ORIGINAL ARTICLE

Prognostic Outcomes in Seropositive and Seronegative Autoimmune Encephalitis

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ABSTRACT

Objectives: Autoimmune Encephalitis (AE) is an immune-mediated inflammatory disorder of the central nervous system with heterogeneous clinical manifestations and variable outcomes. The prognostic significance of antibody status (seropositive vs. seronegative) remains incompletely understood, particularly in Iranian populations. This study aimed to compare clinical characteristics, therapeutic interventions, and prognostic outcomes between seropositive and seronegative patients with AE (≤ 18 years) admitted to two tertiary referral hospitals in Tehran, Iran.

Material & Methods: In this study, medical records of 58 patients diagnosed with AE between 2019 and 2024 at Ali Asghar and Hazrat Rasool Hospitals were reviewed. Patients were classified as seropositive or seronegative based on antibody testing.

Results: Of the 58 patients, 31 (53.4%) were seropositive and 27 (46.6%) were seronegative. The mean age was 41.94 ± 24.87 months, and 72.4% were male. Seizures were the most common clinical manifestation. No significant differences were observed between seropositive and seronegative groups in initial disease severity, functional outcomes, neurological complications, treatment allocation (all $p > 0.05$). In multivariable analysis, initial disease severity (OR = 13.3, $p = 0.032$) and the presence of underlying diseases (OR = 31.4, $p = 0.007$) were independently associated with poor prognosis, whereas serologic status was not.

Conclusion: Serologic status does not significantly influence disease severity, treatment response, or prognosis in patients with AE. Initial clinical severity and comorbidities are the primary determinants of poor outcome. Management strategies should prioritize early recognition, assessment of disease severity, and timely immunotherapy regardless of antibody status.

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Introduction

Autoimmune Encephalitis (AE) represents a diverse spectrum of immune-mediated central nervous system conditions characterized by neuro-inflammation stemming from aberrant autoimmune responses (1). As an increasingly identified clinical entity, AE presents significant diagnostic complexity and affects a wide demographic, ranging from pediatric to adult populations. Common subtypes are often associated with antibodies targeting neuronal epitopes on the cell

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surface, synaptic structures, or intracellular proteins (2).

AE can be broadly classified as seropositive or seronegative, depending on whether antibodies against neuronal antigens are detectable (3). Patients with identifiable antibodies targeting neuronal cell-surface or intracellular antigens are classified as seropositive, whereas seronegative AE refers to patients who meet clinical diagnostic criteria but lack detectable antibodies. In some cases, seronegative AE may involve antibodies against yet-unidentified neuronal antigens, or T-cell-mediated mechanisms may play a primary role (2, 3). Consequently, seropositive AE is generally associated with well-characterized IgG antibodies, while seronegative cases do not have currently identifiable antibodies (4).

The clinical presentation of AE is highly variable. Psychiatric symptoms, encephalopathy, and seizures are among the most common manifestations (5). Although AE is rare, with acumulative incidence of 3–9 cases per million person-years, increasing awareness has led to more frequent diagnoses over recent decades (6). Specifically, incidence rose from 0.4 per 100,000 person-years in 1995–2005 to 1.2 per 100,000 person-years in 2006–2015 (1). Population-based studies have reported prevalence as high as 13.7 cases per 100,000 in 2014 (7).

Several factors influence prognosis, including age, treatment-resistant seizures, and the severity of encephalopathy (5). Additionally, AE is categorized according to the location of the target antigen. Antibodies against intracellular proteins, such as anti-Hu, Ma, glutamic acid decarboxylase (GAD), amphiphysin, and Ri are frequently linked to paraneoplastic syndromes, including small-cell lung carcinoma. In contrast, antibodies targeting neuronal cell-surface receptors, called synaptic antibodies, play a key role in synaptic transmission and neuronal signaling (8, 9).

Initial disease severity is an essential prognostic factor. Children presenting with severe encephalopathy, status epilepticus, or coma may experience a longer and more complicated recovery (10). While many pediatric patients achieve substantial neurological improvement, some may continue to have persistent cognitive deficits affecting memory, attention, and executive function (11).

Despite these advances, significant gaps remain. Although seropositive AE subtypes are relatively well characterized, many pediatric patients are seronegative, and their disease mechanisms, course, and response to treatment are not fully understood. This knowledge gap complicates clinical decision-making and outcome prediction. Most previous studies have focused on adults or specific antibody-defined subgroups, and few pediatric studies have compared prognosis between seropositive and seronegative patients. In Iran, no study has systematically assessed these differences.

Several worldwide studies have explored prognostic factors and treatment outcomes in pediatric AE.

In 2024, Melha et al. conducted a multicenter retrospective observational study to identify prognostic indicators and treatment outcomes in children with AE. They analyzed clinical characteristics, autoantibody levels, treatment modalities, and disability scores at baseline and follow-up. Psychiatric symptoms, encephalopathy, and seizures were the most common manifestations. Younger age, treatment-resistant seizures, severe encephalopathy, and refractory disease were associated with higher disability scores. Notably, patients receiving combined immunotherapy showed marked improvement, highlighting the benefits of early, multifaceted immunotherapy (5).

Moreover, in 2024, Gao et al. carried out a retrospective case-control study comparing seropositive and seronegative AE. Among 60 pediatric patients (33 seropositive, 27 seronegative), seropositive patients more often presented with multiple symptoms, higher serum IgG levels, and increased CSF white blood cell counts. Besides, they received first-line combination immunotherapy more frequently. However, patients with seronegative exhibited higher CSF protein and albumin quotient, indicating more pronounced blood-brain barrier disruption. Treatment responses were better in seropositive patients, particularly among severely ill children (17).

In 2021, Lee et al. studied 46 children with AE, comparing seropositive and seronegative cases. Both groups showed similar neuropsychiatric symptoms, including altered mental status, cognitive deficits, seizures, speech disturbances, and psychosis. First-line immunotherapy produced favorable outcomes in both groups, but seronegative patients responded particularly well and required fewer second-line interventions (18).

Similarly, in 2024, Berger et al. conducted a multicenter retrospective study of 150 pediatric AE patients. Clinical and paraclinical findings were comparable between seropositive and seronegative groups. High response rates to immunotherapy were observed in both groups, with no significant differences, suggesting that immunotherapy should be considered regardless of antibody status (19).

In Iran, studies are limited. Etemadifar et al. described demographic, clinical, and paraclinical features of Iranian pediatric patients with autoantibody-positive AE. Anti-NMDAR antibodies were most common, followed by anti-GABABR, anti-

Zic4, and anti-GAD65. Clinical manifestations included cognitive decline, seizures, parkinsonism, and stiff-person syndrome (20).

Overall, few studies have addressed AE in pediatric populations, and direct comparisons of prognosis between patients with seropositive and seronegative remain scarce both in Iran and internationally. This gap underscores the need for further research. Accordingly, the present study aims to address, providing guidance for the monitoring, management, and treatment of children with AE.

Materials & Methods

Study design and setting

This multicenter, cross-sectional observational study was conducted between 2019 and 2024 at the Pediatric Wards of Ali Asghar and Hazrat Rasool Hospitals, affiliated to the Iran University of Medical Sciences, Tehran, Iran.

Study population

The study included all pediatric patients (≤ 18 years) diagnosed with AE based on GRAUS criteria who referred to the two hospitals during the study period and had documented antibody testing. Patients without antibody evaluation or who declined participation were excluded.

Inclusion and exclusion criteria

Inclusion criteria: Acute or subacute AE onset (< 3 months) presenting with at least one of the following: Altered mental status, working memory deficits, psychiatric symptoms, seizures, language or motor disturbances, gait instability, or limb weakness. Supportive evidence from at least one of these: Unexplained seizures, CSF leukocytosis (> 5 cells/mm³), CSF-specific oligoclonal bands or IgG index > 0.85, elevated CSF protein, or MRI findings suggestive of AE.

Exclusion criteria: Confirmed infectious encephalitis, pre-existing metabolic/toxic encephalopathy, brain tumors, vitamin deficiency, primary psychiatric disorders, other immune-mediated encephalitides (e.g., Bickerstaff brainstem encephalitis), incomplete records, or lack of consent.

Data collection

Data were extracted from medical records, antibody tests, MRI, EEG, and CSF analyses. Follow-up assessments of functional and clinical outcomes were collected via chart review or telephone interviews using the modified Rankin Scale (mRS) and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE). Patients were categorized into seropositive and seronegative groups. Through performing the AE panel included, NMDA, CASPR, AMPA, LGI1, GAD65, VGKC, GABA, DDPX, and based on case criteria, they were divided into three groups: Mild, moderate and severe. In this study all patients were re-evaluated for a standard time period 6-24 months based on mRS.

Variables

Dependent variables: Clinical recovery, long-term neurological complications (cognitive/motor deficits, persistent seizures, & behavioral changes), treatment interventions (steroids, immunotherapy, & plasmapheresis), abnormal MRI/EEG, relapse, mortality, ICU stay, and poor prognosis (CASE score 10–27).

Independent variables: Demographics, diagnostic delay, initial disease severity, treatment type, CSF parameters, time to immunotherapy, antibody type, and comorbidities.

Statistical analysis

Continuous variables are presented as mean ± SD or median (IQR), based on normality (assessed via histograms, P–P/Q–Q plots, skewness/kurtosis, and Kolmogorov–Smirnov test). Comparisons used Student's t-test or Mann–Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Analyses were performed in STATA v17, with $P < 0.05$ considered significant.

Results

In this study, 58 patients diagnosed with AE were included, of whom 27 (46.6%) were seronegative and 31 (53.4%) were seropositive. Data were collected from medical records, clinical evaluation, and standardized CASE and mRS questionnaires. The mean age of patients was 41.94 ± 24.87 months, with an average hospital stay of 14.74 ± 31.85 days and a mean diagnostic delay of 3.50 ± 2.74 days. The majority of patients were male (n=42, 72.4%) and resided in urban areas (n=55, 94.8%), with the highest prevalence in Tehran province. Among patients with seropositive, the most frequent positive antibody was NMDA (n=20, 34.5%). Comorbidities were present in 13 patients (22.4%), and 51.7% of patients experienced at least one long-term complication, including cognitive impairment, behavioral disorders, persistent seizures, and motor or sensory deficits.

Table 1. Demographic and clinical characteristics of patients (N = 58)

Variable	Category	Value
Age (months)	Mean ± SD	41.94 ± 24.87
Length of hospital stay (days)	Mean ± SD	14.74 ± 31.85
Delay in diagnosis (Days)	Mean ± SD	2.74 ± 3.50
Sex	Male	42 (72.4%)
	Female	16 (27.6%)
Place of residence	Urban	55 (94.8%)
	Rural	3 (5.2%)
Type of encephalitis	Seropositive	31(53.4%)
	Seronegative	27 (46.6%)
Antibody type	GAD65	10 (17.2%)
	Anti-TPO	1(1.7%)
	Anti-NMDA	20 (34.5%)
	Negative	27 (46.6%)
Underlying disease	Present	13 (22.4%)
	Absent	45 (77.6%)
Long-term complications	Present	23 (51.7%)
	Absent	20 (34.5%)
MRI abnormalities	Yes	14 (24.1%)
	No	44 (75.9%)
EEG abnormalities	Yes	35 (60.3%)
	No	23 (39.7%)
CSF analysis	Normal	50 (86.2%)
	Abnormal	8 (13.8%)
Relapse	Yes	2 (3.4%)
	No	56 (96.6%)
ICU admission	Yes	45 (77.6%)
	No	13 (22.4%)
Disease severity	Mild	14 (24.1%)
	Moderate	18 (31.0%)
	Severe	26 (44.8%)
Treatment received	Steroid	37 (63.8%)
	IVIG	14 (24.1%)
	Plasmapheresis	14 (24.1%)
	Rituximab	20 (34.5%)
	Cyclophosphamide	5 (8.6%)
	Tocilizumab	1 (1.7%)
	Methotrexate	10 (17.2%)
	Bortezomib	1 (1.7%)
Clinical manifestations	Seizures	41 (70.7%)
	Motor dysfunction	24 (41.4%)
	Sensory disturbance	31 (53.4%)
	Behavioral disturbance	17 (29.3%)
	Psychiatric symptoms	7 (12.1%)
	Other	6 (10.3%)

Regarding treatment, 44 patients (75.9%) received IVIG, 37 patients (63.8%) received corticosteroids, and 24 patients (24.1 %) underwent plasmapheresis. Second-line immunotherapy included rituximab (34.5%) and cyclophosphamide (8.6%). Paraclinical findings revealed that 14 patients (24.1%) had MRI abnormalities and 35 patients (60.3%) had EEG changes. Disease relapse occurred in two patients (3.4%), while CSF analysis was abnormal in eight patients (13.8%). The majority of patients (77.6%) required ICU admission. Regarding disease severity, 26 patients (44.8%) presented with severe disease, 18 (31%) with moderate disease, and 14 (24.1%) with mild disease. The most common clinical manifestation was seizures (70.7%), followed by taste disturbances, motor deficits, and behavioral abnormalities. These results indicate that most patients presented with moderate to severe disease, requiring advanced care and treatment interventions. Detailed demographic and clinical characteristics are summarized in Table 1.

In assessing functional outcomes using the modified Rankin Scale (mRS), the mean score was 1.88 ± 1.12. The most frequent score was 0, observed in 37 patients (63.8%), while no patients had a score of 5, and a score

of 6 was observed in five patients (8.6%). For the CASE, the mean score was 2.28 ± 2.11, with the most frequent score being 0 in 18 patients (31%), followed by scores of 3 (17.2%) and 1 (15.5%).

Table 2. Distribution and comparison of mRS and CASE scores in patients with seronegative and seropositive with AE

	Score	Number of cases	Frequency	Mean ± Standard Deviation		
MRS	0	37	63.8	1.12 ± 1.88		
	1	5	8.6			
	2	6	10.3			
	3	2	3.4			
	4	3	5.2			
	5	0	0			
	6	5	8.6			
CASE	0	18	31	2.11 ± 2.28		
	1	9	15.5			
	2	5	8.6			
	3	10	17.2			
	4	3	5.2			
	5	4	6.9			
	7	1	1.7			
	8	3	5.2			
Variable	**Group**	**Number of cases**	**Mean Rank**	**Mann–Whitney U test**	**Standardized test statistic (Z)**	**p-value**
MRS	Seronegative	27	26.63	341.0	-1.406	0.160
	Seropositive	31	32			
CASE	Seronegative	25	25.16	3.4	- 0.842	0.4
	Seropositive	28	28.64			

Based on Shapiro–Wilk and Kolmogorov–Smirnov tests, the mRS and CASE scores were not normally distributed in either group. Therefore, the Mann–Whitney U test was used to compare the two groups. According to the results, no statistically significant difference was observed in mRS scores between the seropositive and seronegative groups (U = 341.0, p = 0.160). Similarly, CASE scores did not differ significantly between the groups (U = 304.0, p = 0.400).

These findings indicate that initial disease severity and functional disability were comparable between patients with seropositive and seronegative (Table 2).

Comparison of the occurrence of neurological complications between patients with seropositive and seronegative showed no significant differences in any of the assessed outcomes, including cognitive impairment, motor dysfunction, persistent seizures, behavioral disturbances, and long-term complications (all p > 0.05). Additionally, sensory disorders were not observed in any patient and could not be analyzed statistically due to uniformity. These findings indicate that long-term neurological status was independent of serologic status (Table 3).

Table 3. Clinical manifestations and long-term neurological complications

Neurologic complication	Seronegative	Seropositive	p-value
Long-term complication	15 (60)	18 (64)	0.748
Cognitive disorder	11 (44)	12 (43)	0.933
Movement disorder	6 (24)	9 (32)	0.511
Sensory disorder	-	-	-
Persistent seizure	5 (20)	3 (11)	0.346
Behavioral disorder	8 (32)	14 (50)	0.184

Most patients received IVIG (75.9%) and corticosteroids (63.8%). Advanced immunotherapies included rituximab (34.5%), cyclophosphamide (8.6%), and rarely tocilizumab, methotrexate, or bortezomab. MRI abnormalities were found in 24.1% and EEG abnormalities in 60.3% of patients. No significant differences were observed between patients with seropositive and seronegative in treatment allocation, MRI or EEG findings, disease relapse, or mortality (all p > 0.05).

Analysis of MRI and EEG findings showed no significant differences between patients with

seropositive and seronegative in the occurrence of MRI abnormalities (p = 0.750) or EEG abnormalities (p = 0.487). These results indicate that serologic status is not significantly associated with the likelihood of imaging or electroencephalographic abnormalities (Table 5).

Table 4. Type and frequency of therapeutic interventions in seronegative and seropositive patients with AE

Therapeutic intervention	Seronegative (n = 27) n (%)	Seropositive (n = 31) n (%)	p-value (Fisher/Chi-square)
Required treatment	27 (100)	31 (100)	—
Corticosteroids	16 (59)	21 (68)	0.503
IVIG	25 (92.6)	31 (100)	0.123
Plasmapheresis	5 (18.5)	9 (29)	0.351
Rituximab	7 (25.9)	13 (38.2)	0.201
Cyclophosphamide	1 (3.7)	4 (12.9)	0.359
Tocilizumab	0	1 (2.94)	1
Methotrexate	3 (11.1)	7 (22.5)	0.249
Bortezomib	0	1 (2.94)	1

Table 5. Treatment modalities and paraclinical findings by serostatus

Para-clinic findings	Seronegative cases and percentage	Seropositive cases and percentage	p-value (Fisher/Chi-square)
Abnormal MRI	6 (22.2)	8 (25.8)	0.750
Abnormal EEG	15 (55.6)	20 (64.5)	0.487

Analysis of disease relapse showed no significant difference between patients with seropositive and seronegative (p = 0.179). Although relapses occurred only in the seropositive group, the low frequency prevented the difference from reaching statistical significance. Therefore, serologic status had no clear impact on the likelihood of disease relapse.

Similarly, comparison of mortality between the two groups revealed no significant difference (p = 0.759). Although the mortality rate was slightly higher in the seropositive group, this difference was not statistically significant. These findings indicate that serologic status had no significant effect on patient mortality (Table 6).

Table 6. Disease relapse in patients with seropositive and seronegative

Variable	Seronegative cases and percentage	Seropositive cases and percentage	p-value (Fisher/Chi-square)
Relapse	0	2 (6.5)	0.179
Mortality	2 (7.4)	3 (9.7)	0.759

Table 7. Comparison between ICU admission duration in seropositive and seronegative groups

Variable	Group	N	Mean rank	U	Z	p-value
ICU admission in days	Seronegative	27	25.69	315.5	-1.616	0. 106
	Seropositive	31	32.82			

ICU admission was required in 77.6% of patients. The median ICU stay did not differ significantly between seropositive and seronegative patients (U = 315.5, p = 0.106). Relapse was rare (n = 2, 3.4%), and mortality was low (n = 5, 8.6%), with no statistically significant differences by serostatus.

Based on the Shapiro–Wilk test, ICU length of stay was not normally distributed. Therefore, the Mann–Whitney U test was used to compare the two groups. The results showed no significant difference in ICU length of stay between seronegative and seropositive patients (U = 315.5, p = 0.106). Although the mean ranks indicate a slightly longer ICU stay in the seropositive group, this difference was not statistically significant. These findings suggest that serologic status does not have a significant effect on ICU length of stay (Table 7).

In the bivariate analysis of factors associated with poor prognosis in patients with AE admitted to Ali-Asghar and Hazrat Rasoul hospitals in Tehran, Iran, between 2019 and 2024, several factors were found to be significantly associated with adverse clinical outcomes. Based on chi-square and Fisher's exact tests, the presence of underlying diseases (p = 0.002), receipt

of plasmapheresis (p = 0.004), and initial disease severity (p = 0.005) were significantly associated with poor prognosis. Among immunotherapy agents, rituximab (p < 0.001) and methotrexate (p < 0.001) were also significantly associated with poor outcomes, likely reflecting their use in patients with more severe disease, treatment-resistant cases, or more complicated clinical courses.

Although bortezomib reached significance in the chi-square test (p = 0.027), the very small number of patients and non-significant Fisher's test (p = 0.172) limit the reliability of this finding. Therefore, a definitive association between bortezomib and prognosis cannot be reported. In contrast, age (p = 0.453), sex (p = 0.334), delay in diagnosis (p = 0.952), as well as corticosteroid (p = 0.653) and intravenous immunoglobulin (p = 0.511) use were not significantly associated with prognosis.

Notably, based on the Shapiro–Wilk test and assessment of skewness and kurtosis, age was normally distributed, whereas delay in diagnosis was not; therefore, parametric tests were applied for age, and non-parametric tests for delay in diagnosis. Overall, these findings highlight the importance of initial disease severity, the presence of underlying diseases, and the need for advanced therapeutic interventions in predicting poor outcomes, which can play a key role in early management and therapeutic decision-making (Table 8).

Table 8. Bivariate analysis of factors associated with poor prognosis in patients with AE

Factors associated with poor prognosis	χ^2 (Chi-square)	Significance
Age	47.48	0.453
Sex	0.932	0.334
Underlying Disease	9.816	0.002
Steroid	0.20	0.653
IVIG	0.43	0.511
Rituximab therapy	22.95	0
Cyclophosphamide	0.02	0.864
Tocilizumab	0.21	0.645
Methotrexate	15.48	0
Bortezomib	4.88	0.027
Plasmapheresis	8.48	0.004
Delay in diagnosis	3.27	0.952
Initial disease severity	10.46	0.005

Table 9. Multivariable Logistic Regression Model for predictors of poor prognosis

Independent variable	B	S.E.	Wald	OR (Exp(B))	%95 CI OR	p-value
Initial disease severity	2.589		4.615	13.32	-1.26	0.032
Plasmapheresis	1.723	1.008	2.920	5.60	40.43 – 0.78	0.087
Underlying diseases	3.447	1.282	7.227	31.42		0.007
Rituximab therapy	20.699	6494.173	0.000	$10^8\times$ 9.76	–	0.997
Methotrexate therapy	1.253	0.945	1.758	3.50	-0.549	0.185
Model constant	-21.259	6494.173	0.000	0.000	–	0.997

B: Regression coefficient; S.E.: standard error; OR: odds ratio; CI: confidence interval

To more precisely evaluate factors associated with poor prognosis, variables with p < 0.02 in the bivariate analyses were included in a multivariable logistic regression model.

In the multivariable logistic regression model assessing factors associated with poor prognosis, initial disease severity (OR = 13.3, 95% CI: 1.26–141.35, p = 0.032) and the presence of underlying diseases (OR = 31.4, 95% CI: 2.55–387.96, p = 0.007) were significantly associated with increased odds of poor prognosis. Plasmapheresis was associated with higher odds (OR = 5.6) but did not reach statistical significance (p = 0.087). Overall, the model was statistically significant (Omnibus $\chi^2 = 26.07$, $p < 0.001$) and demonstrated good fit (Hosmer–Lemeshow p = 0.944).

However, in a logistic regression model including rituximab and methotrexate, the estimation algorithm encountered complete separation, meaning that the presence/absence of poor prognosis was almost perfectly predicted by rituximab use. This resulted in extremely large coefficients, inflated standard errors, and unreliable odds ratios for rituximab ($\text{Exp(B)} \approx 9.7 \times 10^8$, SE ≈ 6494, p = 0.997), rendering it uninterpretable. Methotrexate showed an estimated OR of 3.50 (95% CI: 0.55–22.30) but was not statistically

significant (p = 0.185). Despite this, the model was overall statistically significant (Omnibus $\chi^2 = 27.44$, p < 0.001) with good fit (Hosmer–Lemeshow p = 1.000) and a prediction accuracy of 87.9%.

Due to the presence of complete separation and unstable estimates, this model should not be used for clinical inference. A more reliable final model includes only the robust, significant predictors—initial disease severity, underlying diseases, and plasmapheresis—and is recommended for reporting and clinical interpretation.

Discussion

In this study, 58 patients with (AE were evaluated. The obtained findings indicate that AE patients in Iran predominantly present during childhood and with moderate to severe disease. The most common clinical manifestation was seizure, with most patients requiring intensive care and ICU admission. EEG abnormalities were more frequent than MRI changes. These results suggest that clinical severity and the need for advanced therapeutic interventions play a primary role in treatment decisions, whereas serologic status (seropositive vs. seronegative) does not significantly influence initial disease severity.

International studies support these findings. Melha et al. reported that psychiatric symptoms, seizures, and encephalopathy are common in AE, with disease severity associated with younger age, refractory seizures, and severe encephalopathy (5). Gao et al. (2024) demonstrated that patients with seronegative exhibit more severe blood-brain barrier disruption, yet clinical severity is comparable to patients with seropositive (17). Additionally, Lee et al. reported similar clinical presentations and favorable responses to immunotherapy in both patients with seronegative and seropositive (18). Similarly, Berger et al. emphasized that therapeutic outcomes do not significantly differ between seronegative and seropositive groups, and both benefit from immunotherapy (19). Collectively, these findings indicate that serologic status alone is not the primary determinant of functional outcome, whereas initial clinical severity and the presence of comorbidities are more predictive.

First-line interventions, including corticosteroids and IVIG, were administered in most patients and were associated with favorable outcomes. Second-line therapies (rituximab, cyclophosphamide, methotrexate, tocilizumab, & bortezomab) did not differ significantly between seropositive and seronegative groups. International studies highlight that early combined immunotherapy significantly improves disability scores in treatment-resistant patients (5). Gao et al. reported that seropositive patients may respond better to immunotherapy, though seronegative patients also achieved satisfactory outcomes with first-line therapy (17). Lee et al. found that seronegative patients responded better to first-line therapy and required second-line treatment less frequently (18). Berger et al. further confirmed that AE patients, regardless of antibody status, benefit from immunotherapy (19). These findings align with our data, indicating that serologic status did not influence treatment selection or response, and clinical severity was the main determinant of therapeutic decisions. Minor differences among studies likely reflect geographic, methodological, and population-specific factors.

Analysis of factors associated with poor prognosis revealed that initial disease severity, comorbidities, need for plasmapheresis, and administration of advanced immunotherapies (rituximab & methotrexate) were associated with adverse outcomes in univariate analysis. In multivariate logistic regression, only initial disease severity (OR = 13.3, p = 0.032) and comorbidities (OR = 31.4, p = 0.007) were independently associated with increased odds of poor prognosis. Plasmapheresis showed a trend toward higher risk, but it was statistically insignificant (p = 0.087). These results are consistent with Melha et al.'s study (5) who identified severe initial disease, refractory seizures, and encephalopathy as predictors of poor outcomes in pediatric AE. The need for advanced therapies generally reflects higher disease severity rather than serving as an independent prognostic factor.

Overall, both this study and international literature indicate that serologic status alone does not determine disease severity or treatment response. Management should be guided primarily by clinical severity and the need for specialized care. Early, combined immunotherapy, including corticosteroids, IVIG, and second-line agents when indicated can substantially improve patient outcomes (5). Patients with comorbidities and higher initial severity require closer monitoring and advanced care, as they are at increased risk for poor prognosis. Serologic status should not limit therapeutic decision-making, and interventions should be tailored to clinical presentation and disease severity (17–19).

Iranian and worldwide studies consistently confirm that AE is a disease with a broad clinical spectrum, and factors associated with poor prognosis are more closely related to initial clinical severity, refractory seizures, and comorbidities than to antibody status (5, 17–19). In the present cohort, clinical presentation and response to therapy were similar between patients with seropositive and seronegative, emphasizing that serologic status is only a complementary factor in patient management.

Limitations of this study include its retrospective design, which may introduce information bias and incomplete data. The limited number of patients seronegative and seropositive restricted the statistical power for analyses of rare treatments. Additionally, limited long-term follow-up in some patients reduced the ability to evaluate late outcomes comprehensively. Despite these limitations, the current findings indicate that initial disease severity and comorbidities are the primary predictors of poor prognosis, while seropositive or seronegative status does not significantly affect disease severity, treatment response, or functional outcome. Early, combined immunotherapy can improve patient function, and clinical management should be guided by disease severity and need for specialized care rather than serologic status. These findings provide valuable guidance for therapeutic decision-making and planning of intensive care for patients with AE in Iran and other countries.

Study limitations

Data quality depended on hospital records, which could be incomplete or inconsistent. Cross-sectional design limits causal inference, and future prospective cohort studies are recommended for more robust outcome evaluation.

In Conclusion

This study, in conjunction with international literature, demonstrates that AE exhibits a wide clinical spectrum. Initial disease severity and comorbidities are the primary determinants of poor prognosis, whereas seropositive or seronegative status is not a significant factor. Response to immunotherapy, particularly early and combined treatment, plays a key role in improving functional outcomes. Therapeutic decisions should be based on clinical severity, need for intensive care, and presence of treatment-resistant symptoms. Clinical management of AE should rely on thorough clinical assessment and therapeutic needs, with serologic status serving only as a complementary factor. These findings offer important guidance for improving clinical care, treatment planning, and minimizing adverse outcomes in patients with AE patients in Iran and globally.

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Authors' contributions

MVS and AT analyzed and interpreted the patient data regarding the neurologic disease. VN and MK performed follow up the patient. LT and AR were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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