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Comorbidities and Their Influence on Outcomes and Infectious Complications in Autoimmune Encephalitis

A Multicenter Cohort Study

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Abstract

Background and Objectives

Comorbidities greatly influence the course of many diseases. However, systematic data on comorbidities in patients with autoimmune encephalitis (AE) are scarce. We aimed to characterize comorbidities in patients with common AE variants and assess their influence on outcome and occurrence of infectious complications.

Methods

This multicenter, retrospective cohort study analyzed adult patients with definite anti-N-methyl-D-aspartate receptor (NMDAR), anti-leucine–rich glioma-inactivated-1 (LGI1), anti-contactin–associated protein-like-2 (CASPR2), and anti-immunoglobulin–like cell adhesion molecule-5 (IgLON5) AE registered by the GErman NEtwork for REsearch on AuToimmune Encephalitis between June 2004 and July 2023. Preexisting conditions (PECs), secondary diagnoses, and infectious complications documented during hospitalization were analyzed. Outcome was evaluated using a modified Rankin Scale (mRS), with unfavorable outcome defined as mRS >2 after a minimum of 12 months of follow-up.

Results

Among 308 patients with AE (144 NMDAR-AE, 98 LGI1-AE, 47 CASPR2-AE, and 19 IgLON5-AE), nearly half had cardiovascular and metabolic/endocrine, one-third neurologic, and one-fifth psychiatric comorbidities. Accompanying autoimmunity was observed in 12.7%. Univariable analysis showed that the presence of ≥3 PECs (OR 2.80, 95% CI 1.57–4.92), especially cardiovascular (OR 1.93, 95% CI 1.09–3.30) and psychiatric PECs (OR 3.84, 95% CI 1.96–7.31), was associated with unfavorable outcome. Multivariable regression analysis confirmed psychiatric PECs as independent risk factors (OR 4.55, 95% CI 1.99–10.60). During hospitalization, 13.6% of patients developed severe infections, although these were not associated with unfavorable outcome (OR 1.94, 95% CI 0.97–3.89). AE disease severity (OR 5.41, 95% CI 1.38–27.67) and intensive care unit admission emerged as the only independent predictors of severe infections (OR 20.76, 95% CI 7.02–75.10).

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Supplementary Material

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Coinvestigators are listed online at Neurology.org/NN.

Glossary

Ab+ = antibody-positive; **AE** = autoimmune encephalitis; **CASE** = Clinical Assessment Scale in Autoimmune Encephalitis; **$CASE_{fu}$** = Clinical Assessment Scale in Autoimmune Encephalitis after a minimum follow-up period of 12 months; **$CASE_{max}$** = Clinical Assessment Scale in Autoimmune Encephalitis at disease peak; **CASPR2** = contactin-associated protein-like-2; **GENERATE** = GErman NEtwork for REsearch on AuToimmune Encephalitis; **HLA** = human leukocyte antigen; **HSE** = herpes simplex encephalitis; **ICU** = intensive care unit; **IgLON5** = immunoglobulin-like cell adhesion molecule-5; **LGI1** = leucine-rich glioma-inactivated-1; **mRS** = modified Rankin Scale; **mRS_{dis}** = modified Rankin Scale at the time of hospital discharge; **mRS_{fu}** = modified Rankin Scale after a minimum follow-up period of 12 months; **mRS_{max}** = modified Rankin Scale at disease peak; **MS** = multiple sclerosis; **NMDAR** = N-methyl-D-aspartate receptor; **NMOSD** = neuromyelitis optica spectrum disorder; **PEG** = percutaneous endoscopic gastrostomy; **PEC** = preexisting condition; **SD** = secondary diagnosis; **SIADH** = syndrome of inappropriate antidiuretica hormone secretion.

Discussion

As premorbid psychiatric conditions are main factors associated with unfavorable outcomes, these patients would highly benefit from integrated interdisciplinary treatment centers, or at least heightened awareness of these factors. Concomitant autoimmunity affecting other organs is frequent and should be sought. The risk of severe infections during the acute phase of AE is moderate and, given their lack of effect on outcome, should not justify withholding appropriate immunotherapy, even in elderly patients with comorbidities. Future prognostic models should incorporate comorbidities, particularly psychiatric ones, to enhance risk assessment and guide personalized care strategies.

Introduction

Autoimmune encephalitis (AE) circumscribes a group of rare, treatable inflammatory conditions of the brain. These disorders affect individuals across all age groups and cause substantial morbidity and mortality.[1] The most common variants are defined by pathogenic autoantibodies targeting synaptic receptors (e.g., anti-N-methyl-D-aspartate receptor [NMDAR], anti-contactin–associated protein-like-2 [CASPR2], and anti-immunoglobulin–like cell adhesion molecule-5 [IgLON5]) and scaffolding proteins (e.g., anti–leucine-rich glioma-inactivated-1 [LGI1]).[2] Although amenable to treatment, relapses are not uncommon, and outcomes vary widely.[3] Known risk factors associated with poor outcomes in certain AE subtypes, particularly in NMDAR-AE, include advanced age,[4] impaired consciousness,[5] intensive care unit (ICU) admission,[6,7] delayed initiation of immunotherapy,[6] and sepsis.[8] In contrast to NMDAR-AE, other common variants (e.g., LGI1, CASPR2, and IgLON5) preferentially affect elderly patients, who frequently suffer from comorbidities.

It is well known from other diseases that comorbidities can have a significant effect on disease severity and outcome and may serve as risk factors for infectious complications.[9] However, comorbidities have not yet been systematically incorporated into the risk assessment of AE outcomes. There are only limited data on whether certain comorbidities (e.g., autoimmune disorders, cardiovascular, or cerebrovascular preexisting conditions) are associated with the occurrence of AE in general or specific subtypes, and whether and to what extent comorbidities influence the clinical course, the occurrence of infectious complications, and the overall disease outcome.

This study aimed to provide a systematic analysis of preexisting conditions (PECs), newly acquired secondary diagnoses (SDs), and infectious complications in antibody-positive (ab+) AE, with a focus on its most common subtypes, including anti-NMDAR, anti-LGI1, anti-CASPR2, and anti-IgLON5 encephalitis. In addition, we investigated whether comorbidities influence long-term outcomes and the occurrence of infectious complications during hospitalization. The findings provide important insights into real-world clinical management and outcomes of patients with AE.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The data were obtained retrospectively through the GErman NEtwork for REsearch on AuToimmune Encephalitis (GENERATE), a collaborative initiative encompassing AE competence centers in Germany, Austria, and Switzerland. GENERATE functions as both a prospective and retrospective registry, enabling the pseudonymized collection of patient data diagnosed with AE. Ethical approval was obtained from the institutional review boards of the University of Lübeck (Germany; reference number: 13–162) and all actively recruiting centers. Written informed consent was provided by all patients or their legal representatives.

Study Population

Twenty centers participated in this multicenter study. The following inclusion criteria were applied: (1) age 18 years or older; (2) diagnosis of definite ab + AE (NMDAR, LGI1, CASPR2, and IgLON5) according to the consensus criteria[10]; (3) patient inclusion between June 11, 2004, and July 31, 2023; (4) availability of a complete data set in the GENERATE registry, including initial examination and at least 1 follow-up examination ≥12 months after initial hospital admission; and (5) availability of primary medical reports enabling coding of comorbidities and any infectious complications.

Data Collection and Assessment of Comorbidities, Infectious Episodes, Disease Severity, and Outcome

Demographic and clinical data were collected retrospectively through the GENERATE database, where they were initially entered by local investigators at each participating center. To ensure completeness, particularly regarding diagnoses documented in medical reports, these data were subsequently reviewed for missing information by the respective centers and supplemented either through direct entry into the GENERATE database or through the transmission of pseudonymized diagnosis lists. Diagnoses were categorized by organ system. A distinction was made between SDs, which referred to additional conditions diagnosed during the hospital stay alongside the primary diagnosis, and PECs, defined as previously diagnosed diseases that were documented in the patient's medical history before the current medical event. Comorbidity was used as an umbrella term encompassing both SDs and PECs.

Infectious episodes documented at the centers were systematically reviewed, and their severity was retrospectively assessed using the Common Terminology Criteria for Adverse Events (v5.0) for infections.[11] Disease severity and outcomes were evaluated using the Clinical Assessment Scale of Encephalitis (CASE; range 0–27) and the modified Rankin Scale (mRS; range from 0 to 6). Clinical Assessment Scale in Autoimmune Encephalitis (CASE) and mRS scores were recorded at the peak of the disease during the initial hospitalization (mRS_{max}, $CASE_{max}$), at hospital discharge (mRS_{dis}, mRS only), and at the last follow-up (mRS_{fu}, $CASE_{fu}$), conducted at least 12 months after the initial hospital admission. This minimum 12-month follow-up period was determined by the nature of the retrospective data collection to ensure the longest possible observation period after initial hospitalization and any therapies while maintaining a sufficiently large study population. Furthermore, potential or known factors influencing outcome or the occurrence of infectious complications were recorded, including sex, age, ICU admission, duration of hospitalization, and number of immunotherapies used during hospitalization.

Statistical Analysis

Data were analyzed using GraphPad Prism 10 (GraphPad Software Inc., San Diego, CA). The normality of distribution was evaluated using the Shapiro-Wilk test. Nominal and ordinal data were compared using the χ^2 test or Fisher exact test. For metric data that were not normally distributed, the Kruskal-Wallis test was applied, followed by the Dunn multiple comparison test. Multivariable analyses were conducted using a binary logistic regression model; the variables used are described in Tables 1 and 2. For analysis, a dichotomous classification of the mRS and CASE scores was performed into mildly affected/favorable outcome (CASE ≤4, mRS ≤2) and severely affected/unfavorable outcome (CASE >4, mRS >2). Further variables were dichotomized based on the median, including the presence of SD (≥1 vs <1), the presence of PECs (≥3 vs <3), and the number of immunotherapies administered (≥3 vs <3). In the univariable analysis, age was dichotomized using the median, rounded to the nearest decade, into categories of ≥50 vs <50 years. Nominal variables were reported as numbers and percentages, while ordinal and metric variables were presented as medians with interquartile ranges. All tests were two-tailed, and p values were set at $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, and $^{***}p \leq 0.001$.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

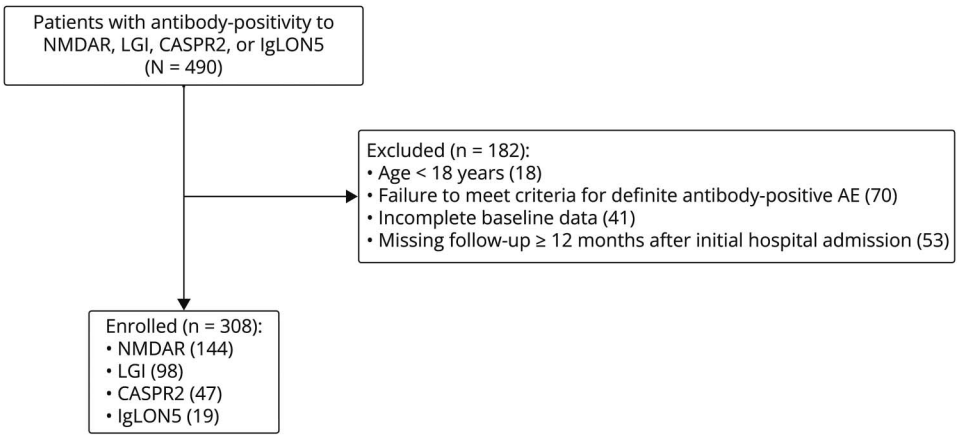
Results

Characterization of the Patient Cohort

We screened 490 patients with anti-NMDAR-AE, LGI1-AE, CASPR2-AE, or IgLON5-AE in participating GENERATE centers. Of these, 308 patients who met our inclusion criteria were included in our primary analysis cohort (Figure 1; n = 144 NMDAR-AE, n = 98 LGI-AE, n = 47 CASPR2-AE, and n = 19 IgLON5-AE). Most patients were excluded for not meeting the criteria for definite ab + AE according to the consensus criteria[10] (n = 70); other reasons for exclusion are detailed in Figure 1.

Demographic and clinical characteristics of the primary analysis cohort are given in eTable 1. As expected, patients with NMDAR-AE were younger (median age 29 years), more often female, more functionally impaired at onset, hospitalized the longest, and required ICU treatment in 38% of cases. By contrast, patients with LGI1-AE, CASPR2-AE, and IgLON5-AE were older (median ages: 65, 65, and 61 years), had less female predominance, had less impairment at onset, and especially in LGI1-AE and CASPR2-AE patients, required ICU treatment less frequently (9%–15% in LGI1-AE and CASPR2-AE patients vs 21% in IgLON5-AE patients). The clinical course and outcome of patients in the 4 AE subgroups assessed by mRS are illustrated in eFigure 1. NMDAR-AE patients continued to improve over time, whereas LGI1-AE and CASPR2-AE patients showed initial recovery followed by mostly stable, although often residual, disability. IgLON5-AE patients initially improved, but tended to have worse disability at follow-up, with 10.5% of patients having died by the last follow-up.

Figure 1 Patient Selection



Screening of 490 patients with antibody positivity to NMDAR, LGI1, CASPR2, or IgLON5 from the GENERATE database, resulting in 308 patients remaining after applying the inclusion criteria. Definitive antibody-positive AE was determined according to the consensus criteria.[10] AE = autoimmune encephalitis; CASPR2 = contactin-associated protein-like-2; GENERATE = GErman NEtwork for REsearch on AuToimmune Encephalitis; IgLON5 = immunoglobulin-like cell adhesion molecule-5; LGI1 = leucine-rich glioma-inactivated-1; NMDAR = N-methyl-D-aspartate receptor.

Comorbidities in Patients With AE

Across the 4 AE subtypes, a variety of comorbidities were observed, grouped by organ system, and categorized as either PECs or SDs (Figure 2, A and B). This categorization distinguished previously diagnosed diseases documented in the patient's medical history before the current medical event (PECs), potentially influencing disease onset or progression, from newly emerging conditions during hospitalization (SDs), often reflecting complications related to the primary diagnosis or its treatment. Detailed information on the frequency of each disease is provided in eTable 2. Nearly half of the patients presented with cardiovascular and metabolic/endocrine comorbidities (eTable 2). Approximately one-third had neurologic comorbidities, and around one-fifth were affected by psychiatric comorbidities (eTable 2).

Autoimmune comorbidities, shown in Figure 3, were observed in 12.7% of patients (female/male 15.5%/9.3%) and were most frequent in NMDAR-AE and CASPR2-AE patients. Among NMDAR-AE patients, 14.6% had autoimmune comorbidities, which was substantially higher than the expected 4.1% for individuals aged 18–44 years.[12] These included multiple sclerosis ([MS]; applied diagnostic criteria not specified), found in 4.9%, compared with only 0.5% in the White population aged 35–44 years,[13] while aquaporin-4-positive neuromyelitis optica spectrum disorder (NMOSD) was present in 0.7% (1 patient), exceeding its estimated prevalence of 0.004% (ages 15–64 years).[14] Similarly, 14.9% of CASPR2-AE patients exhibited autoimmune comorbidities, exceeding the expected 7.6% for individuals older than 65 years.[12] The most common conditions were Hashimoto thyroiditis (6.4%, compared with 8.0% in the European adult population)[15] and ulcerative colitis (4.3%, well above the estimated 0.7% prevalence for individuals 60 years or older by 2030).[16] In LGI1-AE patients, 10.2% had autoimmune comorbidities, again higher than expected,[12] including type 1 diabetes mellitus (2.0%, vs 0.5% in the general ≥65-year population)[17] and Sjögren syndrome (1.0% (1 patient), vs 0.2% in the 65–74-year population).[18] By contrast, IgLON5-AE patients had the lowest prevalence of autoimmune comorbidities (5.3%), which was lower than the expected 7.6% for individuals older than 65 years[12]

PECs in Patients With AE

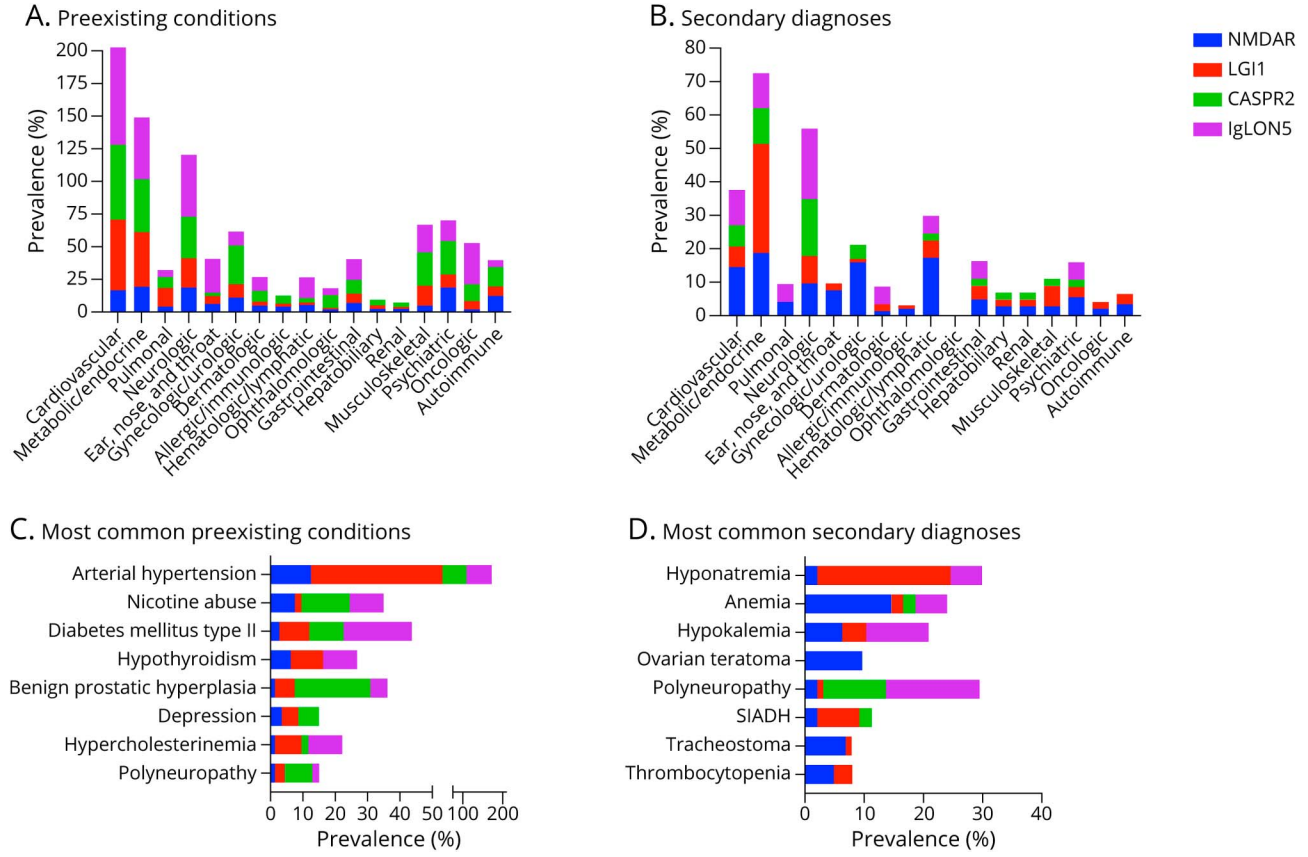
The distribution of PECs across the AE subgroups, categorized by organ system, is shown in Figure 2A, with the most common individual PECs depicted in Figure 2C. In the overall cohort, 76.0% of patients had at least 1 PEC, with 37.3% having more than 3.

IgLON5-AE patients exhibited the highest prevalence of PECs (78.9% with ≥3) and had increased rates of polyneuropathy (21.1% vs 3.9% in the general population aged 60–70 years),[19] restless legs syndrome (15.8% vs 8.6% in the general population aged 60–64 years),[20] and malignancies (31.6% vs 11.3% in individuals aged ≥65 years)[21] (eTable 2). In addition, 1 patient had a history of herpes simplex encephalitis (HSE) (eTable 2). NMDAR-AE patients had the lowest overall rate of PECs (22.9% with ≥3). However, a notable but not higher than expected proportion of these patients had psychiatric PECs (18.8% vs 29.2% in the general population aged 25–29 years),[22] including substance use disorder, nicotine abuse, anxiety disorder, panic disorder, posttraumatic stress disorder, and borderline personality disorder (eTable 2). A history of HSE was recorded in 6.3% of NMDAR-AE patients (eTable 2).

Influence of PECs on Outcomes in AE

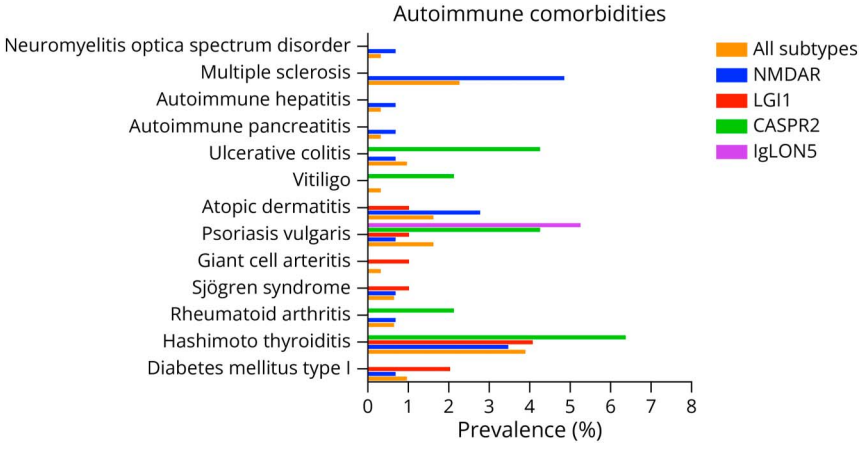
We investigated whether clinical and demographic factors known or potentially influencing outcome (Figure 4A) and PECs (Figure 4B) were associated with adverse outcome (mRS >2) in patients with AE. First, a univariable analysis was performed, revealing several factors associated with an unfavorable outcome (Figure 4). These included the IgLON5-AE subtype (OR 4.95, 95% CI 1.84–11.81, $p = 0.001$), a high

Figure 2 Prevalence of Comorbidities in 4 Autoimmune Encephalitis Subtypes, Grouped by Preexisting Conditions and Secondary Diagnoses



(A) Preexisting conditions (PECs) and (B) secondary diagnoses (SDs) categorized by affected organ systems. (C) Most common PECs and (D) most common SDs in the overall cohort. "Comorbidities" serves as an umbrella term encompassing both PECs, defined as previously diagnosed diseases that were documented in the patient's medical history before the current medical event, and SDs, defined as additional diagnoses made during hospitalization alongside the primary condition. The y-axis (A and B) or x-axis (C and D) represent prevalence (%), calculated within each subtype. Note that the stacked bars show contributions from different subtypes and may exceed 100% in total. Blue bars represent the NMDAR-AE cohort (n = 144), red bars the LGI1-AE cohort (n = 98), green bars the CASPR2-AE cohort (n = 47), and purple bars the IgLON5-AE cohort (n = 19). Diagnoses were identified directly from the GENERATE database, as well as from discharge summaries and inpatient documentation. AE = autoimmune encephalitis; CASPR2 = contactin-associated protein-like-2; GENERATE = GErman NEtwork for REsearch on AuToimmune Encephalitis; IgLON5 = immunoglobulin-like cell adhesion molecule-5; LGI1 = leucine-rich glioma-inactivated-1; NMDAR = N-methyl-D-aspartate receptor; PEC = preexisting condition; SD = secondary diagnosis.

Figure 3 Prevalence of Autoimmune Comorbidities Across 4 Subtypes of Autoimmune Encephalitis



NMDAR (n = 144, blue), LGI (n = 98, red), CASPR2 (n = 47, green), IgLON5 (n = 19, purple), and combined data across all subtypes (n = 308, orange). Autoimmune diseases are listed on the y-axis, the x-axis represents the prevalence as a percentage (%). Each bar indicates the frequency of each autoimmune comorbidity within each encephalitis subtype, highlighting subtype-specific comorbidity patterns among patients. Diagnoses were identified directly from the GENERATE database, as well as from discharge summaries and inpatient documentation. AE = autoimmune encephalitis; CASPR2 = contactin-associated protein-like-2; GENERATE = GErman NEtwork for REsearch on AuToimmune Encephalitis; IgLON5 = immunoglobulin-like cell adhesion molecule-5; LGI1 = leucine-rich glioma-inactivated-1; NNMDAR = N-methyl-D-aspartate receptor.

mRS score (>2) at disease peak (OR 3.01, 95% CI 1.36–7.20, $p = 0.01$), and having 3 or more PECs (OR 2.80, 95% CI 1.57–4.92, $p < 0.001$). In addition, cardiovascular (OR 1.93, 95% CI 1.09–3.30, $p = 0.03$) and psychiatric PECs (OR 3.84, 95% CI 1.96–7.31, $p < 0.001$) were linked to unfavorable outcomes. Following this, a multivariable regression analysis was conducted to identify independent risk factors (Table 1). In this adjusted model, a high mRS score (>2) at disease peak (OR 3.47, 95% CI 1.39–9.85, $p = 0.01$) and the IgLON5-AE subtype (OR 5.03, 95% CI 1.42–18.62, $p = 0.01$) remained significant independent risk factors. In addition, increasing age emerged as an independent risk factor (OR 1.04, 95% CI 1.01–1.09, $p = 0.01$), along with the presence of psychiatric PECs, which continued to show a robust association with unfavorable outcomes (OR 4.55, 95% CI 1.99–10.60, $p < 0.001$).

SDs in Patients With AE

Figure 2B shows the distribution of SDs grouped by organ system. The highest proportion of SDs was observed in NMDAR-AE patients, with 54.9% having at least 1 SD. Notable SDs in this subgroup included cardiovascular conditions (e.g., asystole [4.9%], pacemaker implantation [3.5%], atrioventricular block [2.8%], and pulmonary embolism [2.1%]), metabolic/endocrine disorders (e.g., electrolyte imbalance [11.8%], syndrome of inappropriate antidiuretic hormone secretion [SIADH] [2.1%]), and hematologic/lymphatic conditions (e.g., anemia [14.6%]) (eTable 2). Ovarian teratomas, as gynecologic SDs, were observed in 9.7% of NMDAR-AE patients (eTable 2). Other notable SDs included invasive procedures, such as tracheostomy (6.9%) and percutaneous endoscopic gastrostomy (PEG) (2.8%) (eTable 2).

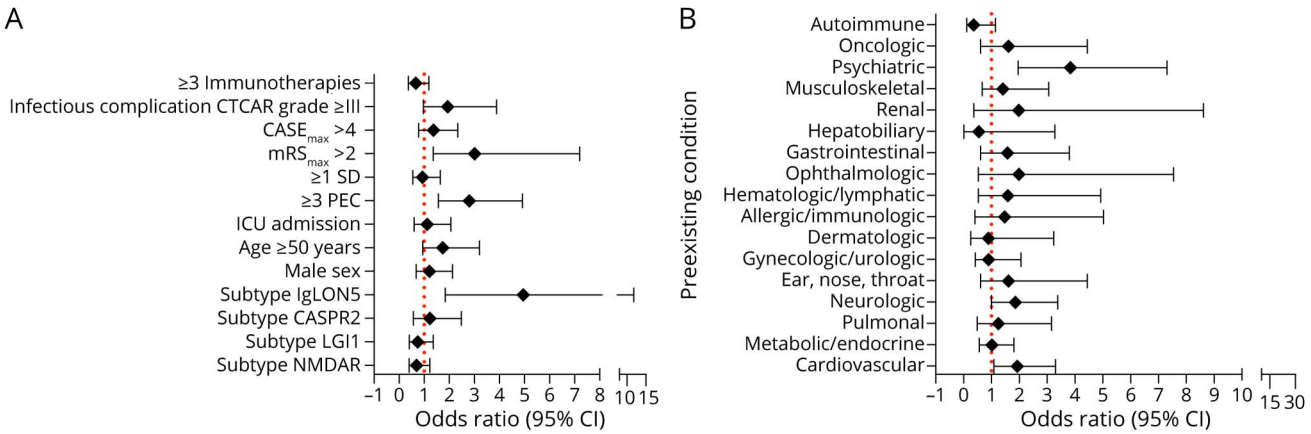
In LGI1-AE patients, prevailing SDs included metabolic/endocrine conditions, such as hyponatremia (22.5%) and SIADH (7.1%), neurologic SDs (8.2%), and musculoskeletal SDs (6.1%), including femoral neck fracture requiring surgery (2.0%) and vertebral fracture (2.0%) (eTable 2).

CASPR2-AE and IgLON5-AE patients exhibited the lowest rate of SDs, with neurologic SDs, particularly polyneuropathy (10.6% in CASPR2-AE and 15.8% in IgLON5-AE patients), being the most common (Figure 2D, eTable 2).

Infectious Complications in Hospitalized Patients With AE

Infectious complications recorded during the initial hospitalization are detailed in eTable 3. Across all AE subtypes, 43 patients (14.0%) experienced at least 1 infection, including 42 patients (13.6%) with severe infections, defined as infections necessitating IV medication and/or invasive procedures, while 83.3% of those with severe infections also required intensive care. Notably, severe infections affected about 21% of patients with NMDAR-AE, 9% with LGI1-AE, 5% with IgLON5-AE, and 4% with CASPR2-AE. Hospital-acquired pneumonia was the most common infection, affecting 8.8% of all patients and 16.0% of those with the NMDAR-AE subtype. The second most frequent infection was urinary tract

Figure 4 Risk Factors Associated With Unfavorable Functional Outcome in Patients With Autoimmune Encephalitis (Univariable Analysis)



Factors associated with unfavorable functional outcomes in patients with antibody-positive autoimmune encephalitis (n = 308): NMDAR (n = 144), LGI1 (n = 98), CASPR2 (n = 47), and IgLON5 (n = 19). (A) Associations of clinical and demographic factors with unfavorable functional outcome. (B) Associations of preexisting conditions, categorized by organ system, with unfavorable functional outcome. Each diamond represents the odds ratio, with horizontal lines indicating the 95% CIs. Odds ratios >1 indicate an association with an unfavorable functional outcome, defined as an mRS >2. Outcome was measured after a follow-up period of at least 12 months. Univariable analysis was performed using the Fisher exact test. Diagnoses and infectious episodes were identified directly from the GENERATE database, as well as from discharge summaries and inpatient documentation. The severity of infectious complications was retrospectively assessed using the CTCAE (v5.0) for infections. Note that the variable "≥3 immunotherapies" refers to the use during the first hospitalization (disease peak) and that the variable "infectious complication CTCAE grade ≥ III" refers only to the occurrence during the first hospitalization (disease peak). CASEmax = Clinical Assessment Scale in Autoimmune Encephalitis at disease peak; CASPR2 = contactin-associated protein-like-2; CTCAE = Common Terminology Criteria for Adverse Events; GENERATE = GErman NEtwork for REsearch on AuToimmune Encephalitis; ICU = intensive care unit; IgLON5 = immunoglobulin-like cell adhesion molecule-5; LGI1 = leucine-rich glioma-inactivated-1; mRS = modified Rankin Scale; mRSmax = modified Rankin Scale at disease peak; NMDAR = N-methyl-D-aspartate receptor; PEC = preexisting condition; SD = secondary diagnosis.

Table 1 Independent Risk Factors Associated With Unfavorable Functional Outcome in Patients With Autoimmune Encephalitis (Multivariable Analysis)

Variable	Estimate (95% CI)	Odds ratio (95% CI)	*p* Value
Clinical/demographic factors			
Male sex	−0.35 (−1.13 to 0.41)	0.71 (0.32–1.51)	0.37
Age	0.04 (0.01–0.06)	1.04 (1.01–1.05)	**0.01**
Subtype NMDAR	0.32 (−0.72 to 1.37)	1.38 (0.49–3.93)	0.54
Subtype CASPR2	0.33 (−0.78 to 1.42)	1.39 (0.46–4.15)	0.55
Subtype IgLON5	1.62 (0.35–2.92)	5.03 (1.42–18.62)	**0.01**
mRS_{max} >2	1.24 (0.33–2.29)	3.47 (1.39–9.85)	**0.01**
ICU admission	−0.02 (−0.99 to 0.91)	0.98 (0.37–2.49)	0.97
Duration of hospitalization	−0.01 (−0.02 to 0.00)	0.99 (0.98–1.00)	0.29
Infectious complications CTCAE grade ≥ III	0.82 (−0.24 to 1.89)	2.26 (0.79–6.61)	0.13
Number of PEC ≥3	0.73 (−0.32 to 1.80)	2.08 (0.73–6.05)	0.17
Preexisting conditions			
Cardiovascular	−0.15 (−1.14 to 0.80)	0.86 (0.32–2.22)	0.76
Metabolic/endocrine	−0.59 (−1.45 to 0.22)	0.55 (0.24–1.25)	0.16
Pulmonal	−0.45 (−0.74 to 1.76)	1.58 (0.48–5.83)	0.47
Neurologic	0.36 (−0.42 to 1.12)	1.44 (0.66–3.08)	0.35
Ear, nose, throat	−0.29 (−1.64 to 0.91)	0.75 (0.19–2.49)	0.65
Gynecologic/urologic	−0.57 (−1.70 to 0.45)	0.56 (0.18–1.57)	0.29
Dermatologic	−0.68 (−2.61 to 1.06)	0.51 (0.07–2.87)	0.46
Allergic/immunologic	0.79 (−1.14 to 2.61)	2.21 (0.32–13.56)	0.40
Hematologic/lymphatic	0.43 (−1.11 to 1.80)	1.53 (0.33–6.03)	0.56
Ophthalmologic	1.15 (−0.95 to 3.04)	3.17 (0.39–20.99)	0.25
Gastrointestinal	0.27 (−1.06 to 1.54)	1.32 (0.35–4.66)	0.68
Hepatobiliary	−1.03 (−4.25 to 1.18)	0.36 (0.01–3.25)	0.43
Renal	0.36 (−1.89 to 2.46)	1.43 (0.15–11.66)	0.74
Musculoskeletal	−0.62 (−1.72 to 0.41)	0.54 (0.18–1.50)	0.25
Psychiatric	1.52 (0.69–2.36)	4.55 (1.99–10.60)	**<0.001**
Oncologic	−0.68 (−2.05 to 0.59)	0.51 (0.13–1.81)	0.31
Autoimmune	−0.96 (−2.66 to 0.42)	0.38 (0.07–1.51)	0.21

Abbreviations: AE = autoimmune encephalitis; AUC = area under the receiver operating characteristic curve; CASPR2 = contactin-associated protein-like-2; CTCAE = Common Terminology Criteria for Adverse Events; ICU = intensive care unit; IgLON5 = immunoglobulin-like cell adhesion molecule 5; LGI1 = leucine-rich glioma-inactivated-1; mRS_{max} = modified Rankin Scale at disease peak; NMDAR = N-methyl-D-aspartate receptor; PEC = preexisting condition.
Multivariable analysis was performed using a binary logistic regression model (n = 308). Odds ratios >1 indicate an association with an unfavorable functional outcome, defined as an mRS >2. Outcome was measured after a follow-up period of at least 12 mo. For the regression analysis, dummy coding was applied to the categorical variable "AE subtype" with the LGI1 subtype set as the reference category. *p* Values that reached statistical significance ($p \leq 0.05$) are highlighted in bold. Regarding the goodness of fit of the regression model, the following values were obtained: an AUC of 0.80 (CI 0.74–0.86, *p* value < 0.001), a Tjur *R*-square of 0.21, and a *p* value in the Hosmer-Lemeshow test of 0.74.

infection, which occurred in 5.5% of the cohort. Sepsis was observed in 1.4% of NMDAR-AE patients and 1 patient with LGI1-AE. However, severe infections were not associated with an unfavorable outcome in either univariable (OR 1.94, 95% CI 0.97–3.89, $p = 0.10$; Figure 4) or multivariable analysis (OR 2.26, 95% CI 0.79–6.61, $p = 0.13$; Table 1).

Risk Factors for Severe Infectious Complications in Hospitalized Patients With AE

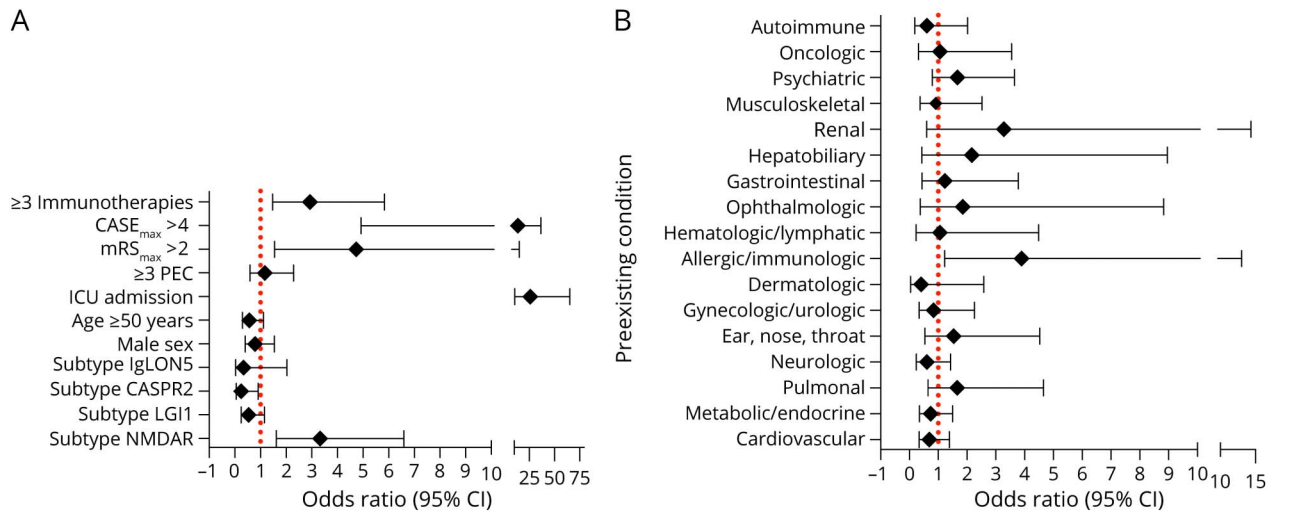
Figure 5 illustrates the univariable analysis of clinical, demographic, and preexisting conditions as potential risk factors for severe infectious complications in hospitalized patients with AE. Several factors were associated with an increased risk of severe infections. These included the NMDAR-AE subtype (OR 3.33, 95% CI 1.62–6.60, $p < 0.001$), a high mRS (>2) (OR 4.73, 95% CI 1.55–14.97, $p = 0.006$) or CASE score (>4) (OR 13.68, 95% CI 4.92–36.45, $p < 0.001$) at disease peak, the use of 3 or more immunotherapies during hospitalization (OR 2.93, 95% CI 1.47–5.84, $p = 0.002$), and ICU admission (OR 25.93, 95% CI 10.55–65.47, $p < 0.001$) (Figure 5A). Among PECs, allergic or immunologic disorders were linked to severe infectious complications (OR 3.90, 95% CI 1.22–13.05, $p = 0.05$) (Figure 5B). In the multivariable analysis, disease severity (OR 5.41, 95% CI 1.38–27.67, $p = 0.02$), as indicated by a high CASE score (>4) at disease peak, and ICU admission (OR 20.76, 95% CI 7.02–75.10, $p < 0.001$) emerged as the only independent risk factors, maintaining a strong association with the occurrence of severe infectious complications (Table 2).

Discussion

In this study, we performed a comprehensive characterization of comorbidities in ab + AE variants, including NMDAR-AE, LGI1-AE, CASPR2-AE, and IgLON5-AE, using data from a multicenter cohort of 308 patients. Our findings reveal a significant burden of comorbidities in AE, with notable differences across subtypes and a high prevalence of autoimmune conditions. The presence of 3 or more PECs was associated with unfavorable outcomes, with psychiatric PECs in particular proving to be independent risk factors. Severe infections occurred in 13.6% of cases during hospitalization, especially in patients with NMDAR-AE and those requiring ICU treatment, but were not associated with unfavorable outcomes. Although disease severity and the need for intensive medical treatment were linked to severe infections, the presence of 3 or more PECs was not.

Our study highlights the high burden of multimorbidity in patients with AE, with three-quarters of patients presenting with at least 1 PEC at the time of initial diagnosis, and over one-third having 3 or more. Cardiovascular conditions were frequently observed. However, their prevalence was comparable with that in the general population,[23] indicating these may be age-related or risk factor-related rather than specifically linked to AE. By contrast, the prevalence of autoimmune comorbidities was considerably higher than in the general population. A UK study involving 22 million individuals reported an autoimmune disease prevalence of 10.2%.[24] A large US study found an age-dependent increase, with prevalence rates of 4.1% in individuals aged 18–44 years,

Figure 5 Factors Associated With Severe Infectious Complications in Hospitalized Patients With Autoimmune Encephalitis (Univariable Analysis)



Factors associated with severe infectious complications in patients with antibody-positive autoimmune encephalitis (n = 308): NMDAR (n = 144), LGI1 (n = 98), CASPR2 (n = 47), and IgLON5 (n = 19). (A) Associations of clinical, demographic, and therapeutic factors with severe infectious complications. (B) Associations of preexisting conditions, categorized by organ system, with severe infectious complications. Each diamond represents the odds ratio, with horizontal lines indicating the 95% CIs. Odds ratios >1 indicate an association with the occurrence of severe infectious complications, defined as CTCAE grade ≥ III. Univariable analysis was performed using the Fisher exact test. Diagnoses and infectious episodes were identified directly from the GENERATE database, as well as from discharge summaries and inpatient documentation. The severity of infectious complications was retrospectively assessed using the CTCAE (v5.0) for infections. Note that only infectious episodes during the first hospitalization (disease peak) were assessed and that the variable "≥3 immunotherapies" refers to use during the first hospitalization (disease peak). CASE$_{max}$ = Clinical Assessment Scale in Autoimmune Encephalitis at disease peak; CASPR2 = contactin-associated protein-like-2; CTCAE = Common Terminology Criteria for Adverse Events; GENERATE = GErman NEtwork for REsearch on AuToimmune Encephalitis; ICU = intensive care unit; IgLON5 = immunoglobulin-like cell adhesion molecule-5; LGI1 = leucine-rich glioma-inactivated-1; mRS = modified Rankin Scale; mRS$_{max}$ = modified Rankin Scale at disease peak; NMDAR = N-methyl-D-aspartate receptor; PEC = preexisting condition.

Table 2 Independent Risk Factors Associated With Severe Infectious Complications in Hospitalized Patients With Autoimmune Encephalitis (Multivariable Analysis)

Variable	Estimate (95% CI)	Odds ratio (95% CI)	*p* Value
Clinical/demographic factors			
Male sex	−0.02 (−1.11 to 1.06)	0.98 (0.33–2.88)	0.96
Age	0.03 (−0.01 to 0.07)	1.03 (0.99–1.07)	0.13
Subtype NMDAR	0.38 (−0.96 to 1.75)	1.47 (0.38–5.78)	0.58
Subtype CASPR2	−0.85 (−3.33 to 1.10)	0.43 (0.04–2.99)	0.44
Subtype IgLON5	−1.24 (−4.48 to 1.09)	0.29 (0.01–2.97)	0.35
mRS_{max} >2	−0.19 (−1.91 to 1.74)	0.83 (0.15–5.68)	0.84
$CASE_{max}$ >4	1.69 (0.32–3.32)	5.41 (1.38–27.67)	**0.02**
ICU admission	3.03 (1.95–4.32)	20.76 (7.02–75.10)	**<0.001**
Number of PEC ≥3	0.46 (−1.11 to 2.06)	1.59 (0.33–7.84)	0.56
≥3 immunotherapies	0.50 (−0.52 to 1.56)	1.66 (0.59–4.76)	0.34
Preexisting conditions			
Cardiovascular	−0.46 (−1.97 to 0.99)	0.63 (0.14–2.70)	0.54
Metabolic/endocrine	−0.10 (−1.30 to 1.05)	0.90 (0.27–2.86)	0.86
Pulmonal	0.17 (−1.64 to 1.84)	1.18 (0.19–6.32)	0.85
Neurologic	−0.27 (−1.55 to 0.92)	0.76 (0.21–2.52)	0.67
Ear, nose, throat	0.06 (−2.00 to 1.98)	1.06 (0.14–7.26)	0.95
Gynecologic/urologic	−0.22 (−1.77 to 1.18)	0.80 (0.17–3.25)	0.76
Dermatologic	−1.07 (−4.99 to 1.80)	0.34 (0.01–6.02)	0.53
Allergic/immunologic	1.98 (−0.61 to 4.90)	7.22 (0.55–134.60)	0.16
Hematologic/lymphatic	−0.25 (−2.93 to 1.99)	0.78 (0.05–7.32)	0.83
Ophthalmologic	1.75 (−1.76 to 4.45)	5.75 (0.17–86.00)	0.25
Gastrointestinal	1.12 (−1.18 to 3.18)	3.07 (0.31–24.01)	0.30
Hepatobiliary	−1.26 (−5.78 to 2.43)	0.28 (0.00–11.35)	0.56
Renal	1.30 (−1.93 to 4.68)	3.68 (0.15–108.00)	0.44
Musculoskeletal	0.08 (−1.57 to 1.61)	1.08 (0.21–5.00)	0.92
Psychiatric	0.73 (−0.56 to 2.03)	2.08 (0.57–7.61)	0.26
Oncologic	0.12 (−2.08 to 2.13)	1.13 (0.12–8.42)	0.91
Autoimmune	−1.30 (−3.93 to 0.74)	0.27 (0.02–2.10)	0.26

Abbreviations: AE = autoimmune encephalitis; AUC = area under the receiver operating characteristic curve; CASPR2 = contactin-associated protein-like-2; CTCAE = Common Terminology Criteria for Adverse Events; ICU = intensive care unit; IgLON5 = immunoglobulin-like cell adhesion molecule-5; LGI1 = leucine-rich glioma-inactivated-1; mRSmax = modified Rankin Scale at disease peak; NMDAR = N-methyl-D-aspartate receptor; PEC = preexisting condition.
Multivariable analysis was performed using a binary logistic regression model (n = 308). Odds ratios >1 indicate an association with the occurrence of severe infectious complications. The severity of infectious complications was retrospectively assessed using the CTCAE (v5.0) for infections. A CTCAE grade III infection is defined as severe, requiring IV medication and/or hospitalization and/or invasive procedures. Note that only infectious episodes during the first hospitalization (disease peak) were assessed and that the variable "≥3 immunotherapies" refers to use during the first hospitalization (disease peak). For the regression analysis, dummy coding was applied to the categorical variable "AE subtype" with the LGI1 subtype set as the reference category. *p* Values that reached statistical significance ($p \leq 0.05$) are highlighted in bold. Regarding the goodness of fit of the regression model, the following values were obtained: an AUC of 0.91 (CI 0.86–0.95, *p* value < 0.001), a Tjur *R*-square of 0.38, and a *p* value in the Hosmer-Lemeshow test of 0.76.

6.7% in those aged 45–64 years, and 7.6% in those aged 65 years or older.[12] In our NMDAR-AE cohort, 14.6% had autoimmune comorbidities, although a lower prevalence was previously reported in a Chinese cohort.[25] This discrepancy may reflect regional differences because autoimmune diseases are less frequently observed in China.[26]

Subtype-specific analysis revealed a notably high occurrence of MS among patients with NMDAR-AE, reaching 4.9%, compared with the 0.7% prevalence observed in an age-matched non-Hispanic White female population.[13] Overlapping demyelinating syndromes have been reported in 3.3% of NMDAR-AE patients, some of which involved aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies.[27] In our cohort, half of the patients with concurrent NMDAR-AE and MS received their MS diagnosis at the onset of NMDAR-AE, mirroring previously reported findings.[27] Such co-occurrence may indicate a shared underlying mechanism or bidirectional disease interactions, possibly mediated by the release of autoantigens, because NMDA receptors are expressed on myelin sheaths.[28] Similarly, the prevalence of NMOSD was 0.7%, consistent with previous findings[27] and exceeding rates in the general population by more than 150-fold.[14] Of interest, among LGI1-AE patients, the prevalence of type I diabetes (2.0%) was considerably higher than in the general ≥65-year population (0.5%),[17] with both diseases sharing an association with human leukocyte antigen (HLA)-DRB1*07:01.[29,30] In our CASPR2-AE patients, autoimmune comorbidities were present in 14.9%, comparable with a Chinese cohort[25] but lower than reported in another Caucasian cohort.[29] Strikingly, ulcerative colitis prevalence was more than 6 times higher than the estimated prevalence for individuals 60 years or older by 2030.[16] We did not identify any published cases linking ulcerative colitis with CASPR2-AE in the current literature. Disruptions in the gut microbiome, as seen in ulcerative colitis[31] as well as in AE,[32] may play a role, suggesting that further investigation of gut-brain interactions in AE is warranted.

The co-occurrence of autoimmune diseases likely reflects a complex interplay of genetic-related, environmental-related, and therapy-related factors. Shared genetic risk factors, especially HLA class I and II polymorphisms, are associated with all AE subtypes studied here[29] and may drive systemic immune dysregulation. Environmental factors, such as infections, malignancies, and the microbiome, can initiate or exacerbate autoimmune responses through mechanisms such as virus-induced cell lysis, molecular mimicry, or disruptions in immune tolerance, often accompanied by immune-mediated cell damage and compromised barrier integrity.[32-34] Chronic systemic inflammation may promote ongoing activation of lymphocytes, fostering conditions for additional autoimmune diseases.

Beyond autoimmune comorbidities, several other disease clusters were observed in our study. In NMDAR-AE patients, approximately 10% had an underlying teratoma, a well-documented association that has been known for over a decade.[34] However, higher rates have been reported in other cohorts.[35] This discrepancy may reflect, at least in part, increased recognition of the disease, leading to more frequent diagnosis in older patients who are less likely to harbor teratomas, and potentially higher loss to follow-up in less chronic, less relapse-prone teratoma-associated cases. In addition, 6.9% of NMDAR-AE cases and 1 patient in the IgLON5-AE subgroup had a diagnosis of HSE, further supporting the link between HSE and subsequent AE.[33] In the LGI1-AE subgroup, hyponatremia was observed in one-third of patients, a known association reported with similar or even higher prevalence in other cohorts.[36] Although commonly attributed to SIADH,[36] only one-quarter of cases were diagnosed as such (eTable 2), suggesting underdiagnosis. Within the CASPR2-AE and IgLON5-AE subgroups, a substantial proportion of patients presented with polyneuropathy, a finding consistent with other studies.[37,38] For patients in the IgLON5-AE subgroup, an elevated prevalence of restless legs syndrome was observed, affecting 15.8% of the cohort. This rate exceeds the expected prevalence in the age-matched general population[20] and may reflect an overlap with symptoms of akathisia, which could present similarly in this context.[39] Notably, a history of malignancies was found in one-third of IgLON5-AE patients, a rate exceeding previous reports[38] and the age-matched general population.[21] However, the timing of these malignancies in relation to AE diagnosis is unclear, and no malignancies were identified in parallel with AE onset. Given that IgLON5-AE has not been classified as a paraneoplastic syndrome and the advanced age of the patients, these findings may reflect coincidence rather than causality.

A critical aspect of the management of AE patients is the occurrence of severe secondary complications. In our NMDAR-AE cohort, there was a notable rate of serious cardiac complications, including cases of asystole and the need for pacemaker implantation. Furthermore, a substantial proportion of NMDAR-AE patients required tracheostomy or PEG tube placement due to respiratory and nutritional challenges. Patients with LGI1-AE, on the other hand, frequently experienced complications related to falls, such as fractures, potentially linked to ictal events. These complications emphasize the importance of close monitoring, preventive strategies, and a multidisciplinary management of AE.

In addition to systematically assessing comorbidities, we also conducted a comprehensive evaluation of infectious complications in hospitalized AE patients all of whom underwent various immunomodulatory treatments. Nearly all infections were severe, and the majority of these patients required ICU management. Infection rates exceeded those typically observed in general wards, but were lower than in ICU settings.[40] However, ICU-treated patients in our cohort exhibited infection rates higher than ICU norms.[40] The types of infections observed in our cohort were consistent with those typically seen in hospitalized patients, except for postoperative wound infections.[40]

Several factors were linked to severe infectious complications, including the NMDAR-AE subtype, significant disease burden at onset, ICU admission, and the use of 3 or more immunotherapies during hospitalization. These factors seem to be interrelated because the severe initial presentation of NMDAR-AE likely necessitated ICU-level care and intensified immunosuppressive treatment. Among these variables, a high CASE score at disease peak and ICU admission stood out as independent predictors of severe infections, highlighting the pivotal role of critical illness in elevating infectious vulnerability. Of interest, the presence of 3 or more PECs was not associated with severe infectious complications, emphasizing the role of acute disease severity over comorbidity burden. Despite their severity, infections did not affect overall outcomes, suggesting effective management and favorable recovery and justifying aggressive immunomodulatory therapy when clinically indicated.

Mainly studied in NMDAR-AE patients, previous studies have sought to identify predictors of poor outcomes. These included delayed onset of therapy,[6] impaired consciousness,[5] CSF inflammation,[5,6] and MRI abnormalities.[5,6] In line with our findings, advanced age was also associated with worse outcomes,[1,4,5] likely due to multimorbidity,[41] preexisting organ dysfunctions,[41] and reduced neuronal plasticity,[42] all of which may hinder recovery. Our data also demonstrated subtype-specific outcome differences, with IgLON5-AE showing the poorest outcomes. Besides delayed diagnosis,[39] a neurodegenerative component associated with IgLON5-AE, such as the accumulation of tau protein in brainstem regions,[43] may limit the reversibility of the disease. High disease burden at peak was also associated with poorer outcomes, likely reflecting complications such as cardiac arrhythmias or irreversible brain damage, although this link is inconsistently observed across studies.[1,7] Regarding ICU treatment, the literature presents conflicting results.[6,7,44] In our cohort, it was not associated with a worse outcome. Differences in the timing of ICU admission between institutions may partly explain this discrepancy.

Although demographic and clinical factors have been studied in predicting outcomes, the role of comorbidities has been largely overlooked, despite their established prognostic value in other diseases.[9] Only a few studies have addressed this issue. For example, the absence of comorbidities was linked to favorable outcomes in ICU AE patients,[1] while complications such as sepsis predicted poor outcomes.[8] Similarly, in a cohort of NMDAR-AE patients, complication burden predicted mortality.[45] In our cohort, psychiatric PECs independently predicted unfavorable outcomes in multivariable analysis. This aligns with findings in other inflammatory CNS diseases, where psychiatric conditions have also been shown to adversely affect prognosis.[46] Psychological stress and negative emotional states are known to provoke increases in proinflammatory cytokines and chronic inflammation.[47] Psychiatric disorders also involve hormonal dysregulation[48] with systemic effects and often correlate with lower therapeutic adherence[49] and unhealthy lifestyle factors.[50] Overall, it is likely that psychiatric conditions and AE interact synergistically and mutually reinforce each other, contributing to worse outcomes. Greater awareness of these factors, along with treatment in interdisciplinary centers involving psychiatrists and neurologists, may be beneficial. Rigorous and proactive management of psychiatric symptoms through medication adjustments and psychological support could further enhance patient outcomes.

This study has several limitations, primarily due to its retrospective design. The patient data were sourced from a multicenter registry, which inherently introduces selection bias. These centers typically had experience in managing AE, potentially limiting generalizability. Information bias was also a concern because reliance on electronic health records meant that only documented diagnoses were captured without reinterpretation. This distinction between diagnostic prevalence and true prevalence of conditions carries the risk of both underrepresentation (e.g., missed diagnoses) and overrepresentation, including potential misclassification of early psychiatric AE symptoms as independent psychiatric disorders. However, only explicitly documented diagnoses by the treating physicians were classified as preexisting or secondary, excluding symptoms attributed to AE. Of note, the prevalence of psychiatric PECs in our cohort did not exceed that of the age-matched general population,[22] suggesting that systematic misclassification of psychiatric symptoms of AE as independent psychiatric PECs was unlikely. Comparisons with the general population were constrained by the availability of age-matched data. The categorization of comorbidities posed challenges, with overlapping definitions complicating precise analyses (e.g., nicotine abuse, traditionally classified as a psychiatric disorder). Follow-up data were inherently limited by the availability of routinely collected health information. As a result, the study used a minimum follow-up period of 12 months so that follow-up durations varied to an unknown extent, potentially introducing heterogeneity into the outcome assessments. The mRS used here as an outcome parameter effectively reflects overall functional disability in daily life but may overlook cognitive or emotional dysfunction. Despite these limitations, it is crucial to emphasize that AE is an extremely rare disease, making prospective studies challenging to conduct.

This study has important implications for the management of patients with AE. First, the frequent co-occurrence of autoimmune comorbidities underlines the need to raise awareness about overlapping autoimmune conditions. Future studies should focus on uncovering shared pathomechanisms to develop unified therapeutic strategies, potentially optimizing outcomes for patients with multiple autoimmune conditions. Second, the moderate rate of severe infections, coupled with their lack of effect on overall outcomes, reinforces the use of aggressive immunomodulatory therapies. Infections, when managed appropriately, should not deter clinicians from using intensive immune-directed treatments to control the disease

effectively. Third, psychiatric PECs emerged as independent predictors of unfavorable outcome. This highlights the necessity for timely and accurate differentiation between the symptoms of psychiatric disorders and the appearance of AE, emphasizing the importance of early and integrated treatment for both conditions. Finally, these findings call for the incorporation of comorbidities—particularly psychiatric ones—into future prognostic models. Recognizing their effect can guide personalized therapeutic strategies and improve prognostication, contributing to better overall care for patients with AE.

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Author Contributions

A. Bohn: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K. Angstwurm: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.G. Bien: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Doppler: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Ehmke: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Havla: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Hoffmann: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Hudasch: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Klausewitz: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F.F. Konen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Korporal-Kuhnke: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Kraft: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data, T. Kümpfel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Leypoldt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. M. Madlener: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L.K. Pfeffer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Pfeuffer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Pul: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Rada: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Rauer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Sänger: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Seifert-Held: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K-W. Sühs: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F.S. Thaler: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Tsaktanis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Vlad: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K-P. Wandinger: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Wickel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.C. Tauber: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Appendix Coinvestigators

Coinvestigators are listed online at Neurology.org/NN

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