 15 (35.7%) had fever within 24 hours before seizure, 18 (42.9%) had abnormal head MRI, 33 (78.6%) had abnormal EEG, and 26 (61.9%) required mechanical ventilation. The median MRS score at admission was 5, the median Glasgow score was 6, and the median MRS score at discharge was 2. Twenty-four patients received intravenous injection (IV) methylprednisolone, 19 (45.2%) received IV immunoglobulin, and four received immunosuppressants. Among them, 6 (14.3%) patients received more than 3 immunotherapy treatments, and 36 (85.7%) patients were treated with 3 or more antiseizure medications. Four patients died in the hospital, 17 (40.5%) patients improved and went home, and 21 (50.0%) patients were transferred to other hospitals to continue to observe the treatment effect and rehabilitation treatment.

Among the 15 fever patients, 7 were female, with an average age of 25.79 ± 9.44 years, an average hospital stay of 61.60 ± 98.38 days, and a total cost of 594.06 ± 220.19 thousand yuan. Compared with patients with NORSE due to other causes, patients with AEs had higher costs and longer hospital stays. All 15 patients were treated with IV methylprednisolone, 12 patients were treated with IV immunoglobulin, and 12 patients were treated concurrently. None of the 15 patients died, 9 patients went home, and 6 patients went to other hospitals to continue their rehabilitation, with a median MRS score of 2 at the time of discharge.

Of the 42 patients included in the study, 4 patients died in the hospital, 2 males and 2 females, 2 patients over 90 years old, 3 patients with unknown etiology, and 1 patient due to acute CNS infection. All seizure types were convulsive status epilepticus, and 1 patient required tracheal intubation and was admitted to the ICU. All 4 patients were complicated with pulmonary infection during hospitalization, and 2 patients over 90 years old suffered from hypertension and diabetes at the same time. The cause of death in 4 patients was heart failure in 2 patients, respiratory failure in 1 patient, and brain herniation in 1 patient (Supplemental material (available here)).

After 4 years of follow-up, 36 of the 38 patients at discharge were enrolled in the follow-up study, 1 patient was lost to follow-up, and 1 patient died during follow-up. At follow-up, 14 patients still had seizures, 4 of them had autoimmune encephalitis, and the median MRS score was 2. As can be seen in Table 2, analysis of patients who later developed epilepsy found that the only risk factor was etiology, and patients with nonautoimmune encephalitis etiology were more likely to develop later epilepsy ($P = 0.030$ (OR = 16.767, 95% CI: 1.454-213.395)). The MRS score at the time of discharge and follow-up was analyzed for risk factors. The P values were all > 0.05, and no clear risk factors were found (Tables 3 and 4).

Comparison of MRS scores at discharge and follow-up of NORSE patients in the AE group and non-AE group showed that the OR value and 95% CI at discharge were 1.46 (0.68-3.13), and the P value was 0.339. After 0.5-7 years of follow-up, the MRS scores of the two groups were compared; the OR value and 95% CI were 0.28 (0.14-8.59), and the P value was ≤ 0.001, which was statistically significant (Tables 5 and 6), with the autoimmune group having better functional outcome.

4. Discussion

In our population of 320 patients with status epilepticus, 42 patients had NORSE, and the etiology of the majority of patients was unknown (52.4%), which is consistent with the results of previous studies [20]. NORSE patients with

Table 1: Normal information and clinical data of all patients.

	Total (%)	AE (%)	Non-AE (%)	*P* value
N	42	15	27	—
Female/male	19/23 (45.2/54.8)	7/8 (46.7/53.3)	12/15 (44.4/55.6)	0.048
Age (year)	38.24 ± 20.83 (14-91)	25.79 ± 9.44 (14-48)	39.32.±21.49 (14-91)	0.23
Hospital stays (day)	36.71 ± 63.53 (5-401)	61.60 ± 98.38 (15-401)	33.71 ± 62.58 (5-397)	0.003
Etiology				
AE	15 (35.7)	15 (100)	—	—
NMDAR	10 (23.8)	10 (66.7)	—	—
LGI1	3 (7.1)	3 (20)	—	—
$GABA_BR$	2 (4.8)	2 (13.3)	—	—
CNS infection, acute	3 (7.1)	—	3 (11.1)	—
Unknown	24 (57.1)	—	24 (88.9)	—
Cost (thousand RMB)	217.85 ± 131.67	594.06 ± 220.19	1867.45 ± 101.63	0.009
Direct nonmedical	6.35 ± 8.72	7.23 ± 9.32	6.25 ± 8.96	0.012
Professional care	7.77 ± 19.75	17.27 ± 31.22	7.23 ± 23.26	0.016
Direct medical	69.02 ± 178.78	79.03 ± 168.63	65.42 ± 173.76	0.047
Immunotherapy	25.68 ± 36.41	38.84 ± 30.18	25.68 ± 36.41	0.001
SE type				
CSE	30 (71.4)	11 (73.3)	19 (70.4)	0.005
Tumor	3 (7.1)	3 (20)	0	—
Oophoroma	1 (2.4)	1 (6.7)	0	—
Lung cancer	2 (4.8)	2 (13.3)	0	—
Fever occurred 24 hours before the seizure	15 (35.7)	7 (46.7)	8 (29.6)	0.064
MRI, abnormality	18 (42.9)	4 (26.7)	14 (51.9)	0.537
Diffusion restriction	4 (9.5)	4 (26.7)	0	—
Temporal/hippocampal T2 hyperintensities	12 (28.6)	10 (66.7)	2 (7.4)	—
Meningeal enhancement	5 (11.9)	2 (13.3)	3 (7.1)	—
Psychosis	21 (50.0)	12 (80)	9 (33.3)	1.000
EEG, abnormality	33 (78.6)	11 (73.3)	22 (81.5)	≤0.001
Burst suppression	5 (11.9)	3 (20)	2 (7.4)	—
LPDs	12 (28.6)	4 (26.7)	8 (29.6)	—
ASIDs	7 (16.7)	2 (13.3)	5 (18.5)	—
GPDs	9 (21.4)	2 (13.3)	7 (25.9)	—
Mechanical ventilation	26 (61.9)	10 (66.7)	16 (59.3)	0.732
Non-invasive ventilator	12 (28.6)	4 (26.7)	8 (29.6)	0.264
ICU admission	10 (23.8)	3 (20)	7 (26.0)	0.001
ICU hospital stays (day)	59.40 ± 93.81 (7-307)	153.33 ± 142.39 (26-307)	53.42 ± 87.76 (7-286)	0.051
MRS on admission, median (IQR)	5 (4-5)	5 (4-5)	5 (4-5)	0.438
Glasgow on admission, median (IQR)	6 (4-14)	7 (5-14)	6 (4-14)	0.438
MRS at discharge, median (IQR)	2 (0-6)	2 (0-5)	2 (0-6)	0.442
Complication	35 (83.3)	12 (80)	23 (92.6)	≤0.001
IV methylprednisolone	24 (57.1)	15 (100)	9 (33.3)	0.355
IV immunoglobulin	19 (45.2)	12 (80)	7 (25.9)	0.537
Immunosuppressant	4 (9.5)	3 (20)	1 (3.7)	≤0.001
IVMP and IVIG	13 (31.0)	9 (60)	4 (14.8)	0.006
2 IVIG	7 (16.7)	3 (20)	4 (14.8)	≤0.001
≥3 Immunotherapy	6 (14.3)	3 (20)	3 (11.1)	≤0.001
≥3 ASMs	36 (85.7)	14 (93.3)	22 (81.5)	≤0.001

Table 1: Continued.

	Total (%)	AE (%)	Non-AE (%)	*P* value
Parenteral feeding	22 (52.4)	9 (60)	13 (52)	0.758
Antiviral therapy	26 (61.9)	13 (86.7)	13 (52)	0.123
Antibiotic drugs	32 (76.2)	12 (80)	20 (74)	0.001
Antifungal drugs	6 (14.3)	2 (13.3)	4 (14.8)	≤0.001
Cerebrospinal fluid				
Trace proteins (g/ml), median (IQR)	0.49 ± 0.58	0.34 ± 0.22	0.51 ± 0.61	0.064
Nucleated cells $\times 10^6$/L, median (IQR)	35 (0-189)	6 (0-10)	45 (0-189)	0.035
Pleocytosis (>5 wbc)	23 (54.8)	7 (46.7)	16 (59.3)	0.234
Discharge disposition				0.123
Home	17 (40.5)	9 (60)	8 (29.6)	—
Other hospital	21 (50)	6 (40)	15 (55.6)	—
Inpatient death	4 (0.10)	0 (0.0)	4 (14.8)	—
Follow-up years (year)	4	4	4	—
Number of patients of follow-up	36 (85.7)	15 (100)	21 (77.8)	—
Epilepsy at follow-up	14 (33.3)	4 (26.7)	10 (37)	0.252
Still on antiseizure medications at follow-up	20 (47.6)	6 (40)	14 (51.9)	0.067
MRS at follow-up, median (IQR)	2 (0-5)	1(0-3)	2 (0-5)	0.014

AE: autoimmune encephalitis; ICU: intensive care unit; SE: status epilepticus; EEG: electroencephalogram; EEG, abnormality including burst suppression (spontaneous), lateralized periodic discharges (LPDs), after status ictal discharges (ASIDs), and generalized sharply and/or triphasic periodic potentials (GPDs); MRI: magnetic resonance imaging; CNS: central nervous system; CSE: convulsive status epilepticus; NCSE: nonconvulsive status epilepticus; IQR: interquartile range; MRS: modified Rankin scale; IV: intravenous injection; IVIG: IV immunoglobulin; IVMP: IV methylprednisolone; ASM: antiseizure medications; RMB: renminbi; wbc: white blood cell; MRS: modified Rankin scale. Complication refers to the symptoms of pulmonary infection, gastrointestinal bleeding, abnormal liver function, and cardiac insufficiency during hospitalization.

Table 2: Analysis of risk factors associated with later epilepsy at follow-up in patients with NORSE.

	Data	*P* value	OR	95% CI
Male	6	0.116	7.278	0.442-119.835
Etiology (AE)	4	0.030	16.767	1.454-213.395
Glasgow score < 8 points on admission	8	0.318	4.965	0.213-115.596
Mechanical ventilation	10	0.332	4.622	0.059-641.192
MRI abnormal	7	0.812	0.759	0.078-7.401
EEG abnormal	9	0.155	0.090	0.003-2.487
Pneumonia	9	0.056	0.032	0.001-0.946
Complication	12	0.063	0.004	0.013-0.927
Immunotherapy	13	0.410	4.119	0.142-119.770
≥3 ASMs during hospital	11	0.118	0.014	0.002-2.989
Parenteral feeding	8	0.317	5.471	0.197-152.151

OR: odds ratios; CI: confidence intervals; MRI: magnetic resonance imaging; MRI abnormal: abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke); EEG: electroencephalograms; EEG abnormal: focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms; ASMs: antiseizure medications; AE: autoimmune encephalitis. Complication refers to the symptoms of pulmonary infection, gastrointestinal bleeding, abnormal liver function, and cardiac insufficiency during hospitalization.

autoimmune encephalitis had no in-hospital deaths, and patients with autoimmune encephalitis had better long-term outcomes than patients with other or unexplained NORSE [21]. Convulsive status epilepticus was the seizure type in 30 of 45 NORSE patients, and a higher proportion of autoimmune encephalitis patients had convulsive status epilepticus [22].

NORSE patients have higher hospitalization costs and longer hospital stays, and the economic burden on both patients and the health care system is heavy in China [23]. Simultaneously, our research found that the nonmedical direct costs were much lower than the direct medical costs, consistent with the findings of a recent Canadian study on epilepsy [24]. The non-AE patients have worse outcomes

Table 3: Analysis of risk factors associated with MRS score at the time of discharge in patients with NORSE.

	Data	*P* value	OR	95% CI
Male	23	0.070	0.071	0.004-1.239
Etiology (AE)	15	0.484	0.389	0.028-5.480
Glasgow score < 8 points on admission	21	0.130	8.102	0.540-121.549
Mechanical ventilation	26	0.101	0.066	0.003-1.704
MRI abnormal	18	0.404	0.408	0.303-1.704
EEG abnormal	33	0.717	0.653	0.065-6.533
Pneumonia	31	0.736	1.840	0.053-63.402
Complication	33	0.187	6.962	0.391-124.007
Immunotherapy	40	0.132	3.285	0.105-61.668
≥3 ASMs during hospital	36	0.742	1.713	0.070-41.999
Parenteral feeding	22	0.422	0.400	0.043-3.746

OR: odds ratios; CI: confidence intervals; MRS: modified Rankin scale; MRI: magnetic resonance imaging; MRI abnormal: abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke); EEG: electroencephalograms; EEG abnormal: focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms; ASMs: antiseizure medications; AE: autoimmune encephalitis. Complication refers to the symptoms of pulmonary infection, gastrointestinal bleeding, abnormal liver function, and cardiac insufficiency during hospitalization.

Table 4: Analysis of risk factors associated with MRS score at follow-up in patients with NORSE.

	Data	*P* value	OR	95% CI
Male	20	0.579	0.368	0.011-12.566
Etiology (AE)	15	0.630	0.767	0.454-13.475
Glasgow score < 8 points on admission	17	0.666	0.636	0.044-12.566
Mechanical ventilation	22	0.471	3.299	0.133-78.429
MRI abnormal	14	0.567	3.464	0.049-243.149
EEG abnormal	28	0.593	2.294	0.109-48.295
Pneumonia	26	0.174	0.135	0.108-1.898
Complication	29	0.263	0.304	0.216-8.954
Immunotherapy	35	0.312	3.175	0.248-79.720
≥3 ASMs during hospital	30	0.568	0.414	0.307-28.347
Parenteral feeding	17	0.434	0.268	0.010-7.244

OR: odds ratios; CI: confidence intervals; MRS: modified Rankin scale; MRI: magnetic resonance imaging; MRI abnormal: abnormalities in the marginal system T2 or FLAIR, unilateral or bilateral, or other areas of T2 or FLAIR abnormalities (except specific white matter changes and stroke); EEG: electroencephalograms; EEG abnormal: focal epilepsy or epileptiform discharges, or diffuse or multifocal distribution of slow wave rhythms; ASMs: antiseizure medications; AE: autoimmune encephalitis. Complication refers to the symptoms of pulmonary infection, gastrointestinal bleeding, abnormal liver function, and cardiac insufficiency during hospitalization.

Table 5: Endpoints at discharged and at follow-up.

	AE group	Non-AE group	*P* value
Lower MRS scale people, *n* (%) at			
Discharged	9/15 (60)	19/27 (70.4)	0.442
At follow-up	13/15 (86.7)	17/21 (80.9)	0.014
Later epilepsy, *n* (%) at			
At follow-up	4/15 (26.7)	10/21 (37)	0.252
Anti-seizure medications at			
Discharged	15/15 (100)	27/27 (100)	Ref.
At follow-up	6/15 (40)	14/21 (66.7)	0.067

AE: autoimmune encephalitis; lower MRS scale: better outcomes were defined as MRS 0-3.

Table 6: ORs for a lower MRS scale (better outcomes were defined as MRS 0-3) at discharged and at follow-up.

	Total	Lower MRS scale people (%)	Unadjusted OR (95% CI)	*P* value
Discharged				
AE group	15	9 (60)	1.46 (0.68-3.13)	0.339
Non-AE group	27	19 (70.4)	Ref.	
At follow-up				
AE group	15	13 (86.7)	0.28 (0.14-8.59)	≤0.001
Non-AE group	21	17 (80.9)	Ref.	

OR: odds ratios; CI: confidence intervals; AE: autoimmune encephalitis; MRS: modified Rankin scale.

with regard to seizures, but the median hospital stay is half that of the AE patients. The reason is that AE patients use immunotherapy earlier, and part of the reason may be that AE patients receive more care. Almost all patients in our study used immunotherapy, but immunotherapy is often not covered by health insurance, imposing a heavy economic burden on patients [25]. We compared autoimmune encephalitis patients with other patients and found that autoimmune encephalitis patients have higher costs, which may be related to the use of one or more immunotherapies in autoimmune patients, and some patients even use multiple immunotherapies of the same type [26]. Moreover, patients with autoimmune encephalitis need their cerebrospinal fluid re-examined multiple times, and antibody testing is relatively expensive [27].

Thirty-three (78.6) patients had abnormal EEG, including focal and/or multifocal SE, and generalized periodic epileptiform discharges. Five patients failed to complete the EEG examination due to severe convulsions at the time of the seizure, and 4 patients had terminated the seizure in the emergency department, but the current conditions of our hospital prevented them from completing the EEG. There is no comparable study among adults. Most series reported periodic discharges and multiple seizure patterns. 18 (42.9) patients had brain MRI abnormalities, including diffusion restriction and temporal/hippocampal T2 hyperintensity, which were consistent with previous findings by Gaspard et al. Previous studies have shown that 43% of NORSE patients initially had meningeal enhancement and 58% of NORSE patients developed hippocampal and cortical atrophy, which was associated with poor functional outcomes [28].

The pathogenesis of NORSE is still unclear; it may be a burst infection response in the central nervous system, and it may be that T lymphocytes, perivascular cells, and glial activation products accumulate and burst within a few days, which may explain some patients with SE being preceded by fever [29]. Some studies have shown that the case basis of NORSE may be caused by immune activation mechanisms or whether early use of immunotherapy at home will lead to better outcomes for patients, which needs more research to be confirmed [30].

In our study, 4 patients died in the hospital. None of the 4 patients had autoimmune encephalitis, and the cause of death was more related to the underlying disease. Another patient died during the follow-up period. The cause of death was the recurrence of status epilepticus 1 month after the patient was discharged from the hospital, and it was difficult to control secondary respiratory failure. The symptoms were still not relieved by treatment.

Analysis of the patient's primary and secondary outcomes identified that the only risk factor for seizures at follow-up was etiology, and patients with AE had a lower risk of symptomatic seizures than non-AE. This may be because the seizures of autoimmune encephalitis are usually controlled after the autoimmune encephalitis has improved, and there is no persistence. The main pathological mechanism of acute symptoms secondary to AE is the specific binding of antigens on the surface or inside of nerve cells with antibodies, leading to changes in cell electrical activity and synaptic function, which leads to seizures. The function of antigens can be gradually restored after the removal of antibodies, so immunotherapy can achieve good therapeutic effects.

Comparing the long-term follow-up prognosis of the AE group and the non-AE group, the long-term prognosis of the AE group was better. The better long-term prognosis in the AE group may be related to the earlier use of immunotherapy. A systematic review of autoimmune encephalitis variables found that delaying immunotherapy leads to worse outcomes. The hypothesis of the immune/inflammatory pathogenesis of NORSE has prompted the use of immunomodulatory drugs [31]. First-line drugs usually include intravenous corticosteroids, intravenous immune globulin, and plasma exchange. Second-line drugs include cyclophosphamide, rituximab, tocilizumab (IL-6 inhibitor), and anakinra (IL-1 inhibitor), with a more recent focus on interleukin inhibitors [32]. While NORSE is infrequently studied, treatment of NORSE is very challenging, and many factors may delay treatment, including regulatory and funding barriers [33, 34]. While research suggests that immune modulation should be started early, there is no high-quality published evidence to support this strategy [3, 35].

Our study has several key limitations. First, our study was small and retrospective at a single center with variability in diagnostic work-up and management. Second, a brain MRI is often difficult to obtain in a ventilated patient with NORSE or cannot be performed on a patient with contraindications (e.g., implanted pacemakers and iron-based metal implants). Third, a clear seizure EEG was not obtained for some patients due to obvious convulsions during seizures. And no continuous EEG monitoring was performed, and the EEG monitoring lasted from half an hour to 24 hours. The reason is that some critical patients need to use

electrocardiograph monitoring and ventilator equipment, which will affect the EEG results. Another reason is the instrument, the number of mobile EEGs is less, the fixed video EEG bedside does not have rescue conditions, and the fixed video EEG number can not meet the patients with continuous EEG monitoring. Fourth, the data on the patients who died were few, and they were older, which did not represent the characteristics of the overall population. Fifth, the follow-up of this study was a cross-sectional study, and the follow-up time of each patient was inconsistent, which may affect the results.

5. Conclusions

The incidence of NORSE in patients with status epilepticus was 16.67%, and the mortality rate was 9.5%. NORSE due to autoimmune encephalitis seems to have a better prognosis, but more studies are needed to support this view and to verify whether early immunotherapy helps to avoid adverse outcomes.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

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Supplementary Materials

Table 7: Normal information and clinical data of death patients. *(Supplementary Materials)*

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