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# **Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study**

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**Keywords:**

Meningoencephalitis, Encephalitis, Meningitis, Intensive care unit, Outcome

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## Abstract

**Purpose:**

We aimed to characterize the outcomes of patients with severe meningoencephalitis requiring intensive care.

**Methods:**

We conducted a prospective multicenter international cohort study (2017–2020) in 68 centers across 7 countries. Eligible patients were adults admitted to the intensive care unit (ICU) with meningoencephalitis, defined by an acute onset of encephalopathy (Glasgow coma scale (GCS) score  $\leq 13$ ), a cerebrospinal fluid pleocytosis  $\geq 5$  cells/mm<sup>3</sup>, and at least two of the following criteria: fever, seizures, focal neurological deficit, abnormal neuroimaging, and/or electroencephalogram. The primary endpoint was poor functional outcome at 3 months, defined by a score of three to six on the modified Rankin scale. Multivariable analyses stratified on centers investigated ICU admission variables associated with the primary endpoint.

**Results:**

Among 599 patients enrolled, 589 (98.3%) completed the 3-month follow-up and were included. Overall, 591 etiologies were identified in those patients which were categorized into five groups: acute bacterial meningitis ( $n = 247$ , 41.9%); infectious encephalitis of viral, subacute bacterial, or fungal/parasitic origin ( $n = 140$ , 23.7%); autoimmune encephalitis ( $n = 38$ , 6.4%); neoplastic/toxic encephalitis ( $n = 11$ , 1.9%); and encephalitis of unknown origin ( $n = 155$ , 26.2%). Overall, 298 patients (50.5%, 95% CI 46.6–54.6%) had a poor functional outcome, including 152 deaths (25.8%). Variables independently associated with a poor functional outcome were age  $> 60$  years (OR 1.75, 95% CI 1.22–2.51), immunodepression (OR 1.98, 95% CI 1.27–3.08), time between hospital and ICU admission  $> 1$  day (OR 2.02, 95% CI 1.44–2.99), a motor component on the GCS  $\leq 3$  (OR 2.23, 95% CI 1.49–3.45), hemiparesis/hemiplegia (OR 2.48, 95% CI 1.47–4.18), respiratory failure (OR 1.76, 95% CI 1.05–2.94), and cardiovascular failure (OR 1.72, 95% CI 1.07–2.75). In contrast, administration of a third-generation cephalosporin (OR 0.54, 95% CI 0.37–0.78) and acyclovir (OR 0.55, 95% CI 0.38–0.80) on ICU admission were protective.

**Conclusion:**

Meningoencephalitis is a severe neurologic syndrome associated with high mortality and disability rates at 3 months. Actionable factors for which improvement could be made include time from hospital to ICU admission, early antimicrobial therapy, and detection of respiratory and cardiovascular complications at admission.

# Introduction

Meningoencephalitis is an inflammatory process involving the brain and meninges, most often produced by pathogens which invade the central nervous system, and occasionally by autoimmune disorders, toxins, and other conditions [1]. Traditionally, patients with meningoencephalitis develop an acute-onset encephalopathy with a combination of fever, focal signs and/or new-onset seizures, together with cerebrospinal fluid (CSF) pleocytosis, brain imaging features of inflammation, and/or electroencephalography (EEG) alterations [2]. Epidemiological studies conducted in adult patients suggest that approximately one in two will require care in an intensive care unit (ICU) [3–5]. In those patients requiring ICU admission, meningoencephalitis is associated with a poor prognosis, including refractory seizures, prolonged hospital stay, neurological disability, and death [6–9].

Herpes simplex encephalitis (HSE) remains the most common viral cause of sporadic meningoencephalitis in immunocompetent adults, and is associated with a poor functional outcome [5, 10–12]. Patients with acute bacterial meningitis may also develop encephalitis symptoms, including coma, seizures, and/or focal signs which are, respectively, reported in 13–50%, 7–14%, and 14–22% of adult patients in multicenter cohort studies [13–15].

The etiological profile of meningoencephalitis has changed considerably in recent years, with the emergence of a wide variety of autoimmune causes (i.e., acute disseminated encephalomyelitis (ADEM), and anti-*N*-methyl-*D*-aspartate receptor (anti-NMDAR) encephalitis) that may require ICU care and urgent immunomodulatory therapies [16–18]. The development of new diagnostic tools, such as multiplex polymerase chain reaction (PCR) CSF analysis and metagenomics now permits a better identification of uncommon infectious causes of meningoencephalitis [19, 20]. However, the proportion of cases with meningoencephalitis of unknown origin remains high, ranging from 30 to 48% [6–8].

Available data on the epidemiology and outcomes of ICU patients with all-cause acute meningoencephalitis are mainly based on single-center retrospective cohorts [6–8], whereas multicenter studies have been conducted in patients with specific infectious or autoimmune etiologies, such as HSE and anti-NMDAR meningoencephalitis [11, 17]. A previous prospective multicenter study conducted in patients with severe pneumococcal meningitis requiring ICU care reported high mortality rates and disability at 3 months in one-third of survivors [13].

In the present study, we aimed to characterize the clinical presentation, etiologies, and outcomes in adult patients with severe meningoencephalitis requiring care in the ICU. Specifically, we aimed to identify baseline factors independently associated with an increased risk of poor functional outcome.

## Methods

### Study design and population

The EUROpean study on Encephalitis in intensive Care (EURECA) is a prospective international multicenter cohort study endorsed by the European Society of Intensive Care Medicine (ESICM). The study is registered in Clinical Trials (NCT03144570). The entire protocol has been reviewed and approved by the Comité de protection des personnes sud

méditerranée 2 (ID RCB 2017- A00139-44). National/local approvals at the international study sites were obtained by the national coordinators and local investigators according to the local regulations. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines. Participating centers were asked to recruit consecutive patients for a duration of at least 6 months. Eligible patients were adults admitted to the ICU with symptoms suggestive of meningoencephalitis, defined by an acute onset of encephalopathy (a score on the Glasgow coma scale (GCS)  $\leq 13$ ), a CSF pleocytosis  $\geq 5$  cells/mm<sup>3</sup>, and at least two of the following criteria: (a) fever ( $\geq 38^{\circ}\text{C}$  within 72 h before or after admission), (b) generalized or partial seizures non-attributable to pre-existing epilepsy, (c) new-onset focal neurological deficit, (d) parenchymal abnormalities on neuroimaging compatible with encephalitis, and (e) EEG alterations compatible with encephalitis. Therefore, all eligible patients met the Infectious Diseases Society of America 2013 diagnostic criteria for “probable” or “confirmed” encephalitis at inclusion [2]. Patients with missing core data and those lost-to-follow-up at 3 months were excluded.

### **Collected data**

Epidemiological data were entered prospectively into a password-protected and secured web-based electronic case record form (CRF), including age, gender, premorbid score on the modified Rankin Scale (mRS), ethnicity, chronic immunodepression (i.e., HIV infection, solid organ transplantation recipient, hematology/cancer patient, and long-term use of steroids and/or immunosuppressant drugs), pre-existing neurologic disease and other comorbidities. Data collected within the first 24 h following ICU admission included the main reason for ICU admission, each component of the GCS [21], the Simplified Acute Physiology Score (SAPS) II [22], and of the sequential organ failure assessment (SOFA) score [23]. Coma was defined by a score on the GCS  $< 8$  [24], and fever was defined by a body temperature  $\geq 38^{\circ}\text{C}$  [2]. Acute respiratory failure and cardiovascular failure were defined as a respiratory and cardiovascular component of the SOFA score  $> 2$ , respectively [23].

### **Meningoencephalitis etiology**

Routine investigations (i.e., CSF and serum analyses, imaging, EEG, oriented samples in case of non-neurological manifestations) were suggested to investigators in patients without an obvious etiological diagnosis, in accordance with most recent Infectious Diseases Society of America encephalitis guidelines [2]. Additional investigations were suggested in other circumstances, such as immunocompromised status, specific clinical presentation (i.e., psychiatric signs/abnormal movements), or depending on topography of brain lesions on neuroimaging. Etiologies of meningoencephalitis were categorized into 5 groups: (1) acute bacterial meningitis; (2) infectious encephalitis of viral, bacterial, or fungal/parasitic origin; (3) autoimmune encephalitis; (4) neoplastic/toxic encephalitis; (5) encephalitis of unknown origin. Definitions of these groups are provided in the Appendix (ESM Table 1).

Patients included in the study were treated according to local guidelines, depending on the identified etiology. Dose and duration of antimicrobials (i.e., intravenous acyclovir and antibiotics) and/or immunomodulating agents (i.e., intravenous steroids, intravenous immunoglobulins, and plasma exchange) were left to the discretion of local investigators.

**Table 1 Baseline characteristics**

	Total (n=589)	mRS 0–2 (n=291)	mRS 3–6 (n=298)	p value
<b>Demographics and comorbidities</b>				
Age, years	61 [44–71]	57 [39–67]	65 [50–74]	<0.01
Male sex	346 (58.7)	167 (57.4)	179 (60.1)	0.56
Diabetes	111 (18.8)	50 (17.2)	61 (20.5)	0.34
Chronic heart failure	34 (5.8)	5 (1.7)	29 (9.7)	<0.01
Previous stroke	29 (4.9)	12 (4.1)	17 (5.7)	0.45
Epilepsy	29 (4.9)	14 (4.8)	15 (5)	1.00
Immunodepression	137 (23.3)	52 (17.9)	85 (28.5)	<0.01
HIV infection	33 (5.6)	20 (6.9)	13 (4.4)	<0.01
Solid organ transplantation	21 (3.6)	5 (1.7)	16 (5.4)	0.22
Hematology/cancer	66 (11.2)	18 (6.2)	48 (16.1)	0.01
Steroid or immunosuppressant therapy	31 (5.3)	14 (4.8)	17 (5.7)	0.40
<b>Characteristics at ICU admission</b>				
Time from hospital to ICU admission, days	1 [1–3]	1 [1–2]	1 [1–4]	<0.01
Reason for ICU admission				0.03
Altered mental status <sup>a</sup>	431 (73.2)	217 (74.6)	214 (71.8)	
Seizures / status epilepticus	88 (14.9)	48 (16.5)	40 (13.4)	
Sepsis / respiratory failure	43 (7.3)	12 (4.1)	31 (10.4)	
Other	27 (4.6)	14 (4.8)	13 (4.4)	
SAPS II, points	42 [30–57]	37 [26–50]	46 [35–64]	<0.01
GCS score < 8, indicating coma	202 (34.3)	78 (26.8)	124 (41.6)	<0.01
<b>Non-neurologic organ failure</b>				
Respiratory SOFA > 2 <sup>b</sup>	97 (16.5)	33 (11.3)	64 (21.5)	<0.01
Cardiovascular SOFA > 2 <sup>c</sup>	136 (23.1)	50 (17.2)	86 (28.9)	<0.01
Renal SOFA > 2 <sup>d</sup>	48 (8.1)	21 (7.2)	27 (9.1)	0.45
Liver SOFA > 2 <sup>e</sup>	7 (1.2)	1 (0.3)	6 (2)	0.12
Coagulation SOFA > 2 <sup>f</sup>	23 (3.9)	4 (1.4)	19 (6.4)	<0.01

Data are median (IQR) or n (%).

mRS modified Rankin Scale, HIV human immunodeficiency virus, ICU intensive care unit, GCS Glasgow Coma Scale, SAPS Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment

<sup>a</sup> Altered mental status is defined by a GCS score ≤ 13.

<sup>b</sup> A respiratory SOFA score > 2 indicates a PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 200 with respiratory support.

<sup>c</sup> A cardiovascular SOFA score > 2 indicates the use of norepinephrine or epinephrine (any dose).

<sup>d</sup> A renal SOFA score > 2 indicates a serum creatinine > 300 μmol/L.

<sup>e</sup> A liver SOFA score > 2 indicates a bilirubin concentration > 100 μmol/L.

<sup>f</sup> A coagulation SOFA score > 2 indicates a platelet count < 50 platelets × 10<sup>9</sup>/μL.

## Endpoints

Local investigators prospectively entered all study endpoints into the electronic CRF. The primary endpoint was poor functional outcome 3 months after ICU admission, defined by a score on the modified Rankin scale (mRS) of 3 to 6, indicating moderate-to-severe disability or death. Causes of death were divided into two categories, i.e., systemic causes (cardiovascular failure, multiple organ failure) or neurological causes (withdrawal of care because of diffuse neurological injury or brain death). Secondary endpoints included need for organ support (i.e., mechanical ventilation, tracheostomy, vasopressors, renal replacement therapy), neurosurgery (i.e., intracranial pressure monitoring, external ventricular drainage, brain biopsy), development of systemic complications (i.e., septic shock, nosocomial pneumonia, pulmonary embolism, overt gastrointestinal bleeding), neurological complications (i.e., status epilepticus, empyema/cerebral abscess, cerebral ischemia, intracranial bleeding, and brain death), and hospital outcomes (i.e., ICU and hospital lengths of stay).

**Table 2 Meningoencephalitis characteristics at ICU admission**

	Total (n=589)	mRS 0-2 (n=291)	mRS 3-6 (n=298)	p value
<b>Clinical characteristics</b>				
Glasgow coma scale				
Score	9 [6-11]	10 [7-12]	8 [6-11]	<0.01
Eye component $\leq$ 3	439 (74.5)	212 (72.9)	227 (76.2)	0.34
Verbal component $\leq$ 3	462 (78.4)	214 (73.5)	248 (83.5)	<0.01
Motor component $\leq$ 3	156 (26.5)	54 (18.6)	102 (34.2)	<0.01
Temperature				
Degrees, °C	38.4 [37.5; 39.1]	38.4 [37.7; 39.3]	38.3 [37.5; 39]	0.04
$\geq$ 38 °C, indicating fever	379 (64.5)	189 (65.2)	190 (63.8)	0.79
Hemiparesis/hemiplegia	91 (15.4)	31 (10.7)	60 (20.1)	<0.01
Cranial nerve involvement	84 (14.3)	37 (12.7)	47 (15.8)	0.35
Seizures	217 (36.8)	105 (36.1)	112 (37.6)	0.73
Focal	92 (15.6)	38 (13.1)	54 (18.1)	0.11
Generalized	143 (24.3)	76 (26.1)	67 (22.5)	0.34
Status epilepticus	66 (11.2)	32 (11)	34 (11.4)	0.90
Psychiatric symptoms	134/588 (22.8)	88/291 (30.2)	46/297 (15.5)	<0.01
<b>Paraclinical tests</b>				
CSF				
Time from ICU admission to LP, days	1 [1-1]	1 [1-1]	1 [1-2]	0.10
Leucocytes, cells/mm <sup>3</sup>	142 [26-839]	150 [36-810]	116 [20-839]	0.10
Protein level, g/L	1.3 [0.6-3.3]	1.3 [0.6-3.1]	1.3 [0.6-3.5]	0.86
CSF glucose/blood glucose ratio	0.5 [0.1-0.6]	0.5 [0.2-0.6]	0.4 [0.1-0.6]	0.10
Brain imaging				
CT scan performed	495 (84)	244 (83.8)	251 (84.2)	0.91
Time from ICU admission to CT scan, days	1 [1-1]	1 [1-1]	1 [1-1]	0.33
Normal CT scan	317/495 (64)	181/244 (74.2)	136/251 (54.2)	<0.01
MRI performed	356 (60.4)	177 (60.8)	179 (60.1)	0.87
Time from ICU admission to MRI, days	2 [1-4]	2 [1-4]	2 [1-4]	0.24
Normal MRI	94/356 (26.5)	64/177 (36.4)	30/179 (16.8)	<0.01
EEG				
EEG performed	404 (68.7)	193 (66.3)	211 (71)	0.25
Time from ICU admission to EEG, days	2 [1-2]	2 [1-3]	2 [1-2]	0.39
<b>Antimicrobial therapy and steroids</b>				
Acyclovir on day 1	284/588 (48.3)	158/290 (54.5)	126 (42.3)	<0.01
Third-generation cephalosporin on day 1	324/588 (55.1)	180/290 (62.1)	144 (48.3)	<0.01
Adjunctive steroids on day 1	168 (28.5)	95 (32.6)	73 (24.5)	0.03

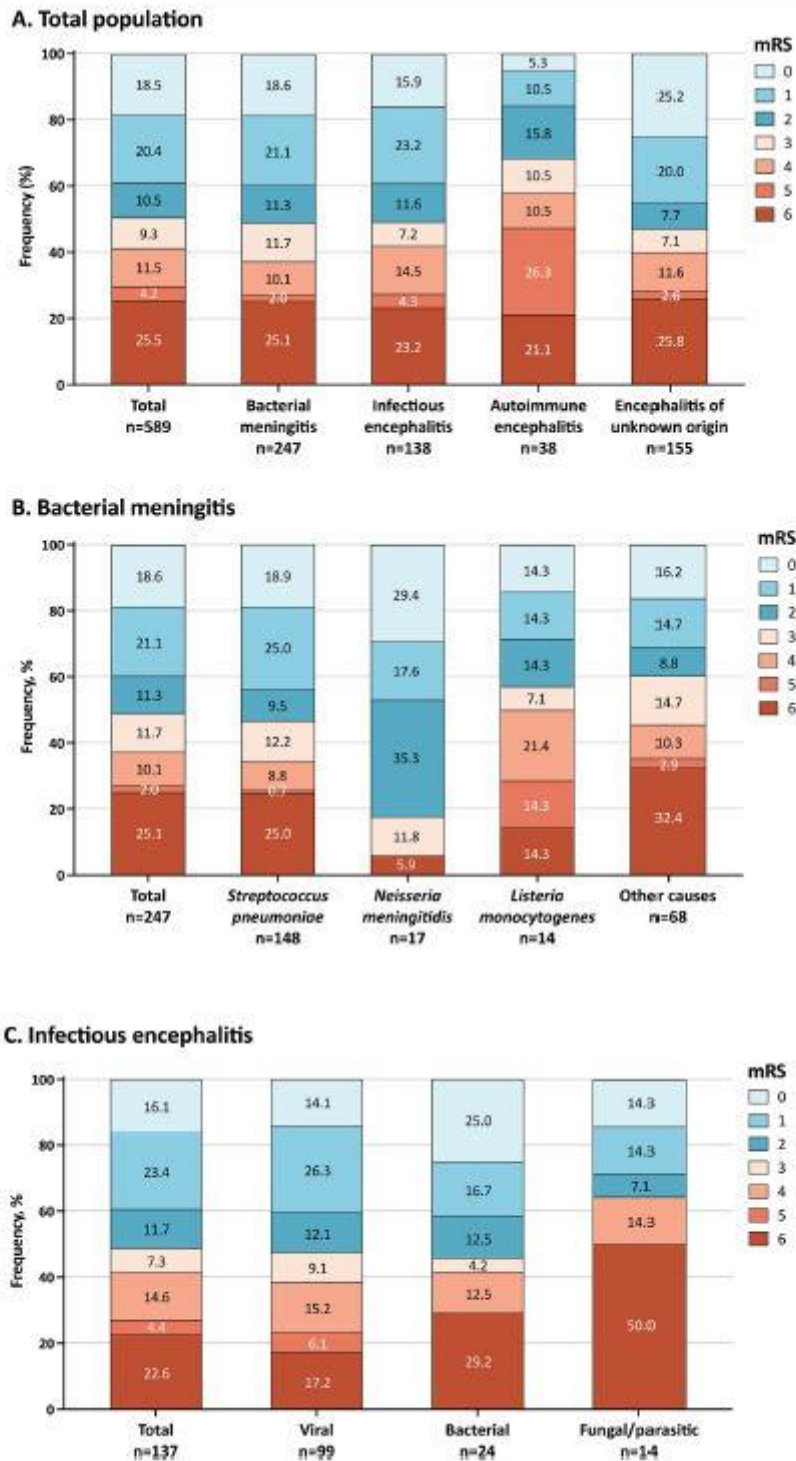
Data are median (IQR) or n (%)

mRS modified Rankin Scale, CSF cerebrospinal fluid, ICU intensive care unit, LP lumbar puncture, CT computed tomography, MRI magnetic resonance imaging, EEG electroencephalogram

## Statistical analysis

Data management and statistical analysis were performed by independent statisticians (QS, SR, ICUREsearch). Data are presented as numbers (interquartile range) or numbers (percentage), as appropriate. Multivariable logistic regression analysis stratified on centers explored the association between baseline characteristics and the primary endpoint. Clinically relevant variables associated with the primary endpoint ( $p < 0.2$ ) in univariate analysis were entered into the multivariable analysis. Two-by-two interactions and collinearity between selected variables were tested. Missing values were imputed to the median or mode for quantitative and qualitative variables, respectively. Statistics were performed using SAS 9.4 software (SAS Institute Inc.). A  $p$  value  $< 0.05$  was considered significant. Based on a syndromic approach, sensitivity analyses were performed to investigate two a priori defined subgroups of patients, namely patients diagnosed with bacterial meningitis, and patients with primary encephalitis of any cause, after adjustment for main etiologies (e.g., infectious, autoimmune, and unknown origin).





**Fig. 1** Distribution of scores on the modified Rankin scale (mRS) at 3 months. Panel **A** shows the distribution of mRS scores in the total study population and in the principal different etiological categories. Two patients with more than one infectious etiology are not shown. Panel **B** shows the distribution of mRS scores in patients with bacterial meningitis overall and according to the main bacterial causes. Panel **C** shows the distribution of mRS score in patients with infectious encephalitis overall and according to the main viral causes. Two patients with more than one infectious etiology are not shown

## Role of the funding source

The European Society of Intensive Care Medicine (ESICM) played no role in study design, data collection, data analysis, data interpretation, or in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

# Results

## Study population

Between June 21, 2017, and April 6, 2020, we identified 599 eligible patients from 68 centers across 7 countries, with a median number of patients per center of 7 (IQR 5–11). Among them, 589 (98%) patients were included, and all completed the 3-month follow-up. The study flowchart is presented in the Appendix (ESM Fig. 1). Baseline characteristics of included patients are shown in Table 1. The median age of the study population was 66 years (IQR 44–71) and 346 (58.7%) were male. The most frequent comorbidities were diabetes ( $n = 111$ , 18.8%) and immunodepression ( $n = 137$ , 23.3%). The time from hospital admission to ICU transfer was 1 (IQR 1–3) day. At ICU admission, the SAPS II score was 42 (IQR 30–57), and 202 (34.3%) patients were comatose. Respiratory and cardiovascular failures were observed in 97 (16.5%) and 136 (23.1%) cases, respectively.

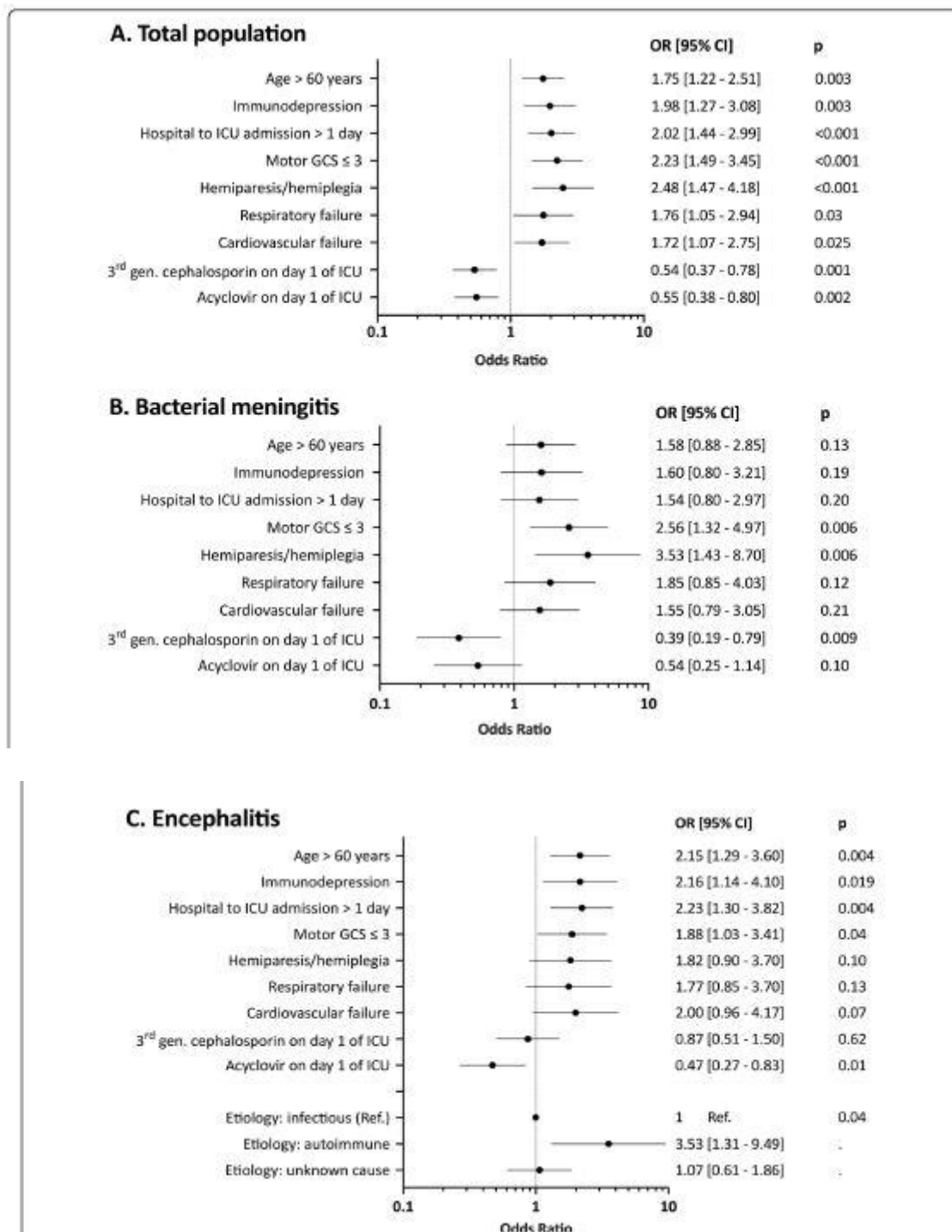
Meningoencephalitis characteristics at ICU admission are shown in Table 2. Patients had a severe clinical presentation with a median score on the GCS of 9 (IQR 6–11), convulsive seizures ( $n = 217$ , 36.8%), and hemiparesis/ hemiplegia ( $n = 91$ , 15.4%). Altered verbal and motor responses on the GCS, and hemiparesis/hemiplegia were associated with poor outcome. The body temperature was 38.4°C (IQR 37.5–39.1), with fever present in 379 (64.5%) patients. A lumbar puncture was performed in all patients, at a median time from ICU admission of one (IQR 1–1) day. Neuroimaging was also performed in all patients, including CT scans in 495 (84%) cases and MRI in 365 (60.4%) cases. The time from ICU admission to the first CT scan and MRI were one (IQR 1–1) and one (IQR 0–7) days, respectively. A normal CT scan and MRI were observed in 317/495 (64%) and 94/365 (25.7%) cases, respectively, and associated with better outcomes in univariate analysis. EEG was performed in 404 (68.7%) cases, with a median time from ICU admission of two (IQR 1–2) days.

The 591 etiologies of meningoencephalitis diagnosed in the 589 included patients are presented in Table 3. The detailed causes of bacterial meningitis and infectious encephalitis are presented in the Appendix (ESM Tables 2, 3). The bacterial meningitis category mainly consisted of community-acquired infections ( $n = 220/247$ , 89%).

Intravenous acyclovir and third-generation cephalosporins were started at admission in 284/588 (48.3%) patients, and 324/588 (55.1%) patients, respectively. Acyclovir, and third-generation cephalosporin prescriptions differed significantly between etiological groups ( $p < 0.01$ ), being more frequently prescribed in infectious encephalitis and bacterial meningitis categories, respectively (Appendix, ESM Table 4).

Adjunctive steroids were given at admission in 202 (34.3%) patients (dexamethasone:  $n = 189$ ; other steroids:  $n = 13$ ). Specifically, 167/247 (67.6%) bacterial meningitis patients received adjunctive steroids (dexamethasone:  $n = 165$ ; other steroids:  $n = 2$ ). Intravenous methylprednisolone pulses were given during ICU stay in 90 (15.3%) patients, including 33/38 (86.8%) cases of autoimmune encephalitis, 26/247 (10.5%) cases of bacterial

meningitis, 9/138 (6.5%) cases of infectious encephalitis, and 19/155 (12.3%) cases of encephalitis of unknown origin, and 3/11 (27.2%) cases of toxic/neoplastic encephalitis.



**Fig. 2** Multivariable logistic regression of factors associated with poor neurological outcome at 3 months. Panel A shows results in the total population. Panel B shows results in patients with bacterial meningitis. Panel C shows results in patients with encephalitis, of infectious, immune-mediated, or unknown origin. Immunodepression: HIV infection, solid organ transplant recipient, hematology/cancer patient, and long-term use of steroids and/or immunosuppressant drugs. Respiratory failure: respiration SOFA score 3–4. Cardiovascular failure: cardiovascular SOFA score 3–4

## Study endpoints

Overall, 298 patients (50.5%, 95% CI 46.6–54.6%) had poor functional outcome at 3 months, including 152 deaths (25.8%). Causes of death included neurologic (102/152 (67.1%) deaths, including  $n = 29/152$  (19.1%) brain deaths) and systemic causes (50/152 (32.8%) deaths). Decisions to withdraw care during ICU stay were reported in 103/152 (67.8%) deaths and were more frequent in neurologic causes of death than in systemic causes of death (71/102 (69.6%) deaths *versus* 15/50 (30%) deaths,  $p < 0.01$ ). The distribution of mRS scores at 3 months in the entire cohort and in the different etiologic groups are presented in Fig. 1 (panel A). Patients with an autoimmune cause of encephalitis had the worst functional outcomes. The distribution of mRS score at 3 months in patients with bacterial meningitis and infectious encephalitis are presented in Fig. 1, panels B and C, respectively. Among patients with infectious encephalitis, those with fungal/parasitic causes had the worst outcomes.

Secondary endpoints are reported in Appendix (ESM Table 5). Overall, 426 (72.3%) required invasive mechanical ventilation during ICU stay, for a duration of eight (4–17) days, and 61 (10.4%) underwent tracheostomy. ICU and hospital lengths of stay were nine (5–19) and 23 (14–46) days, respectively.

Variables independently associated with the primary endpoint were age  $> 60$  years (OR 1.75, 95% CI 1.22–2.51), immunodepression (OR 1.98, 95% CI 1.27–3.08), time between hospital and ICU admission  $> 1$  day (OR 2.02, 95% CI 1.44–2.99), a motor component on the GCS  $\leq 3$  (OR 2.23, 95% CI 1.49–3.45), hemiparesis/hemiplegia (OR 2.48, 95% CI 1.47–4.18), respiratory failure (OR 1.76, 95% CI 1.05–2.94), and cardiovascular failure (OR 1.72, 95% CI 1.07–2.75). In contrast, administration of a third-generation cephalosporin (OR 0.54, 95% CI 0.37–0.78) and acyclovir (OR 0.55, 95% CI 0.38–0.80) on ICU admission were protective (Fig. 2, panel A).

Predefined subgroup analyses are presented in Fig. 2 (panel B and C). Among acute bacterial meningitis patients, a motor response on the GCS  $\leq 3$  (OR 2.56, 95% CI 1.32–4.97), hemiparesis/hemiplegia (OR 3.53, 95% CI 1.43–8.70), and third-generation cephalosporin on day one of ICU admission (OR 0.39, 95% CI 0.19–0.79) remained independently associated with the primary endpoint (Fig. 2, panel B). Among patients with encephalitis, age  $> 60$  years (OR 2.15, 95% CI 1.29–3.60), immunodepression (OR 2.16, 95% CI 1.14–4.10), hospital to ICU admission  $> 1$  day (OR 2.23, 95% CI 1.30–3.82), a motor response on the GCS  $\leq 3$  (OR 1.88, 95% CI 1.03–3.41), acyclovir on day one of ICU admission (OR 0.47, 95% CI 0.27–0.83), and autoimmune etiology (OR 3.53, 95% CI 1.31–9.49) remained independently associated with the primary endpoint (Fig. 2, panel C).

Kaplan Meier survival curves are presented in Fig. 3 (panel A and B).

Characteristics of patients according to meningoencephalitis etiologies (post hoc analyses) are presented in the Appendix (ESM Tables 4, 6, 7). Characteristics of patients with delayed ICU admission (post hoc analysis) are presented in the Appendix (ESM Table 8).

Post hoc analyses investigating the association between adjunctive steroids on day 1 and outcomes are presented in the Appendix (ESM Table 9).

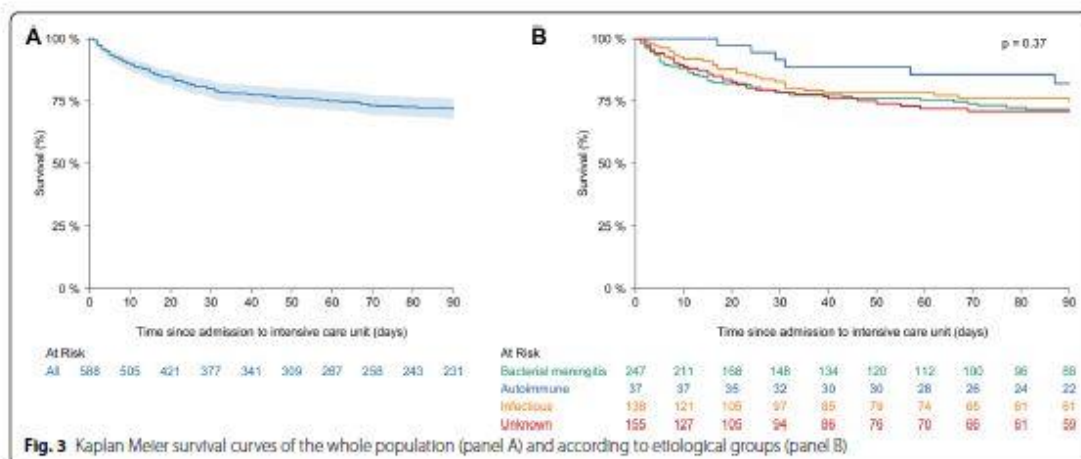
**Table 3 Etiologies of meningoencephalitis (n = 591)**

Categories	n (%)
<b>Acute bacterial meningitis</b>	<b>247 (41.8)</b>
<i>Streptococcus pneumoniae</i>	148 (25)
<i>Neisseria meningitidis</i>	17 (2.9)
<i>Listeria monocytogenes</i>	14 (2.4)
Other causes*	68 (11.5)
<b>Infectious encephalitis</b>	<b>140 (23.7)</b>
Viral causes	101 (17.1)
<i>Herpes simplex virus 1/2</i>	49 (8.3)
<i>Varicella zoster virus</i>	21 (3.6)
<i>Enterovirus</i>	3 (0.5)
Other causes**	28 (4.7)
Subacute bacterial causes	25 (4.2)
<i>Mycobacterium tuberculosis</i>	16 (2.7)
Other causes**	9 (1.5)
Fungal/parasitic causes	14 (2.4)
<i>Toxoplasma gondii</i>	7 (1.2)
<i>Cryptococcus neoformans</i>	3 (0.5)
<i>Aspergillus</i> spp.	2 (0.3)
Other causes**	2 (0.5)
<b>Autoimmune</b>	<b>38 (6.4)</b>
Anti-N-methyl-D-aspartate Receptor antibody	16 (2.7)
Acute disseminated encephalomyelitis	7 (1.2)
Other causes	15 (2.5)
<b>Neoplastic/toxic</b>	<b>11 (1.9)</b>
<b>Unknown origin</b>	<b>155 (26.2)</b>

The sum of aetiologies equals 591 because one patient was classified as having both a viral (*Varicella zoster virus*) and a subacute bacterial cause (*Mycobacterium tuberculosis*) and one patient had 2 concomitant viral aetiologies

\* Other causes of bacterial meningitis are listed in the appendix (ESM Table 2)

\*\* Other causes of infectious encephalitis are listed in the appendix (ESM Table 3)



**Fig. 3** Kaplan-Meier survival curves of the whole population (panel A) and according to etiological groups (panel B).

## Discussion

EURECA is the largest prospective international multicenter cohort study to investigate outcomes of adult patients with meningoencephalitis requiring intensive care. We observed a poor functional outcome at 3 months in about half of patients, in the form of moderate-to-severe functional disability or death. We identified patient characteristics, time to ICU admission, neurologic presentation, antimicrobial therapy, and respiratory and cardiovascular complications at admission as independent indicators of outcome.

Patients with meningoencephalitis often require ICU admission to ensure oxygenation, airway protection, circulatory support, and prevention and treatment of secondary complications that might impact outcomes. These include cerebral edema [6], seizures/status epilepticus [6, 9], and systemic complications, such as fever [11], aspiration pneumonia [8], respiratory failure requiring mechanical ventilation [6, 7, 11], and thrombocytopenia/disseminated intravascular coagulopathy [6, 7]. Due to the lack of prospective studies, there is currently no high-quality evidence suggesting that prevention of secondary complications is associated with improved outcomes. However, early ICU admission for monitoring and prevention of secondary insults has been proposed in encephalitis patients with altered mental status, seizures and/or non-neurologic organ failure(s) [25].

The prognostic variables identified in EURECA are critical to delineate goals of care at ICU admission and to identify patients who may benefit from prolonged aggressive care in the ICU and rehabilitation. We identified older age, and immunodepression as non-modifiable factors associated with a poor functional outcome. Of note, atypical presentations of HSV encephalitis have been described in these populations, which may result in delays in diagnosis and appropriate treatment, and worse outcomes [26–28]. We also identified actionable factors for which improvement could be made in future interventional studies, including time from hospital to ICU admission, time to antimicrobial therapy, and the presence of secondary complications at admission. These findings reinforce the fact that in patients who eventually required intensive care, a delayed ICU admission was an independent marker of poor prognosis [8, 11]. However, decisions of ICU admission depend on many factors and may significantly differ among centers. Although this remains speculative, delayed ICU admission might reflect inappropriate triage at hospital admission or early deterioration because of secondary complications. As such, respiratory failure identified in the multivariable analysis might be a consequence of aspiration pneumonia, frequently observed in patients with acute meningoencephalitis [8], and cardiovascular failure might reflect other complications such as septic shock, stunned myocardium or myocarditis, and dysautonomia. Use of early antimicrobial treatment (i.e., within 1 day of ICU admission) is also strongly associated with a better outcome, consistent with previously published literature for both community-acquired bacterial meningitis [13, 29], and herpes simplex encephalitis [26, 30]. While time to adequate treatment is paramount in patients with allcause meningoencephalitis, it is interesting to note that early antibacterial and antiviral treatment are associated with better outcomes in the total population, including patients with etiologies not requiring such treatments. Early antimicrobial treatment could be considered as a proxy for early identification of meningoencephalitis in the ICU, leading to an implementation of an adequate bundle of care, including an aggressive diagnostic workup and prevention of secondary brain insults.

We observed a relatively low rate of prescription of adjunctive steroids in patients with bacterial meningitis, reflecting uncertainty around their utility in the ICU setting, and a poor compliance to current guidelines [31]. Although we could not find an independent association

between adjunctive steroids and outcome in our post hoc analyses, ancillary studies using appropriate matching methods would be of interest, especially in bacterial meningitis patients.

We detected substantial heterogeneity among etiologies, with the worst outcomes observed in patients with encephalitis of autoimmune origin, compared to patients with acute bacterial meningitis and encephalitis of infectious or unknown origin. These results emphasize that an early etiological diagnosis may not only have important therapeutic implications but may also represent key information for appropriate prognostication [32]. In EURECA, the distribution of etiologies of bacterial meningitis and infectious encephalitis was comparable to current epidemiology in the general population. The prognosis of patients with bacterial meningitis appeared relatively similar to that observed in a recent large nationwide study conducted on patients with pneumococcal meningitis [24]. By contrast, we observed a more severe prognosis in patients with infectious encephalitis, as compared to a recent multicenter cohort study which reported a much lower mortality rate < 10% [5]. Previous single-center retrospective studies conducted in adult ICU patients with all-cause encephalitis, reported poor outcomes in 25 to 50% of cases, with mortality rates ranging from 6 to 17%, depending on the etiology [6–8]. We observed the worst prognosis in patients with autoimmune encephalitis, with higher morbidity but similar mortality compared to other etiological groups. Of note, meaningful delayed post ICU-recovery has been observed in these patients, and it is possible that the 90-day outcome chosen in EURECA may not reflect the final functional outcome in this etiological category [17].

The main strengths of EURECA include a large sample of consecutive patients from 68 centers in 7 countries. Patients were included prospectively based on an internationally accepted definition for probable or confirmed encephalitis. We recorded prospectively major complications and interventions during ICU stay, and we evaluated functional outcomes at 3 months with a validated functional scale.

EURECA also has limitations, including the study's observational nature, with a possible heterogeneity in patient management among centers, notably for antimicrobial therapies, adjunctive therapies, and indication and timing of decisions to withhold/withdraw care in patients with an expected unfavorable outcome. Second, because we did not use a standardized diagnostic protocol among participating centers, it is possible that some patients from the unknown etiology encephalitis group were in fact culture-negative bacterial meningitis patients. Third, many physicians would not consider a mRS score of three at 3 months as an unfavorable outcome, given the high severity of illness at admission. It is not known to what extent moderately to severely disabled patients eventually improved and regained functional independence in the long term. Fourth, we mainly identified clinical indicators of outcome and the additional value of neuroimaging or EEG variables should be investigated [33, 34]. Finally, other important patient-centered endpoints, such as cognitive impairment, psychological problems and post-encephalitic epilepsy were not recorded.

In conclusion, we observed that half of patients with meningoencephalitis requiring intensive care had poor functional outcomes at 3 months, in the form of moderate- to-severe disability or death. We identified several admission variables and the etiology of meningoencephalitis as independent indicators of outcome. While further research aiming at a better characterization of 1-year outcomes in these patients is currently ongoing (Clinical-Trials.gov Identifier: NCT02906631), the findings from this study are critical for better identification of patients who might benefit from prolonged aggressive care in the ICU and rehabilitation.

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## **Author contributions**

RS: conception of the work (PI), funding application, enrollment of participating centers, supervision of the data collection, participation in data analysis, verification of the data and interpretation, drafting the manuscript, critical revision of the manuscript, final approval of the version. RS is the guarantor of the entire manuscript and responsible for the decision to submit the manuscript. EdM: enrollment of participating centers, drafting the manuscript, including tables and figures, participation in data interpretation, critical revision of the manuscript, final approval of the version to be published. JH, RH, IM-L, FST, JdW, GC: participation in the definition of the protocol, critical revision of the manuscript, and final approval of the version to be published. SR, QS: data management, and statistical analysis. JFT: conception of the work, funding application, supervision of the data collection, analysis and interpretation, critical revision of the manuscript, final approval of the version. Other authors: data collection, interpretation of data, critical revision of the manuscript, final approval of the version. The EURECA investigators (listed in the EURECA investigator group), who participated in the data collection are non-author contributors.

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## **Data availability**

The data supporting the findings of the study are available upon reasonable request after approval of a proposal from the corresponding author (RS). Related documents will also be made available, including the study protocol, and the statistical analysis plan.



## Declarations

## Conflicts of interest

RS reports a grant from the European Society of Intensive Care Medicine (ESICM) for the current work and grants from the French Ministry of Health, outside the submitted work. Other authors report no competing interest.

## Ethical approval

The entire protocol has been reviewed and approved by the Comité de protection des personnes sud-méditerranée 2 (ID RCB 2017-A00139-44). National/ local approvals at the international study sites were obtained by the national coordinators and local investigators according to the local regulations. Since meningoencephalitis patients could not be informed at the time of study recruitment, each center referred to local/national law on the issue of lack of capacity. If the patients regained capacity before 3 months, they were asked either to consent to the use of the acute and follow-up data or to refuse to participate in the research.

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