Brain magnetic resonance imaging predictors in anti-N-methyl-D-aspartate receptor encephalitis

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Abstract
Objective: Brain magnetic resonance imaging (MRI) findings in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis are nonspecific and rarely have obvious associations with clinical characteristics and outcomes. This study aimed to comprehensively describe the MRI features of patients with NMDAR encephalitis, examine their associations with clinical characteristics, and evaluate their predictive power for disease recurrence and prognosis.

Methods: We retrospectively extracted the clinical data and brain MRI findings of 144 patients with NMDAR encephalitis. Patients underwent a 2-year follow-up to assess disease outcomes. We evaluated the associations of brain MRI findings at the onset with clinical characteristics, recurrence, and prognosis.

Results: Initial MRI showed typical abnormalities in 65 patients (45.1%); of these, 34 (29.3%) developed recurrence and 10 (9.4%) had poor prognosis (mRS ≥3). Binary logistic regression analyses revealed that insula abnormalities were associated with acute seizure (odds ratio [OR] = 3.048, 95% confidence interval [CI]: 1.026–9.060) and white matter lesions were associated with cognitive impairment (OR = 2.730, 95% CI: 1.096–6.799). Risk factors for a poor 2-year prognosis included a higher number of brain MRI abnormalities (OR = 1.573, 95% CI: 1.129–2.192) and intensive care unit (ICU) admissions (OR = 15.312, 95% CI: 1.684–139.198). The risk factors for 2-year recurrence included abnormalities of the thalamus (HR = 3.780, 95% CI: 1.642–8.699).

Interpretations: Brain MRI features of patients with NMDAR encephalitis were associated with clinical manifestations, prognosis, and recurrence. Higher numbers of MRI abnormalities and ICU admissions were predictive of poor prognosis. Abnormalities of the thalamus constituted a recurrence-related risk factor.

Introduction
Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, the most common type of autoimmune encephalitis mediated by the NMDAR GluN1 subunit,1–5 was first described by Dalmau et al. in 2007.6 Most patients in that study were women (women:men, 8:2), and patient age varied extensively (median age, 21 years; range, 1–85 years). NMDAR encephalitis is particularly prevalent in women of childbearing age and children.2,4–9

NMDAR encephalitis presents diverse clinical symptoms, including fever and pre-onset flu-like prodromal symptoms; further, it has an acute onset with rapid progression and various neuropsychiatric symptoms.4–6,8 Approximately 70%–75% of patients with NMDAR encephalitis are admitted to the intensive care unit (ICU) for monitoring and to receive respiratory and circulatory support.3,4,6,10–13 Diagnoses are confirmed after the detection of specific NMDAR antibodies in the cerebrospinal fluid or serum. NMDAR encephalitis is accompanied by the presence of underlying tumors in 5%–58% of patients,5–8 and surgical resection of the tumors and immunotherapy are the main treatment options.14,15

Early diagnosis and treatment can improve prognosis.3,7,13 Prognosis is good in 75%–81% of patients, with a reported mortality rate of approximately 4% and a recurrence rate in the range of 12%–25%.2,4,16,17
Brain magnetic resonance imaging (MRI) is a common auxiliary modality for examining the central nervous system and is relatively easy to perform. The rate of brain MRI abnormalities at the onset of NMDAR encephalitis ranges from 11% to 83%.\(^6,13,17–20\)

Typical brain MRI abnormalities manifest as hyperintensity on T2-weighted images (T2WI) and fluid-attenuated inversion recovery (FLAIR) sequences. The distribution and degree of brain MRI abnormalities vary widely.\(^20–22\)

Abnormalities may occur in various brain regions and may involve a single site or multiple sites simultaneously.\(^6,11,13,17,18,20–24\) The abnormalities may be unilateral or bilaterally symmetric.\(^6,11,13,17,18,20–24\) Dalmau et al. reported that 55% of MRI abnormalities were located in the temporal lobe, hippocampus, corpus callosum, cerebral and cerebellar cortex, base of the frontal lobe, basal ganglia, and brainstem.\(^1,8\) A 2015 review conducted by Heine et al. reported that 23%–50% of MRI abnormalities were located in the frontal, parietal, and temporal lobes, and that abnormalities were rarely located in the basal ganglia.\(^24\) A systematic review published in 2018 reported that brain MRI abnormalities were most frequently located in the temporal lobe, cortical gray matter, and subcortical white matter.\(^18\)

Atypical or unrelated MRI findings include white matter lesions (WMLs), cerebral atrophy, ventriculomegaly, pituitary disease, and leptomeningeal and brain parenchymal enhancement.\(^18,22,24,25\) Some patients develop cerebral atrophy during follow-up.\(^26,27\) These abnormal brain MRI findings (T2/FLAIR hyperintense lesions) are nonspecific and have little association with clinical manifestations.\(^16,28,29\) Recently, we demonstrated that abnormal MRI is a risk factor for NMDAR encephalitis relapse.\(^30\) Bartels et al. found that children with abnormal MRI exhibited a more severe disease course and worse outcomes.\(^31\) According to Balu et al., MRI abnormalities constitute the NMDAR Encephalitis One-Year Functional Status (NEOS) score.\(^32\) However, the NEOS score and other existing studies do not describe any specific MRI imaging predictors for clinical outcomes.\(^9,16,28,29\)

Thus, we sought to systematically investigate the brain MRI features of NMDAR encephalitis, analyze the associations of each brain MRI feature with various clinical manifestations, and evaluate the imaging predictors associated with long-term prognosis and recurrence. We conducted this study to provide MRI support for effective clinical decision-making, recurrence prediction, and prognosis guidance.

**Methods**

**Experimental design and patient enrollment**

This study retrospectively and continuously enrolled patients with complete MRI data diagnosed with NMDAR encephalitis at the First Affiliated Hospital of Zhengzhou University (January 2013 to October 2019). The inclusion criterion was meeting the diagnostic criteria for NMDAR encephalitis (published by *Lancet Neurology* in 2016).\(^5\) Patients with other central nervous system diseases, such as intracranial infections, metabolic encephalopathy, and neurodegenerative diseases, as well as those who failed to complete the brain MRI examination were excluded from the study.

**Standard protocol approvals and patient consent**

This retrospective observational study was approved by the Scientific Research and Clinical Trial Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2021-KY-0193). The requirement for informed consent was waived by the committee due to the study’s retrospective design.

**Antibody testing and clinical examinations**

NMDAR antibodies in the cerebrospinal fluid and serum of patients were detected at our institution’s Department of Neurology laboratory using two assays: (1) a cell-based assay (CBA) that detects the antibodies through antibody–antigen reactions using a human embryonic kidney cell line (HEK293) transfected with NRI and NR2B (i.e., NRI-NR2B heterodimers forming NMDA receptors) as the substrate (Euroimmun, Lübeck, Germany), and (2) a tissue-based assay (TBA) that detects NMDAR antibodies in frozen sections of rat cerebellum and hippocampal tissue through immunohistochemistry. NMDAR antibodies were considered present only when the patient tested positive on both assays.

**MRI scans**

All patients completed sequential MRI examinations within 1 week of admission, including T1-weighted images (T1WI), T2WI, FLAIR imaging, and diffusion-weighted imaging (DWI) sequences. Some patients were also examined using gadopentetate dimeglumine (Gd-DTPA) contrast-enhanced MRI, and some patients underwent MRI re-examinations 1–3 months after admission. All MRI examinations were performed using 3.0-T MRI scanners (Discovery 750, GE Healthcare, Chicago, IL, USA) with an eight-channel coil; and (Prisma, Siemens, Munich, Germany) with a 64-channel coil. The MRI findings were evaluated independently and reviewed by two neuroradiologists with 5 years of experience blinded to previous diagnoses; a third neuroradiologist with 10 years of experience was asked to evaluate the images in cases of disagreement.
Abnormal brain MRI findings were defined as hyperintense regions on T2WI/FLAIR, which may be accompanied by hypointensities on T1WI or hyperintensities on DWI.\textsuperscript{20,22} The sites showing abnormal MRI findings were the frontal, parietal, temporal, and occipital lobes; insula; basal ganglia; thalamus; lateral ventricle; brainstem; cerebellum; hippocampus; corpus callosum; and pituitary gland. An abnormal MRI region (such as the frontal lobe, temporal lobe, or basal ganglia) was defined as a region with MRI abnormalities. As a dichotomous variable, it was directly included in the regression analysis. The number of abnormal brain regions was recorded. The number of abnormal brain regions defined on this basis was a numerical variable that was included in regression analysis after the removal of extreme values. Abnormal MRI findings were classified as left–right symmetric (i.e., bilateral abnormal signals with fully symmetric sites and distribution ranges) and left–right asymmetric (i.e., unilateral abnormal signals, or bilateral abnormal signals with a lack of full symmetry of the involved sites and their distribution ranges); the symmetry of the distribution of MRI abnormalities was categorized as a dichotomous variable, and the assessment only included the symmetry of the distribution of abnormal MRI findings (T2WI/FLAIR hyperintense lesions) rather than any other radiological findings (e.g., white matter lesions). Compared with MRI examination findings at admission, the MRI re-examination findings 1–3 months after admission were classified as unchanged (i.e., no visible changes in lesion site and range), improved, or aggravated. If multiple MRI re-examinations were performed and the results were inconsistent, only the MRI findings of the most recent re-examination were compared with the findings at hospital admission. Alternatively, the MRI re-examination findings constituted a categorical variable, and “no significant change” served as a reference. “Alleviation” and “Worsening” were subsequently defined by conducting comparisons with respect to this reference value during regression analysis.

MRI findings other than the above-mentioned T2/FLAIR hyperintense lesions (e.g., WMLs, cerebral atrophy, ventriculomegaly, ischemic foci, and leptomeningeal/brain parenchymal enhancement) were analyzed separately. WMLs were defined as hyperintensities on T2WI/FLAIR images involving the subcortical, periventricular, or deep white matter. We classified patients into those with and without WMLs according to their MRI findings. In addition, the presence of WMLs was also a dichotomous variable and was therefore directly included in the regression analysis.

**Data collection, follow-up, and outcome evaluation**

Assessment, documentation, and follow-ups were performed by two trained physicians, each with more than 5 years of clinical experience. Collected data comprised demographic characteristics, clinical symptoms within 1 month of onset, laboratory test results, MRI features, tumor status, and treatments.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) within 1 month of onset, and cognitive impairment was defined as a score <27. The Montreal Cognitive Assessment (MoCA) was used to detect subtle cognitive impairment in patients who could complete the assessment, and cognitive impairment was defined as a score <26.

Patients were followed up by telephone or in the outpatient clinic for 2 years starting from disease onset. Modified Rankin Scale (mRS) scores and recurrences were recorded. The follow-up cutoff date was October 31, 2020. Patients’ mRS scores were used to assess neurological prognosis\textsuperscript{33}; poor prognosis was defined as an mRS score ≥3, and an mRS score = 6 indicated death. Good prognosis was defined as mRS scores ≤2. A recurrence event was defined as the appearance of new symptoms or the worsening of existing symptoms after 2 months of remission, or stabilization accompanied by cerebrospinal fluid positivity or serum antibody positivity.\textsuperscript{34}

**Statistical analysis**

Statistical analyses were performed using the SPSS software program (version 25.0; IBM Corp., Armonk, NY, USA). Normally distributed continuous variables (confirmed by the Shapiro–Wilk test) were expressed as means ± standard deviations (SD), while non-normally distributed variables were expressed as medians and interquartile ranges. Categorical variables were expressed as counts and proportions.

The associations between different imaging features and clinical characteristics were assessed via binary logistic regression analyses evaluating clinical characteristics as dependent variables and brain MRI findings as predictors.

The factors influencing recurrence (e.g., sex, age, symptoms, MRI findings, laboratory results, ICU admission, and treatment) were used as covariates in Cox regression analyses. Each variable was subjected to univariate analyses. Linear regression was used to test the multicollinearity between statistically significant variables ($p < 0.05$) in univariate analyses, and tolerance and variance inflation factor (VIF) were calculated. The variables excluded from multicollinearity were subsequently selected by the forward likelihood ratio method and included in multivariate regression models. Lastly, the proportional hazards assumption of the Cox regression hazard model was verified via log-negative-log survival curves. Prognostic factors were identified using binary logistic regression; variable selection was performed using the same steps as...
delineated above. Statistical significance was set at a threshold of two-sided \( p \)-value of <0.05.

**Results**

**General and clinical characteristics**

This study enrolled 160 patients diagnosed with NMDAR encephalitis. Sixteen patients who did not undergo MRI were excluded. Thus, 144 patients who completed brain MRI examinations were included in our analysis. The baseline data and follow-up clinical outcomes of the patients are shown in Table 1.

Eighty-eight (61.1%) patients presented with prodromal symptoms, including fever, headache, nausea, and vomiting. The most common symptoms at onset were psychobehavioral disorders (\( n = 50, 34.7\% \)) and acute symptomatic seizures (\( n = 44, 30.6\% \)). Overall, 136 (94.4%) patients received first-line immunotherapy with glucocorticoids, intravenous gammaglobulin, or plasma exchange; among these, 10 received additional second-line immunotherapy with cyclophosphamide. Another seven patients underwent tumor resection. Follow-up lasted for 1–7 years (median, 2 years); 107 patients completed the follow-up, and nine patients were re-admitted for recurrence. Thirty-four (34/116, 29.3%) patients developed recurrence, and 10 (10/107, 9.4%) had poor prognosis (mRS score \( \geq 3 \); this included four deaths, 4/107, 3.7%).

**Brain MRI findings**

All 144 patients completed routine 3.0 T brain MRI scans. Among them, 52 (36.1%) had normal brain MRI findings, and 65 (45.1%) had brain abnormalities (T2WI/FLAIR hyperintense lesions) involving the cortex, or white matter in various brain regions; 27 (18.8%) patients presented with WMLs, ischemic foci, lateral ventriculomegaly, and/or cerebral atrophy. Table 2 presents the details of abnormal MRI findings and the outcomes of re-examination MRIs.

MRI abnormalities are often located in multiple regions, some of which are often associated; however, the pattern is diverse. Figure 1 shows the abnormal areas in 65 patients with typical brain MRI abnormalities and intuitively displays the common combination patterns of different regions.

Thirty-seven patients (25.7%) experienced WMLs. WMLs were observed in the frontal lobe, parietal lobe, and lateral periventricular region. Of the 37 patients, 17 (41.8%) presented with abnormal MRI findings and WMLs. The remaining 20 (13.9%) patients presented with WMLs only.

Forty-six patients (31.9%) underwent contrast-enhanced MRI. Among them, nine showed enhanced signals (six patients with leptomeningeal enhancement and three patients with brain parenchymal enhancement). One patient with contrast enhancement also showed abnormalities on noncontrast MRI. The remaining eight patients with enhanced signals showed new abnormalities on MRI when a contrast agent was used: four patients

| Variable | \( N = 144 \) |
|----------|-------------|
| Male     | 61 (42.4%)  |
| Female   | 83 (57.6%)  |
| Age (years) | 25.5 (17–41.75) |
| \( \geq 18 \) | 105 (73%)   |
| \(< 18 \) | 39 (27%)    |
| Hospital days | 24 (15.37)   |
| ICU admission | 75 (52.1%)   |
| Hospital days in the ICU | 14.5 (728.25) |
| Tumor presence \( \text{(n)} \) | 22 (29.7%)   |

| Clinical symptoms within 1 month of admission |
|-----------------------------------------------|
| Psychobehavioral disorders | 83 (57.6%) |
| Acute symptomatic seizures | 71 (49.3%) |
| Consciousness disorders | 70 (48.6%) |
| Dyskinesia | 36 (25%) |
| Aghasia | 32 (22.2%) |
| Cognitive disorders | 30 (20.8%) |
| Central hypoventilation | 21 (14.6%) |
| Autonomic nervous disorders | 13 (9%) |
| Dysphagia | 3 (2.1%) |
| Paresthesia | 3 (2.1%) |
| Sleep disorders | 3 (2.1%) |
| Ataxia | 3 (2.1%) |

| Treatment regimen | \( N = 144 \) |
|-------------------|-------------|
| No immunotherapy | 8 (5.6%) |
| Glucocorticoids only | 48 (33.3%) |
| IVIg only (0.4 g/kg per day for 5 days) | 7 (4.9%) |
| PEX only (40–60 mL/kg of plasma per day for 5 days) | 2 (1.4%) |
| Glucocorticoid + IVIg | 68 (47.2%) |
| Glucocorticoid + PEX | 3 (2.1%) |
| IVIg + PEX | 1 (0.7%) |
| Glucocorticoid + IVIg + PEX | 7 (4.9%) |
| Cyclophosphamide (750 mg/m\(^2\) of body surface area every 4 weeks) | 10 (6.9%) |
| Tumor resection | 7 (4.9%) |

| Two-year follow-up | \( N = 144 \) |
|-------------------|-------------|
| mRS<2 | 97 (90.6%) |
| mRS=3 | 10 (9.4%) |
| Recurrence within 2 years | 34 (29.3%) |
with normal MRI and two patients with abnormal signals on routine MRI showed leptomeningeal enhancement in contrast-enhanced MRI. In one patient with normal MRI and one with abnormal signal on routine MRI, contrast-enhanced MRI revealed new abnormalities in the brain parenchyma.

Eighty-four patients completed MRI re-examinations 1–3 months after admission, including 37 patients with no abnormalities and 57 patients with brain MRI abnormalities on the first brain MRI conducted at the onset. Among the patients who underwent multiple MRI examinations, two presented with worsening abnormalities and subsequent alleviation; these were considered remission patients. One patient presented with substantial cerebral atrophy on the re-examination MRI. Three patients presented with WMLs but no MRI abnormalities at onset; these patients showed a meaningful improvement in WMLs during re-examination. As only 58% of the cohort had follow-up MRI, the subsequent regression analysis did not include the variable of “alleviation or worsening of MRI abnormalities” in the model.

**Associations between brain MRI findings and clinical characteristics**

The associations of different brain MRI findings with common clinical characteristics were evaluated using binary logistic regression analyses. The results suggested that insula abnormalities were associated with seizures (odds ratio [OR] = 3.048, 95% confidence interval [CI]: 1.026–9.060, \( p = 0.045 \)), and WMLs were associated with cognitive impairment (OR = 2.730, 95% CI: 1.096–6.799, \( p = 0.031 \)). A total of 58/126 (46.0%) patients without insula lesions and 13/18 (72.2%) patients with insula lesions had seizures.

We compared the age differences between the WMLs and non-WMLs groups using the independent sample t-test and found that the mean age of patients in the WMLs and non-WMLs groups was 39.42 years and 25.08 years, respectively. A significant difference was observed between groups (mean difference = 14.34, \( p = 0.005 \)). Thus, we adjusted for the multicollinearity of age and WMLs (age: VIF = 1.160, WMLs: VIF = 1.160) and included them in the binary logistic regression analyses. After adjusting for the influence of age (OR = 0.986, 95% CI: 0.961–1.012, \( p = 0.283 \)), WMLs were still associated with cognitive impairment (OR = 2.909, 95% CI: 1.139–7.428, \( p = 0.026 \)).

**Associations between MRI findings and 2-year prognosis**

The influential factors associated with prognosis were assessed via binary logistic regression (Table 3). Linear
regression was used to analyze statistically significant variables in the univariate analysis ($p < 0.05$) before multivariate regression analysis: number of brain MRI abnormalities (VIF = 3.412), temporal lobe abnormalities (VIF = 3.673), insula abnormalities (VIF = 1.613), ICU admissions (VIF = 1.076), and recurrence (VIF = 1.134). There was no indication of severe multicollinearity.

Figure 1. Involvement of each brain region in 65 patients with abnormal brain MRI, where 1 (yellow) indicates abnormal MRI findings, and 0 (blue) indicates normal MRI findings. Some common combination patterns, such as lateral periventricular region + parietal lobe + frontal lobe, frontal lobe + parietal lobe + temporal lobe + insula, parietal lobe + temporal lobe + occipital lobe, and thalamus + basal ganglia + brain stem (among others) can be observed. Both outcome (Poor/Good) and recurrence (Yes/No) columns are included in the figure, with * representing lost to follow-up.
The multivariate analysis of binary logistic regression suggested that a higher number of brain MRI abnormalities (OR = 1.573, 95% CI: 1.129–2.192, p = 0.007) and ICU admissions (OR = 15.312, 95% CI: 1.684–139.198, p = 0.015) were associated with poor 2-year prognosis (Table 3).

Given that the number of patients with eight sites was equal to zero, and the patient with nine sites was lost in the follow-up, the number of abnormalities included in the regression analysis was in the range of 0–7. Figure 2 shows the relationship between “number of MRI abnormalities” and “2-year prognosis.”

### MRI findings and disease recurrence

The influential factors associated with recurrence were assessed via Cox regression hazard models (Table 4). Univariate analyses suggested that the following risk factors were associated with 2-year recurrence, which were included in the linear regression for multicollinearity.

#### Table 3. Univariable and multivariable analyses of patients with anti-NMDA receptor encephalitis who presented with poor prognosis at their 2-year follow-up (N\(^1\) = 107).

| Variable                  | Univariable analysis | Multivariable analysis |
|---------------------------|----------------------|------------------------|
|                           | OR       | 95% CI       | p-value | OR       | 95% CI       | p-value |
| Number of abnormalities   | 1.436    | 1.063–1.939 | 0.018   | 1.573    | 1.129–2.192 | 0.007   |
| Temporal lobe abnormalities| 4.826    | 1.252–18.596 | 0.022   |          |            |         |
| Insula abnormalities      | 4.722    | 1.162–19.190 | 0.030   |          |            |         |
| ICU admission             | 10.400   | 1.268–85.283 | 0.029   | 15.312   | 1.684–139.198 | 0.015 |
| Recurrence                | 3.850    | 1.015–14.610 | 0.048   |          |            |         |

OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging; ICU, intensive care unit.

\(^1\)Follow-up was completed in 107 patients.

#### Table 4. Univariable and multivariable analyses of 2-year relapse in patients with anti-NMDA receptor encephalitis (N\(^1\) = 116).

| Variable                  | Univariable analysis | Multivariable analysis |
|---------------------------|----------------------|------------------------|
|                           | HR       | 95% CI       | p-value | HR       | 95% CI       | p-value |
| Age                       | 1.024    | 1.004–1.045 | 0.017   |          |            |         |
| Parietal lobe abnormalities| 2.203    | 1.089–4.456 | 0.015   |          |            |         |
| Temporal lobe abnormalities| 2.117    | 1.067–4.201 | 0.032   |          |            |         |
| Thalamus abnormalities     | 3.780    | 1.642–8.699 | 0.002   | 3.780    | 1.642–7.699 | 0.002   |
| Lateral periventricular abnormalities | 2.552 | 1.155–5.638 | 0.021   |          |            |         |
| Number of abnormalities    | 1.216    | 1.053–1.404 | 0.008   |          |            |         |

HR, hazard ratio; CI, confidence interval; MRI, magnetic resonance imaging.

\(^1\)A total of 107 patients completed routine follow-up, and nine patients were re-admitted because of recurrence, leading to a total of 116 patients.
tests: age (VIF = 1.100), parietal lobe abnormalities (VIF = 2.084), temporal lobe abnormalities (VIF = −2.693), thalamus abnormalities (VIF = 1.912), lateral periventricular abnormalities (VIF = 1.303), and number of brain MRI abnormalities (VIF = 5.764); there was no significant multicollinearity between these variables.

Results of the COX regression multivariate analysis showed that thalamic abnormalities (HR = 2.896, 95% CI: 1.159–7.238, p = 0.002) were associated with 2-year recurrence (Table 4).

Discussion

There are numerous studies on brain MRI findings in patients with NMDAR encephalitis; however, the results are often inconclusive.16,28,32 The present study showed that various brain MRI findings were associated with clinical manifestations and outcomes: (1) Insula abnormalities were associated with acute seizures, and WMLs were associated with cognitive impairment; (2) higher number of brain MRI abnormalities and ICU admissions were risk factors for poor 2-year prognosis; and (3) thalamus abnormalities constituted a risk factor for recurrence.

Herein, we enrolled 144 patients with NMDAR encephalitis, 45.1% of whom presented with brain MRI abnormalities. Chinese studies typically have a larger proportion of male patients16,20,22,28 and more relapses than studies from Western countries.8,13,32 This was also the case in our study, as 42.4% of the patients were men, and 29.3% had relapses. Since this could be related to race or culture, it may be worth investigating. In our study, 20.8% of patients had cognitive impairment within 1 month of onset, and their cognitive function was not reassessed during follow-up. Heine et al. evaluated the long-term cognitive functions of 43 patients with NMDAR and found that all patients had persistent cognitive deficits 2.3 years after onset.35 These results suggest that persistent cognitive impairment may develop, and future studies should continuously evaluate cognitive impairment through long-term follow-up. Other demographic characteristics, common clinical manifestations (Table 1), and incidence of abnormal MRI were similar to those in prior large-sample studies.3,6,13,16–20,32

MRI abnormalities (T2WI/FLAIR hyperintense lesions) were observed in various brain regions and were mostly found in the temporal, frontal, and parietal lobes (Table 2). According to Zhang et al.,20 hippocampal lesions were the most common MRI abnormalities. Other authors have noted that these were likely driven by herpes simplex encephalitis (HSE) with subsequent NMDAR encephalitis in some patients.36 Hippocampal involvement was rare (6.3%) in the current study. Thus, it is possible that the sample size in the study by Zhang et al. was relatively small, and that the proportion of hippocampus lesions was affected by the patients with post-HSE NMDAR encephalitis. Compared with previous studies, the brain MRI abnormalities observed in this study covered a broader range of brain regions, indicating that brain MRI abnormalities can involve various brain regions and do not occur at typical preferential sites.

Multiple brain MRI findings were associated with clinical manifestations. Namely, insula abnormalities were associated with acute seizures, and WMLs were associated with cognitive impairment. A 2018 cohort study enrolling 106 cases reported that the evaluated associations between MRI abnormalities and clinical manifestations (seizures, hypoventilation, loss of consciousness, and tumors) were not statistically significant.22 Conversely, this study comprised a wider range of clinical characteristics and MRI findings.

Due to the anatomical locations of lesions within the nervous system, insula lesions often clinically manifest as acute seizures. Previous research has been performed on insular epilepsy.37 Isnard et al. showed that in refractory temporal lobe epilepsy patients, temporal lobe cortical resection completely controlled seizures of temporal lobe origin but did not affect insular-origin seizures.38 Previous studies have suggested that WMLs increase the risk of cognitive impairment or dementia in the general older adult population (60–90 years).39 We performed a subgroup analysis and observed differences in the mean age (39.42 years in the WMLs group and 25.08 years in the non-WMLs group), suggesting that age also affects the presence of WMLs in patients with NMDAR encephalitis. However, our results also showed that after adjusting for age, WML was still associated with cognitive impairment. Therefore, the previously reported inconsistency between brain MRI findings and clinical manifestations in NMDAR encephalitis22 may not be entirely correct. Nonetheless, additional research is needed in this regard.

Multivariate analyses suggested that a higher number of brain MRI abnormalities and ICU admissions were risk factors for poor 2-year prognosis. Balu et al.32 and Titiu laer et al.35 suggested that ICU admission is a risk factor for poor prognosis in NMDAR encephalitis; this is consistent with our findings. As mentioned earlier, previous studies by Bartels et al.31 and Balu et al.32 suggested that abnormal MRI was a risk factor for poor prognosis. Wang et al. observed that the mean mRS scores during a 4-month follow-up period were higher in patients with abnormal initial MRI findings; however, neither the abnormal initial MRI findings nor the mRS scores were significantly associated with the prognosis.22

To date, there have been a few studies on specific MRI features. Zhang et al. proposed that lesions in the
hippocampus were the most common abnormal MRI findings and that hippocampal lesions were the main MRI predictors of poor prognosis in NMDAR encephalitis. However, a small sample size of only 53 patients was included in this study, and the researchers defined poor prognosis based on an mRS score of 2–5. Iizuka et al. showed that diffuse cerebral atrophy, proposed as reversible, is not associated with poor prognosis. Cerebellar atrophy is irreversible, and it is uncertain whether MRI findings are predictive of prognosis in this disease. Our results demonstrated that patients with more brain MRI abnormalities had poor 2-year prognosis, suggesting that MRI findings are predictive of prognosis and that this predictive power depends on the number of MRI abnormalities.

In this study, multivariate Cox regression analyses showed that abnormalities in the thalamus identified on brain MRI were risk factors for recurrence. Studies on factors associated with the recurrence of NMDAR encephalitis are lacking, and studies on imaging predictors are even more infrequent. A 25-patient study by Gablondo et al. suggested that immunotherapy at initial onset may reduce the risk of recurrence. However, we previously demonstrated that abnormal MRI is a risk factor for relapse. In a further study, abnormalities in the thalamus identified on brain MRI were a predictor of recurrence. Notably, we observed that some brain regions (e.g., temporal lobe abnormalities) were not independent predictors in the multivariate analyses, even though they were relatively common, thus suggesting that the more frequently affected regions may not be more important in outcome predictions. This finding is novel, and further research is needed to explore the underlying mechanisms.

Herein, we enrolled 144 patients, 37 (25.7%) of whom developed WMLs. As mentioned earlier, patients with WMLs tend to be older and more often experience cognitive impairment. The observation that WMLs were related to cognitive deficits is in line with Phillips et al.’s observations. Furthermore, a link between oligodendrocyte pathology and WMLs has been discussed in NMDAR encephalitis.

In this study, 46 of 144 patients (31.9%) underwent contrast-enhanced MRI examination, among whom nine presented with an enhancement of brain MRI abnormalities. One patient with contrast enhancement also demonstrated abnormalities on noncontrast MRI, and the remaining eight patients showed new abnormalities when a contrast agent was used. Dalmau et al. reported that some patients present with MRI abnormalities accompanied by meningeal enhancement in the involved regions. A systematic review reported that the most common enhancement is a leptomeningeal enhancement, followed by cortical enhancement, consistent with our study findings. In conclusion, contrast-enhanced MRI examination currently presents no substantial advantages for improving the positivity rate for lesion detection; however, it can indicate new lesions that are not detected in routine MRI, particularly when there is meningeal involvement.

The outcomes of brain MRI findings were explored by re-examining the patients 1–3 months after admission. Re-examination was not necessarily synchronized with disease progression. Multiple rounds of re-examination revealed that MRI abnormalities of two patients in our study first aggravated and subsequently improved. Preliminary statistical analyses revealed that the outcomes of brain MRI findings may somewhat be associated with disease recurrence. However, multivariate analyses revealed no significant associations. Admittedly, the follow-up MRI study will be biased by clinical needs, that is, patients without lesions or rapid clinical improvement will not undergo follow-up studies in contrast to patients that do not improve. Thus, we recommend that future studies perform MRI re-examination multiple times and compare the MRI findings during the entire disease course and conduct a long-term follow-up.

This single-center retrospective study was conducted at a provincial tertiary hospital and may be subject to certain biases peculiar to observational epidemiologic research. Notably, complete rounds of brain MRI examination were lacking in the 2-year follow-up, and the follow-up MRI study will be biased by clinical needs. We described the brain MRI findings, and the observed associations identified herein may have implications for clinical practice; nevertheless, further research to understand the mechanism underlying these associations is needed.

In summary, we observed associations between brain MRI abnormalities and clinical characteristics in patients with NMDAR encephalitis and demonstrated that brain MRI is a valuable predictive tool in NMDAR encephalitis that should be validated in larger prospective multicenter studies.

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Author Contributions

Study conception and design: YYZ, HXW, and TWS. Manuscript and figure drafting: YYZ and HXW. All authors reviewed and approved the final manuscript and involved in acquisition and analysis of data.
Conflict of Interest

The authors declare that there are no conflicts of interest in connection with this article.

Data Availability Statement

The data used for this study, although not available in a public repository, will be made available to other researchers upon reasonable request.

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