Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment

Julia Schubert, MD, Dirk Brämer, MD, Hagen B. Huttner, MD, Stefan T. Gerner, MD, Hannah Fuhrer, MD, Nico Melzer, MD, Andre Dik, MD, Harald Prüss, MD, Lam-Than Ly, MD, Kornelius Fuchs, MD, Frank Leypoldt, MD, Gunnar Nissen, MD, Ingo Schirotzek, MD, Christian Dohmen, MD, Julian Bösel, MD, Jan Lewerenz, MD, Franziska Thaler, MD, Andrea Kraft, MD, Aleksandra Juranek, MD, Marius Ringelstein, MD, Kurt-Wolfram Sühs, MD, Christian Urbanek, MD, André Scherag, PhD, Christian Geis, MD, Otto W. Witte, MD, and Albrecht Günther, MD, for the GENERATE and IGNITE network

Correspondence
Dr. Günther
Albrecht.guenther@med.uni-jena.de

Abstract

Objective
To assess intensive care unit (ICU) complications, their management, and prognostic factors associated with outcomes in a cohort of patients with autoimmune encephalitis (AE).

Methods
This study was an observational multicenter registry of consecutively included patients diagnosed with AE requiring Neuro-ICU treatment between 2004 and 2016 from 18 tertiary hospitals. Logistic regression models explored the influence of complications, their management, and diagnostic findings on the dichotomized (0–3 vs 4–6) modified Rankin Scale score at hospital discharge.

Results
Of 120 patients with AE (median age 43 years [interquartile range 24–62]; 70 females), 101 developed disorders of consciousness, 54 autonomic disturbances, 42 status epilepticus, and 39 severe sepsis. Sixty-eight patients were mechanically ventilated, 85 patients had detectable neuronal autoantibodies, and 35 patients were seronegative. Worse neurologic outcome at hospital discharge was associated with necessity of mechanical ventilation (sex- and age-adjusted OR 6.28; 95% CI, 2.71–15.61) tracheostomy (adjusted OR 6.26; 95% CI, 2.68–15.73), tumor (adjusted OR 3.73; 95% CI, 1.35–11.57), sepsis (adjusted OR 4.54; 95% CI, 1.99–10.43), or autonomic dysfunction (adjusted OR 2.91; 95% CI, 1.24–7.3). No significant association was observed with autoantibody type, inflammatory changes in CSF, or pathologic MRI.

Conclusion
In patients with AE, mechanical ventilation, sepsis, and autonomic dysregulation appear to indicate longer or incomplete convalescence. Classic ICU complications better serve as prognostic markers than the individual subtype of AE. Increased awareness and effective management of these AE-related complications are warranted, and further prospective studies are needed to confirm our findings and to develop specific strategies for outcome improvement.

From the Hans-Berger-Department of Neurology (J.S., D.B., C.G., O.W.W., A.G.), Jena University Hospital; Department of Neurology (H.B.H., S.T.G.), University Hospital Erlangen; Department of Neurology and Neurophysiology (H.F), University Hospital Freiburg; Department of Neurology (N.M., A.D.), University Hospital Münster; Department of Neurology (H.P., L.-T.L), Charité University Medicine Berlin; Department of Neurology (K.F.), Bezirksklinikum Regensburg; Neuroimmunology Section (F.L., G.N.), Institute of Clinical Chemistry and Department of Neurology, University Hospital Schleswig-Holstein, Kiel; Department of Neurology (I.S.), University Hospital Giessen; Center for Neurology and Psychiatrics (C.D.), University Hospital Köln; Department of Neurology (J.B.), University Hospital Heidelberg; Department of Neurology (J.B.), Klinikum Kassel; Department of Neurology (J.L.), University Hospital Ulm; Institute of Clinical Neuroimmunology (F.T.), Ludwig-Maximillians-University München; Department of Neurology (A.K.), Martha Maria Hospital Halle; Department of Neurology (A.J.), Dortmund Hospital; Department of Neurology (M.R.), Medical Faculty, Heinrich Heine University Düsseldorf; Department of Neurology (K.-W.S.), University Hospital Hannover; Department of Neurology (C.U.), Hospital Ludwigshafen; Institute of Medical Statistics, Computer and Data Sciences (A.S), Jena University Hospital; and Center for Sepsis Control and Care (A.S., C.G.), Jena University Hospital, Germany.

Glossary

Autoimmune encephalitis (AE) is a potentially life-threatening inflammation of the CNS and constitutes 20%–30% of encephalitis cases in adults.[1] AE often leads to subacute, severe, and debilitating encephalitis necessitating long-term management in a neurologic intensive care unit (ICU). Recent estimations on mortality due to AE range between 12% and 40%,[2–4] although only limited data are available on in-hospital mortality and morbidity. Patients with AE-associated anti-NMDA receptor antibodies in particular,[5] but also those with AE associated with antibodies against other neuronal surface or intracellular antigens, often require long-term ICU management.[4] Moreover, more than 40% of patients with probable AE without antineuronal antibody detection and exclusion of other disorders require ICU treatment.[2] In turn, long-term ICU treatment together with immunosuppression as mandatory therapy puts these patients at high risk of ICU treatment–related complications. Neurologic ICU complications due to AE,[6] such as status epilepticus, severe hyperkinetic movement, and autonomic disorders, are usually dealt with on a case-by-case basis. In fact, there are limited data available on the frequency, management, and potential prognostic value of complications in the ICU for patients with AE.[7]

The ICU-CompoSE study (ICU–Complications of Severe Encephalitis) focuses on demographic and clinical characteristics in a large cohort of AE patients' subtypes requiring neuro-ICU treatment. In the study, we aimed at identifying ICU-specific prognostic factors. In addition, we assessed potential factors for short-term outcome on discharge from hospital instead of long-term outcome, which reflects other factors of individual AE subtypes, e.g., relapse frequency and tumor association. Moreover, we also assessed potential prognostic factors for worse outcome at discharge from hospital.

We hypothesize that short-term outcome of patients with AE requiring ICU treatment is dependent on the occurrence of ICU complications rather than on diagnostic subtypes of AE.

Methods

Design and patients

We conducted a multicenter nationwide cohort study in 18 tertiary neurologic centers in Germany and consecutively included patients between January 1, 2004, and December 31, 2016. The cooperation of 2 German neurologic and neurointensive care networks (German Network for Research in Autoimmune Encephalitis [GENERATE], generate-net.de, and Initiative of German Neurointensive Trial Engagement [IGNITE], dgni.de/forschung/ignite-initiative-klinischer-multizenter-studien/ueber-ignite.html) facilitated compiling information in the GENERATE databank on patients with the clinical syndrome of AE requiring intensive care treatment.

The inclusion criteria for patients were as follows: patients of any age with the clinical syndrome of encephalopathy including disturbance of consciousness for more than 24 hours with accompanying lethargy, irritability, and any change in personality or behavior[1] were included in this study if at least 2 of the following criteria were met: (1) fever or history of fever, (2) epileptic seizures and/or new neurologic deficits, (3) CSF pleocytosis (>4 cells/μl), (4) EEG abnormalities, and (5) pathologic neuroimaging findings (MRI/CT). Furthermore, infectious or other alternative causes of encephalopathic syndrome had to be excluded. In addition, only patients admitted to an ICU during the course of the disease were included. ICU admission was necessary if the patient had one or more of the following symptoms: decreased level of consciousness, severe dyskinesia, autonomic dysfunction, epileptic seizure(s)/status epilepticus, and need for mechanical ventilation or other complications, such as severe sepsis, thrombosis, embolic events, other relevant organ failure, cardiac arrhythmia, resuscitation, and increased intracranial pressure.

Standard protocol approvals, registration, and patient consents

The study protocol was approved by the local research ethics committee at each center. Written informed consent was obtained from every patient or their representative.

Data collection

Data were collected at the participating GENERATE and IGNITE centers on the basis of cooperation within the network. At each collaborating center, a local investigator retrospectively gathered demographic information (sex, age, ethnic background, and patient's medical history) and all clinical AE features (prodromi, symptoms at presentation, and onset and duration dates). In addition, ICU charts were used to retrieve patient data on the management of ICU complications. Major complications and their therapeutic management during the patient's stay in the ICU and patient's clinical outcome were documented using an electronic case report form (ICU-CompoSE-eCRF) extending the existing GENERATE-eCRF.

The major clinical ICU problems consisted of the following:

1. Disturbance of consciousness: coma duration and onset in course of the disease, somnolence, sopor, mutism, and delirium;

2. Autonomic dysfunction: hyperthermia, hypoventilation/hyperventilation, tachycardia/bradycardia, cardiac arrhythmia, cardiac arrest, hypotensive/hypertensive arterial blood pressure, diarrhea, hyperhidrosis, and sialorrhea;
3. Status epilepticus (SE)/seizures: semiology (if available), duration and frequency of seizures/status, refractory status, detection of SE, use of EEG monitoring, and antiepileptic drugs (AEDs) used;
4. Movement disorder and hyperkinetic status: clinical manifestation, management, and drugs used;
5. Other complications: severe sepsis/septic shock, other relevant organ failure, increase in intracranial pressure, resuscitation, surgical complications, and psychiatric complications (e.g., suicide attempt);
6. Ethical conflicts: ovarectomy (prophylactic or diagnostic), change in therapeutic goal, therapy limitation or disruption, and interdisciplinary ethical consultation.

Additional systematically assessed data included the following:

1. Mechanical ventilation: reason for intubation, time of intubation during the course of the disease, duration of ventilation, ventilation mode, time and reason for tracheostomy, reintubation, and other ventilatory problems;
2. Algesia and sedation: duration, drugs used, and use of inhalative sedation (isoflurane and sevoflurane).

Diagnostic workup data included laboratory testing for autoantibodies from CSF and serum, neurophysiologic data (i.e., EEG results), and brain imaging results (pathologic MRI suggestive for AE was defined as a hyperintense signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences highly restricted to one or both medial temporal lobes or in multifocal areas involving gray matter, white matter, or both compatible with demyelination or inflammation).[8] If available, cerebral fluorodeoxyglucose PET (FDG-PET) results were also retrieved. Furthermore, in case a tumor had been detected, the entity of the tumor and antitumor therapy were retrieved.

For outcome analysis, values of the modified Rankin Scale (mRS) were retrieved by the treating physician from clinical charts during the ICU stay, revealing both the poorest value (maximum mRS—obtained at the poorest neurologic/functional status of the patient) and the mRS at the end of the hospital stay. Good neurologic outcome was defined as a dichotomized (mRS) score of 0–3 for no disability to moderate disability at hospital discharge, whereas mRS scores of 4–6 were defined as poor outcome.[9]

Statistical analyses
Descriptive statistics summarize the patient's characteristics (continuous variables: quartiles/count data: absolute and relative frequencies). Because we had to work with the given sample of this rare disease, we performed no formal sample size calculations. Consequently, we limited the modeling, avoided data imputations, did not examine subgroups or interactions, and did not strictly control the type I error rate; results are explorative. We performed crude and adjusted logistic regressions (adjusted for age [linear and per year] and sex) to derive factors associated with good to moderate (mRS scores 0–3) or poor (mRS scores 4–6) neurologic outcome at hospital discharge. Because linear regression models with untransformed mRS scores lead to the same conclusions, we decided to focus on the logistic regression results. In total, we explored 19 potential prognostic factors. In light of only 7 observed in-hospital deaths, we decided not to run additional regression models for hospital mortality. We report crude and adjusted ORs with 2-sided 95% CIs (not corrected for multiplicity) and a significance level α = 0.05 (2-sided). All statistical analyses were performed using the statistical language R 3.4.3. (Source: R Core Team [2014]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL R-project.org/).

Data availability statement
The data used for this study can be supplied by the corresponding author upon request. The STROBE guidelines were used for reporting of this observational study.

Results

Patient characteristics
Of the 602 patients enrolled in the GENERATE database (until December 31, 2016), we included 120 patients in the ICU-CompoSE study. The median age at disease onset was 43 years (interquartile range [IQR] 24–62, range 9–82 years), and 70 patients (58%) were female (table 1). Ethnicity was Caucasian in 99% and Asian in 1%.

Clinically, consistent with the accounts of the treating physicians and the clinical charts, 63% of the 120 patients showed symptoms of limbic encephalitis, whereas 31% were judged to show a generalized form of encephalitis, and 8% exhibited brain stem encephalitis. Other specific clinical syndromes included cerebellitis and Rasmussen encephalitis (table 1).

Prodromal symptoms were found in 34%, and the median duration of these symptoms was 8 days (IQR: 5–34; range 1–1,000 days). Prodromal symptoms consisted of unspecific respiratory or gastrointestinal symptoms (50%), headache (47%), neurologic deficits (41%), psychiatric symptoms (26%), and cognitive impairment (15%). The median delay between first symptoms and hospital admission was 6 days (IQR: 0–32; range 0–3,485 days).

MRI was performed in 98% of patients, and a pathologic result was obtained in 70%. In detail, the main pathologic findings consisted of FLAIR lesions (N = 88), diffusion-weighted imaging lesions (N = 25), MRI-contrast enhancing lesions (N = 15), and limbic lesions (N = 52).

EEG showed pathologic findings in 84% (generalized slow activity in 85%, focal abnormalities in 60%, and epileptic discharges in 41% of patients).

Table 1 Demographic and clinical characteristics and diagnostic workup of the ICU-CompoSE cohort

Variable	All n = 120
Age, median (min/max), y	43 (9/82)
IQR	24/62
Female sex (%)	70 (58)
Prodromi, number of patients (% of n = 120)	41 (34)
Duration of prodromi median (min/max), d	8 (1/1,000)
IQR, d	5/34
Clinical syndrome[a], number of patients	
Limbic encephalitis	76
Encephalitis	37
Movement disorder	9
Encephalomyelitis	4
Rasmussen encephalitis	3
Brainstem encephalitis	2
Cerebellitis	2
Focal encephalitis	2
Progressive encephalomyelitis with rigidity and myoclonus	1
Unknown	1
Diagnostic results, number of patients (%)	
CSF (n = 116)	
Pleocytosis (%, total n = 116)	70 (60)
Elevated CSF protein level (%, total n = 116)	50 (43)
Oligoclonal bands (OCBs) tested (% of n = 116)	89 (77)
OCB-positive CSF (% of n = 89)	26 (29)
OCB-positive CSF and serum (% of n = 89)	25 (28)
OCB negative (% of n = 89)	38 (42)
MRI, number of patients (% of n = 120)	118 (98)
Pathologic	83 (70)
Brain PET, number of patients (% of n = 120)	51 (43)
Pathologic	32 (63)
EEG, number of patients (% of n = 120)	107 (89)
Pathologic	90 (84)
Tumor screening, number of patients (% of n = 120)	112 (93)
Diagnosis of tumor[b]	25 (21)
Autoantibody (AAB) detection, number of patients (%)	120 (100)
Serum tested	110 (92)
CSF tested	93 (76)
AAB found	85 (71)

Table 1 Demographic and clinical characteristics and diagnostic workup of the ICU-CompoSE cohort *(continued)*

Variable	All n = 120
AAB found CSF	57 (48)
AAB found serum	68 (57)
AAB group[a] (% of n=85)	
NMDA	53 (62)
VGKC (4LgI1,2 CASPR2, 4VGKC)	10 (12)
GAD	5 (6)
GABA	4 (5)
Paraneoplastic (anti-Hu, anti-Yo)	4 (5)
Others[c]	12 (14)
Ovarectomy, number of patients (% of n = 120)	10 (8)
Monolateral	4 (3)
Bilateral	3 (3)
Explorative ovarectomy	3 (3)
Incomplete removal	5 (4)
Oocyte removal	1 (1)

Abbreviations: VGKC = voltage-gated potassium channel complex, LgI = leucine-rich glioma inactivated 1, CAPSR2 = contactin-associated protein 2, GABA = gamma-aminobutyric acid, GAD = glutamic acid decarboxylase; OCB = oligoclonal band.
[a] Multiple selection possible.
[b] Tumor entity: 10 teratoma, 6 bronchial carcinoma, 1 lymphoma, rectal carcinoma, breast carcinoma, prostate carcinoma, seminoma (each), 1 undifferentiated unclassified tumor, and 3 undetermined tumors.
[c] Amphiphysin (n = 1), Glycine (n = 2), MAK (male germ cell–associated kinase) (n = 1), ITPR1 (inositol triphosphate receptor) (n = 1), SOX (Sry-like motility group box) (n = 1), AAB against potassium channels (n = 3), not further specified (n = 3).

CSF was analyzed in 97% of the patients; 60% had pleocytosis, and 50% showed an increased total protein content. Isolated oligoclonal bands in CSF were seen in 29%.

Neuronal autoantibodies were examined in 27/120 patients in serum only, 10/120 patients in CSF only, and 83/120 patients in CSF and serum. Autoantibody testing was performed by commercially available mosaic biochip (Euroimmun, Lübeck, Germany) according to the manufacturer's procedures by certified laboratories and by scientific laboratories using immunohistochemistry.[10] Well-characterized neuronal autoantibodies were detected in 85/120 patients (71% total, 57% in serum, 48% in CSF, and 47% both). Anti-NMDA-R antibodies were most common, followed by leucine-rich glioma-inactivated 1, CASPR2, and glutamic acid decarboxylase (table 1). A total of 93% of patients were screened for a tumor, which was found in 21% of the screened patients (table 1).

ICU complications and management

Eighty-four percent of patients had a decreased level of consciousness, and 34% developed delirium. Impairment of

consciousness lasted more than 8 days in 70% and more than 30 days in 32% of patients.

Autonomic dysregulation (33% tachycardia, 19% bradycardia, 18% hypertensive crisis or hypotension, 18% hypoventilation, and 13% hyperthermia) was seen in 45% of patients. The therapeutic strategies including external and internal cooling and administration of IV dantrolene for fever treatment, pacemaker for bradycardia, mechanical ventilation for hypoventilation, and catecholamines/antihypertensives for blood pressure dysregulation are listed in table 2.

Thirty-five percent of patients developed status epilepticus (SE) (43% generalized, 37% nonconvulsive, and 34% focal or complex-focal), and 34% of patients had a relapse SE. The duration of SE was less than 1 day in 36% and more than 7 days in 28% of patients. The median number of different AEDs per patient with SE used to treat epileptic status was 5.

Thirty-three percent of patients showed movement disorders, which were treated with benzodiazepines (74%), AEDs (53%), and propofol (31%). We cannot exclude that some of the movement disorders were actually epileptic events and vice versa, especially without EEG.

Other relevant complications: 26% of patients experienced severe sepsis with organ dysfunction and 7% septic shock. Ten percent underwent cardiopulmonary resuscitation. Eight percent had venous thrombosis.

Mechanical ventilation was necessary in 57% of all patients, with a median duration of 28 days (IQR: 10–54; range 1–350 days). Thirty-seven percent had to be reintubated, and 68% underwent tracheostomy during the course of ICU treatment. Fifty-four percent of the patients developed ventilator-associated pneumonia (Table 3).

Outcome and potential prognostic factors

The median duration of ICU stay was 24 days (IQR: 7–45), and the median duration of hospital stay was 49 days (IQR: 31–100). Ninety percent of patients showed a maximum mRS score of ≥4 (23% mRS score 4, 61% mRS score 5, and 7% mRS score 6). At the time of hospital discharge, 47% of patients showed a mRS score of ≥4 (28% mRS score 4, 15% mRS score 5, and 7.5% mRS score 6). However, 60 patients (50% of the total cohort) had improved mRS values compared with the maximum mRS value [mRS 1 (12 patients), 2 (21 patients), and 3 (27 patients)] (figure).

Fifty-five percent of patients were discharged from the ICU to regular hospital wards, and 38% were transferred to neurologic intensive care rehabilitation centers. In 18% of cases, an ethical conflict had to be resolved during the hospital stay.

Table 4 summarizes the results of the crude and the sex- and age-adjusted logistic regression analyses. Of the 19 potential

Table 2 AE-associated complications and clinical management

Variable	All n = 120
Consciousness disorder, no. of patients (% of n = 120)	101 (84)
Manifestation	
Somnolence	40 (33)
Sopor	30 (25)
Coma	18 (15)
Delirium	41 (34)
Mutism	13 (11)
Duration of consciousness disorder	
Median, d (IQR)	20 (5–40)
Minimum/maximum, d	0–400
<1 d	7
1–7 d	22
8–30 d	28
>30 d	32
Autonomic disorders, no. of patients (% of n = 120)	54 (45)
Manifestation	
Fever without infection	15 (13)
Hypoventilation	22 (18)
Hyperventilation	12 (10)
Tachycardia	40 (33)
Bradycardia	23 (19)
Other heart rhythm disorders	11 (9)
Blood pressure crises	21 (18)
Diarrhea	6 (5)
Hypersalivation	10 (8)
Therapy, no. of patients	
Dantrolene	3
External cooling	12
Internal cooling	7
Pacemaker	11
Status epilepticus (SE), no. of patients (% of n = 120)	42 (35)
Manifestation (% of n = 42)	
Generalized SE	18 (43)
Focal SE	14 (33)
Nonconvulsive SE	15 (36)
SE relapse	13 (31)
	Continued

Table 2 AE-associated complications and clinical management *(continued)*

Variable	All n = 120
Cumulative duration of SE no. of patients (% of n = 42)	
<1 d	8 (19)
1–7 d	15 (36)
>7 d	7 (17)
Unknown	12 (28)
SE detection, no. of patients (% of n = 42)	
Clinical	28 (67)
EEG once	4 (10)
EEG several times	28 (67)
EEG monitoring	10 (23)
Therapy SE, no. of antiepileptic drugs (AEDs) used (% of n = 42)	
AED, median no. of different AEDs	5
AED ≤ 4, no. of patients (%)	21 (50)
AED > 4, no. of patients (%)	21 (50)
Movement disorders, no. of patients (% of n = 120)	39 (33)
Manifestation (% of n = 39)	
Generalized	13 (39)
Focal	23 (58)
Others[a]	22 (56)
Complications of movement disorders	11 (28)
Therapy movement disorders (% of n = 39)	
Benzodiazepines	29 (74)
AED	21 (53)
Isoflurane	2 (5)
Propofol	12 (31)
Others[b]	14 (36)
Other complications, no. of patients (% of n = 120)	63 (53)
Severe sepsis	31 (26)
Septic shock	8 (7)
Cardiopulmonary resuscitation	12 (10)
Surgical complications	7 (6)
Venous thrombosis	10 (8)
Others[c]	49 (42)

[a] Bruxism and axial rigor.
[b] Opioids, atypical neuroleptics, and L-dopa.
[c] Pneumothorax, ICU-acquired weakness, self-injury, pleural effusions, suicide attempt, pulmonary embolism, rhabdomyolysis, allergic reaction, ileus, catheter infection, transfusion-dependent anemia, and severe electrolyte derangement.

Table 3 ICU complications and outcome

| Variable	All n = 120
Mechanical ventilation (MV), no. of patients (% of n = 120)	68 (57)
Duration of MV, median, d (IQR)	28 (10–54)
Minimum/maximum, d	0/350
Reasons for MV, no. of patients (% of n = 68)	
Consciousness disorder	47 (69)
Respiratory insufficiency	36 (53)
Missing protection reflexes	29 (34)
Hypoventilation	6 (9)
Pneumonia	13 (19)
Others[a]	9 (13)
Intubation, no. of patients (% of n = 68)	63 (93)
Reintubation	25 (37)
Tracheal cannula (TC)	46 (68)
Duration intubation to TC, median, d	10
Complications of MV, no. of patients (% of n = 68)	
Pleura drainage	5 (7)
Acute respiratory distress syndrome	4 (6)
Ventilator-associated pneumonia	37 (54)
Others[b]	19 (28)
Ethical consideration, no. of patients (% of n = 120)	21 (18)
Change of therapy target	8 (7)
DNR/DNI	2 (2)
Treatment discontinuation	2 (2)
Ethical counseling	2 (2)
Others[c]	6 (5)
Outcome ICU stay, no. of patients (% of n = 120)	
Transfer to regular hospital ward	68 (57)
Transfer to neurointensive care rehabilitation	46 (38)
Deceased	9 (7.5)
Duration ICU stay, median, d (IQR)	24 (7–45)
Minimum/maximum, d	1/400
Duration hospital stay, median, d (IQR)	49 (31/100)
Minimum/maximum, d	1/1978

Abbreviations: DNR = do-not-resuscitate order; DNI = do-not-intubate order; IQR = interquartile range.
[a] Sedation in psychosis, status epilepticus, and severe sepsis.
[b] Recurrent pneumonia, difficult airway, severe sepsis, intubation injury, and pneumothorax.
[c] Dismissal against medical advice, personal risk, and extraneous endangering.
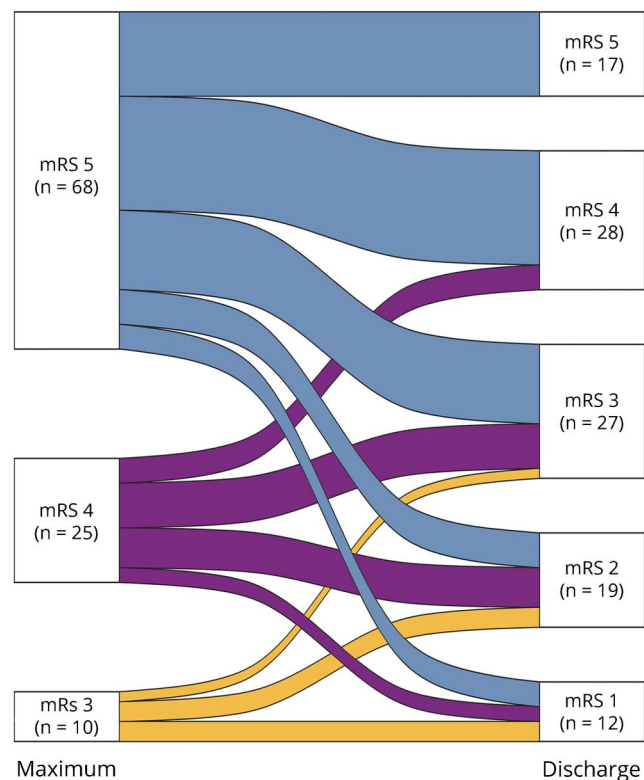
Left: mRS scores 3–5 at maximum mRS during hospitalization, right: mRS scores 1–5 at hospital discharge. The alluvial plot shows the number of patients crossing over from the maximum mRS score during hospitalization to the final mRS score at discharge. In all 3 "maximum" groups, the transition goes downward at a percentage of ≥75%. The height of a mRS block represents the size of the group, and the height of a stream field represents the size of the components contained in both blocks connected by the stream field. Deceased patients (mRS 6) are not included in the figure There were no patients with mRS 0–2 at disease maximum.

prognostic factors, the presence of autonomic dysfunction (OR 2.9), severe sepsis/septic shock (OR 4.5), tracheostomy (OR 6.3), a tumor finding (OR 3.7), and the need for mechanical ventilation (OR 6.3) in addition to its duration (OR per each day 1.03) were all associated with a poor neurologic outcome at hospital discharge. In contrast, we observed no correlation for a correlation of prodromal symptoms, status epilepticus, ethical considerations, diagnostic results such as pathologic brain imaging (MRI and PET), pathologic EEG, or antibody status with the dichotomized neurologic outcome at hospital discharge.

Discussion

The findings of our study provide a number of relevant insights regarding prognostic factors for outcome in severely affected patients with AE. These insights may increase awareness of the potential poor prognostic factors in patients with AE requiring ICU treatment.

First, autonomic dysfunction, associated with worse outcome, is critical in a major subset of patients. It is an intrinsic aspect

of AE, particularly NMDA receptor encephalitis (RE), which represents the largest patient group within our cohort.[5,7,10,11] Thus, autonomic dysfunction can be regarded as being a disease-specific risk factor or indicator for poor outcome. It can be hypothesized to be a causative trigger factor for further intensive care–associated complications, e.g., hypotension requiring vasopressors or respiratory dysfunction requiring mechanical ventilation resulting in ventilator-associated pneumonia.

Second, similar to ICU patients with diseases other than AE, severe sepsis and septic shock were strongly related to worse neurologic outcome.[12] Of interest, the proportion of patients who developed severe sepsis and septic shock that resulted in organ dysfunction (33%) was more than doubled in patients with severe AE compared with the general ICU population in Germany with a rate of 13% in 1 study.[13] Treatment-induced immunosuppression, autonomic dysfunction, and a longer duration of mechanical ventilation most likely contributed to the increased proportion of sepsis and sepsis-induced organ dysfunction in our cohort.

Third, paraneoplastic origin (teratoma and other tumors in 21% of patients) was strongly associated with worse outcome as measured by the dichotomized mRS score. This is in accordance with previous reports focusing on NMDA-RE. Here, tumor removal led to faster improvement and fewer relapses.[5,14]

In addition to the aforementioned disease-related factors, prolonged mechanical ventilation is associated with worse outcome. Here, similar results have been reported in acute encephalitis of all etiologies.[2,15] A number of conditions are associated with the need for long-term respiratory support in this severely affected patient cohort including the increased risk of infection and pneumonia due to immunosuppression and the development of ICU-acquired weakness, which frequently affects critically ill patients and contributes to worse acute outcome and long-term mortality.[16] Surprisingly, status epilepticus was not associated with a deterioration of neurologic outcome, although it was detected in a relevant subset of 35% of all patients. However, there was a slight tendency wherein pathologic EEG findings to be more frequently associated with a worse outcome. In clinical practice, seizure-related myoclonic activity may be difficult to differentiate from dyskinetic and stereotypic movements associated with certain AE subtypes. Therefore, the rate of status epilepticus in these patients may be overestimated, leading to decreased specificity in the evaluation of this factor in correlation with clinical outcome.

Paraclinical findings, e.g., pleocytosis and increased CSF protein levels, abnormal cerebral MRI, or FDG-PET are helpful for the diagnostic workup[17] but are apparently not relevant for evaluating the risk of poor clinical outcome after ICU therapy. Although antineuronal autoantibodies were detected in 85 patients (71%), mostly NMDA-R antibodies (in 53 patients), these findings did not predict a negative or a positive neurologic outcome. This result is of relevance to

Table 4 Potential prognostic factors of the neurologic outcome at hospital discharge according to the dichotomized modified Rankin Scale (mRS)

	Potential prognostic factor	Crude OR (95% CI)	p-value (2-sided)	Adjusted OR (95% CI)	p-value (2-sided)
S	Prodromal symptoms [absent]	1.03 (0.44–2.41)	0.95	1.28 (0.52–3.19)	0.59
Y	Consciousness disorder [absent]	1.80 (0.63–5.57)	0.28	2.39 (0.8–7.84)	0.13
M	Somnolence [absent]	1.41 (0.64–3.09)	0.39	1.36 (0.61–3.05)	0.45
P	Autonomic dysfunction [absent]	1.69 (0.8–3.59)	0.17	2.91 (1.24–7.3)	0.02
T	Status epilepticus [absent]	0.90 (0.42–1.92)	0.78	0.95 (0.43–2.09)	0.91
O	Other complications [absent]	4.21 (1.95–9.42)	3.3×10^{-4}	4.45 (1.99–10.43)	3.9×10^{-4}
M	Sepsis/septic shock [absent]	3.97 (1.67–10.11)	2.4×10^{-3}	4.54 (1.84–12.11)	1.5×10^{-3}
W	Pathologic CSF [absent]	0.76 (0.21–2.71)	0.67	0.94 (0.25–3.5)	0.92
O	Pathologic MRI brain imaging [absent]	0.91 (0.41–2.03)	0.82	0.79 (0.34–1.81)	0.57
R	Pathologic EEG [absent]	0.35 (0.12–0.90)	0.04	0.40 (0.14–1.09)	0.08
K	Pathologic PET brain imaging [absent]	0.76 (0.32–1.73)	0.51	0.53 (0.21–1.28)	0.17
U	Tumor [absent]	3.82 (1.43–11.49)	0.01	3.73 (1.35–11.57)	0.01
P	Autoantibody [absent]	0.84 (0.38–1.85)	0.66	1.01 (0.44–2.33)	0.98
	Autoantibody in CSF [absent]	1.11 (0.53–2.35)	0.78	1.46 (0.66–3.31)	0.35
	Autoantibody in serum [absent]	0.78 (0.37–1.66)	0.53	0.90 (0.41–1.98)	0.80
T	Mechanical ventilation [absent]	5.78 (2.60–13.61)	3.0×10^{-5}	6.28 (2.71–15.61)	3.5×10^{-5}
H	Duration of ventilation [days]	1.03 (1.02–1.05)	3.8×10^{-4}	1.03 (1.02–1.06)	2.1×10^{-4}
E	Tracheostomy [absent]	4.98 (2.24–11.57)	1.2×10^{-4}	6.26 (2.68–15.73)	4.5×10^{-5}
R	Ethical considerations [absent]	1.3 (0.48–3.55)	0.61	1.52 (0.54–4.39)	0.43

Effect size estimates (with 95% CI) are provided such that ORs > 1 indicate a correlation with a worse outcome (usually with the presence of a pathologic finding). The reference category or unit is provided in square brackets. Adjusted ORs were adjusted only for sex and age (linear) because of the limited number of patients. Left column: SYMPTOM—main symptoms and ICU complications; WORKUP—diagnostic findings; THER—therapeutic management and ethical considerations.

clinical-based decision in contrast to relying on the diagnostic test for antineuronal autoantibodies because there are still a number of antibodies that cannot be reliably detected using the available laboratory tests.[18]

Disorders of consciousness such as delirium have recently been identified as a risk factor for developing long-term cognitive dysfunction after surviving sepsis in a large cohort of ICU patients.[19] Our data showed no evidence for an association of altered consciousness with regard to the short-term outcome in our study. However, neurocognitive dysfunction is a major factor influencing the overall condition and is highly relevant for patients for managing their daily activities, it is therefore also relevant for evaluating in the patients' mRS scores. The study design did not include a regular neuropsychological assessment at hospital discharge and no follow-up evaluation of patients. Because most patients exhibited mRS scores above 3, for which cognitive dysfunction is less significant, the relevance of consciousness disorders on overall outcome may be underestimated. It would be interesting to conduct a future study evaluating neurocognitive dysfunction in either this or a similar patient cohort as a long-term follow-up similar to what has already been undertaken in NMDA-RE-cohorts.[20]

Our patients showed severe deficits: 90% of patients had a maximum mRS score 4–6 during their disease course. At the time of ICU discharge, however, this improved remarkably in 75% of the surviving patients, with only 48% of patients showing an mRS value of ≥4 (28% mRS 4 and 15% mRS 5). The hospital mortality rate of 7.5% in our cohort was almost identical with the recently published ICU NMDA-RE study.[7] However, in other cohorts with AE, the reported mortality was much higher.[2,21–23] The reasons for this low mortality might be the improved treatment and earlier recognition and diagnosis of AE. In addition, there might also be a bias attributable to the fact that relatives/spouses of deceased patients refused their informed consent.

Neuro-ICU management in patients with AE frequently involves a long period of care. Therefore, complications, sometimes severe, occur in a majority of patients. More detailed knowledge of the individual prognosis based on well-

defined risk factors will aid decision making by both physicians and family members/spouses with regard to ICU treatment in supposedly treatment-resistant cases. Consequently, ethical decisions will have to be addressed. For example, 10 women underwent ovarectomy and were confronted with a lifelong challenge regarding family planning after surviving their acute illness. The discussion on the necessity of explorative or even prophylactic ovarectomy has increased recently as evidenced in 2 case reports of postencephalitic ovary removal 1 year after initial NMDA-RE in adolescent patients without symptoms.[24] Issues resulting in lifelong consequences for patients need to be further addressed, in particular, because data, for example, on tumor incidence in different age groups[11] and ethnicities[10] show differential results.

Our analysis was performed using retrospectively collected patient data obtained from a subgroup of 120 patients who required IUC treatment. These patients were revealed from a nationwide cohort in Germany, which in the meantime consists of more than 750 patients with AE (GENERATE cohort; generate-net.de/). To our knowledge, this cohort of 120 patients represents the largest reported cohort of critically ill patients with AE who underwent ICU treatment compared with previous studies with patients with AE[3,4,7,21,22] and mixed encephalitis cohorts including AE subgroups.[2,15,25,26]

This notwithstanding, some limitations need to be discussed herein:

First, the study is a noninterventional retrospective analysis and therefore not suitable for detecting cause and effect relationships.

Second, patients with a date of disease onset between 2004 and 2016 were enrolled in the study. During this time, awareness of AEs and antibody testing increased, reducing the time to treatment. Furthermore, while planning the study, the inclusion criteria were based on the encephalitis criteria as published by Granerod et al.[1] Since then, the Graus criteria have been published in February 2016.[8] According to the Graus criteria, the 35 patients without evidence of autoantibody in CSF or serum have been considered as possible AE rather than definite AE. Although, from a clinical standpoint, it still seems reasonable to include these patients in our cohort, although they were antibody negative. In addition, ICU management probably remained relatively unchanged. The continuing analysis of the present cohort will focus on the influence of (German) guidelines on AE management.[27]

Third, the 120 cases included in our study did not allow for a more profound analysis of rare or less frequent potential prognostic factors. Note that the statistical power for 120 patients is rather limited. Therefore, further adjustments or multiple testing corrections were not applied. In addition, a documentation bias should be mentioned. Clearly, extended clinical interpretations of our findings could only be justified on the basis of their confirmation in an independent dataset.

Finally, the primary end point focused on outcome data at "hospital discharge" because it was not possible to obtain follow-up data of the patients, which might provide further important information, e.g., on long-term cognitive function.

Ultimately, our aim is that the data gathered within the tight network and close cooperation will provide evidence-based support with regard to ICU management and may be of advantage for counseling patients and relatives during a severe and threatening course of an autoimmune disease according to the relevant influencing factors.

The spectrum of ICU complications and the severity of the underlying disease reflect some general ICU- and specific AE-related features. Of interest, and despite early targeted immunotherapy,[7] clinically highly threatening courses of AE still occur. Focusing on the earliest possible clinical diagnosis according to the Graus criteria[8] may foster earlier immunotherapy. Moreover, these critical disease courses underscore the need for novel, target-specific treatment approaches beyond immunotherapy. Future studies should reveal whether such clinical rather than diagnostic-based approaches will result in less ICU complications in patients with AE. Cooperation and dialogue within a network such as GENERATE and IGNITE might be beneficial to AE-related ICU treatment because they could lead to an interdisciplinary evaluation of earlier and if necessary more aggressive management of AE resulting in better short- and long-term outcomes.

Disclosure
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Appendix 1 Author contributions

Name	Location	Role	Contribution
Julia Schubert, MD	University of Jena, Jena, Germany	Author	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Dirk Brämer, MD	University of Jena, Jena, Germany	Author	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Hagen B. Huttner, MD	University of Erlangen, Erlangen, Germany	Author	Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content
Stefan T. Gerner, MD	University of Erlangen, Erlangen, Germany	Author	Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content
Hannah Fuhrer, MD	University of Freiburg, Freiburg, Germany	Author	Major role in the acquisition of data and interpretation of data
Nico Melzer, MD	University of Münster, Münster, Germany	Author	Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content
André Dik, MD	University of Münster, Münster, Germany	Author	Major role in the acquisition of data
Harald Prüss, MD	Charité University Medicine, Berlin, Germany	Author	Major role in the acquisition of data and interpretation of data
Lam-Than Ly, MD	Charité University Medicine, Berlin, Germany	Author	Major role in the acquisition of data and interpretation of data
Kornelius Fuchs, MD	University of Regensburg, Germany	Author	Major role in the acquisition of data and interpretation of data
Frank Leypoldt, MD	University of Schleswig-Holstein, Kiel, Germany	Author	Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content
Gunnar Nissen, MD	University of Schleswig-Holstein, Kiel, Germany	Author	Major role in the acquisition of data
Ingo Schirotzek, MD	University of Giessen, Giessen, Germany	Author	Major role in the acquisition of data
Christian Dohmen, MD	University of Cologne, Cologne, Germany	Author	Major role in the acquisition of data
Julian Bösel, MD	University of Heidelberg, Heidelberg, Germany	Author	Major role in the acquisition of data
Jan Lewerenz, MD	University of Ulm, Ulm, Germany	Author	Major role in the acquisition of data and interpretation of data and revised the manuscript for intellectual content
Franziska Thaler, MD	University of Munich, Munich, Germany	Author	Major role in the acquisition of data

Appendix 1 *(continued)*

Name	Location	Role	Contribution
Andrea Kraft, MD	Martha Maria Hospital, Halle, Germany	Author	Major role in the acquisition of data
Aleksandra Juranek, MD	Dortmund Hospital, Dortmund, Germany	Author	Major role in the acquisition of data
Marius Ringelstein, MD	University of Düsseldorf	Author	Major role in the acquisition of data
Kurt-Wolfram Sühs, MD	University of Hannover, Hannover, Germany	Author	Major role in the acquisition of data
Christian Urbanek, MD	Hospital Ludwigshafen, Ludwigshafen, Germany	Author	Major role in the acquisition of data
André Scherag, PhD	University of Jena, Jena, Germany	Author	Planned and performed biostatistical analyses and interpretation of data and revised the manuscript for intellectual content
Christian Geis, MD	University of Jena, Jena, Germany	Author	Major role in the acquisition of data and revised the manuscript for intellectual content
Otto W. Witte, MD	University of Jena, Jena, Germany	Author	Designed and conceptualized the study and revised the manuscript for intellectual content
Albrecht Günther, MD	University of Jena, Jena, Germany	Author	Designed and conceptualized the study, performed acquisition of data, analyzed the data, and drafted the manuscript for intellectual content

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