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ORIGINAL PAPER

Infectious encephalitis in the elderly: a prospective multicentre observational study in France 2016-19

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Abstract

Purpose. Data on encephalitis in the elderly remain scarce. We aimed to describe the characteristics, aetiologies, management, and outcome of encephalitis in patients older than 65 years.

Methods. We performed an ancillary study of ENCEIF, a prospective cohort that enrolled all cases of encephalitis managed in 46 clinical sites in France during years 2016-2019. Cases were categorized in 3 age groups: i) 18-64; ii) 65-79; iii) ≥ 80 years.

Results. Of the 494 adults with encephalitis enrolled, 258 (52%) were ≥ 65 years, including 74 (15%) ≥ 80 years. Patients ≥ 65 years were more likely to present with coma, impaired consciousness, confusion, aphasia, and rash, but less likely to present with fever, and headache ($P < 0.05$ for each). Median cerebrospinal fluid (CSF) white cells count was $61/\text{mm}^3$ [13-220] in 65-79 years, 62 [17-180] in ≥ 80 years, vs. 114 [34-302] in < 65 years ($P = 0.01$). The proportion of cases due to *Listeria monocytogenes* and VZV increased after 65 years ($P < 0.001$), while the proportion of tick-borne encephalitis and *Mycobacterium tuberculosis* decreased with age ($P < 0.05$ for each). In-hospital mortality was 6/234 (3%) in < 65 years, 18/183 (10%) in 65-79 years, and 13/73 (18%) in ≥ 80 years ($P < 0.001$). Age ≥ 80 years, coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis were independently predictive of 6-month mortality.

Conclusion. The elderly represent $> 50\%$ of adult patients with encephalitis in France, with higher proportion of *L. monocytogenes* and VZV encephalitis, increased risk of death, and sequels. The empirical treatment currently recommended, aciclovir and amoxicillin, is appropriate for this age group.

Keywords: Infectious encephalitis; elderly; observational cohort; herpes simplex virus; varicella-zoster virus; *Listeria monocytogenes*; empirical treatment.

Introduction

The diagnosis of encephalitis usually relies on the combination of suggestive clinical presentation and indirect markers of brain inflammation, including meningitis and characteristic brain imaging features [1]. The International Encephalitis Consortium elaborated a case definition [2] to ensure that clinical studies will use similar inclusion criteria, which allows comparability of epidemiological studies throughout the world, and contributes to a better awareness of this puzzling disease.

Aetiologies of acute encephalitis may be infectious or non-infectious, including autoimmune, neoplastic and paraneoplastic causes [3][4][5]. In most recent prospective studies, the cause of acute infectious encephalitis was found in about 50% of cases [3][6][7][8]. Encephalitis is a rare disease, with an incidence estimated between 0.07 and 12.6 cases/year/100,000 inhabitants [9]. The prognosis of infectious encephalitis varies according to the pathogen, with in-hospital mortality rates close to 10% in contemporary studies [5][7][8][10][11]. Other prognostic factors include age, comorbidities, and the extent of brain lesions by the time appropriate treatment is initiated for herpes meningoencephalitis, the most common cause of encephalitis in developed countries. Long-term consequences of encephalitis are common: A large prospective multicentre study performed in France showed that 24% of patients previously active had not returned to work at 3 year-follow up, and 5% had died [12].

French [1], and American [13] guidelines for the management of encephalitis insisted on the challenges associated with aetiological diagnosis of encephalitis, which often requires expert laboratories, and infectious diseases expertise. Indeed, encephalitis may mimic psychiatric [14] or non-infectious neurological diseases [15], particularly in the elderly [16][17].

Infectious diseases in the elderly have become an increasingly important issue with population ageing. According to the world health organization (WHO), one in six people

worldwide will be aged 65 or more in 2050 and the number of people aged 80 or more is expected to triple between 2019 and 2050, to reach 426 million. A better knowledge of the particularities of encephalitis in the elderly could lead to better management, particularly in the choice of diagnostic investigations, and empirical treatments. To date, only one large study focused on encephalitis in the elderly, but it was retrospective [18]. We report a prospective multicentre cohort of encephalitis in the elderly, to decipher the characteristics of encephalitis in patients older than 65 years.

Methods

Patients were enrolled in the National Cohort of Infectious Encephalitis in France (the “ENCEIF” cohort), a multi-centre prospective cohort study, that enrolled all consecutive patients diagnosed with infectious encephalitis in the participating sites from January 1st 2016 to December 31st 2019 [19]. Briefly, the objective of the ENCEIF study was to describe the epidemiology, the characteristics (clinical, biological, imaging), the management, and the outcome of acute infectious encephalitis in metropolitan France.

The study presented herein is an ancillary study which aims to compare the characteristics, the management and the outcome of infectious encephalitis in three different age groups: i) 18 to 64 year-old (comparator group); ii) 65 to 79 year-old; iii) more than 80 year-old. Inclusion and exclusion criteria as well as data collected are described in detail elsewhere [19]. Briefly, all adult patients hospitalised with suspected infectious encephalitis according to the case definition of the International Encephalitis Consortium [2] with no alternative diagnosis, were invited to participate. Acute encephalitis was defined as neurologic symptoms of acute onset, for more than 24 h, without any differential diagnosis, with at least two of the following signs: fever $\geq 38^{\circ}\text{C}$, seizure, recent focal neurologic symptoms, cerebrospinal fluid (CSF) white cells count $\geq 5/\text{mm}^3$, inflammatory

brain lesion on magnetic resonance imaging (MRI), or computed tomography (CT)-scan, and suggestive abnormalities in electroencephalogram (EEG).

Patients or their close relatives received oral and written information about the study, and could refuse to be enrolled, but no written consent was required according to the French regulations for observational studies. Data were collected on a standardized questionnaire and computerized using a secure, web-based application Voozanoo (Epiconcept©, Paris). This study was authorized by French Commission for Data Protection, the "Commission Nationale Informatique et Liberté" (CNIL, DR-2015-300) and was approved by the Advisory Committee on Research Information Processing, the "Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé" (CCTIRS).

Outcomes were categorized using the Glasgow outcome scale (GOS) and the modified Rankin scale (mRS). The GOS scores range from 1 (death) to 5 (minor neuro-psychological deficits with no impact on daily life) [20]. The modified Rankin scale is defined by 7 grades, grade 0 corresponding to a patient without symptoms, and grade 6 to death [21]. Statistical analyses were performed using the R 4.0.5 software with the "survival" package. Categorical variables were described as frequencies and percentages, and quantitative variables as median and interquartile range. Categorical variables were compared by chi-square or Fisher's exact test, and continuous variables were compared by Mann Whitney test or Kruskal-Wallis test as appropriate.

Kaplan-Meier overall survival curves until day 180 were computed and were compared using a log-rank test. Baseline risk factors of death at day 180 were assessed within the whole cohort using univariate and multivariate cox regression. Baseline variables (i.e available during the first hours of hospital admission) included in the multivariate model were those with $P < 0.20$ in univariate analysis with respect of proportional hazard assumption. If this assumption was not respected, the model was stratified on this prespecified variable. The alpha risk was set at 5%.

Results

Demographics and comorbidities

During the study period (2016-2019), 494 patients with complete dataset have been enrolled in the ENCEIF prospective cohort study. Of them, 258 (52%) were older than 65 years, including 184 (37%) in the 65-79 year-old group, and 74 (15%) older than 80 years. Demographics and comorbidities are detailed in Table 1. There was a slight male predominance in all age categories that tended to decrease with age (65% in patients younger than 65 years, 59% in the 65-79 year-old, and 56% in patients older than 80 years). As expected, older patients had more comorbidities, including diabetes, cancer, haematological malignancy, autoimmune diseases, and immunodeficiency ($P<0.01$ for each category). The proportion of patients who travelled abroad within the last 6 months decreased with age, from 24% in patients younger than 65 years, to 7% in patients older than 80 years ($P<0.001$).

Clinical features on admission

Table 1 details clinical features on admission. Older patients were more likely to present with coma, impaired consciousness, confusion, aphasia, and skin rash, but less likely to present with fever, and headache ($P<0.05$ for each).

Investigations

On admission, most findings were similar in the elderlies and in the rest of the population with encephalitis, except for CSF white cells count, almost twice lower in patients older than 65 years ($P=0.01$). Other CSF characteristics were similar, as well as the proportion of patients who underwent brain imaging (>95% in all age groups), the proportion of patients who underwent EEG (>75% in all age groups), and the proportion of these investigations that revealed abnormalities (Table 2).

Aetiologies of infectious encephalitis

Investigations identified the cause of encephalitis in 324/494 patients (66%) overall, and this proportion was similar throughout age groups (Table 3). The proportion of encephalitis due to *Listeria monocytogenes*, and varicella-zona virus (VZV) increased with age ($P<0.001$), the latter becoming the primary cause of infectious encephalitis after 80 years. Conversely, the proportion of cases due to tick-borne encephalitis (TBE) virus, and *M. tuberculosis* decreased with age ($P<0.05$).

Management and outcome

The proportion of patients treated with intravenous aciclovir increased with age ($P=0.045$), but time from symptoms onset to aciclovir treatment was similar (Table 4). Older patients had longer hospital stay, and worse prognosis, whatever the criteria: GOS, mRS, in-hospital as well as 6-month case fatality rate (CFR). During the initial hospital stay, 37/494 patients died (8%).

Univariate and multivariate analysis of risk factors for six-month mortality

On univariate analysis, age ≥ 65 years, immunodeficiency, coma on admission, CSF protein ≥ 0.8 g/L, and CSF white cells count $< 80/\text{mm}^3$ were associated with increased 6-month CFR (Table 5), while headache on admission was associated with decreased 6-month CFR. On multivariate analysis, age ≥ 80 years (Figure 1), coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis were independently predictive of 6-month CFR.

Discussion

The major findings of this multicentre prospective cohort study of acute encephalitis are as follows:
i) the elderly represent a large proportion of cases, as 258/494 adults with encephalitis were older than 65 years (52%), and 74/494 (15%) older than 80 years; ii) the elderly were more likely to present with coma, impaired consciousness, confusion, aphasia, and skin rash, but less likely to

present with fever, and headache ($P<0.05$ for each); iii) CSF white cells count was lower in the elderlies, with a median of $61/\text{mm}^3$ [13-220] in 65-79 years, and 62 [17-180] in ≥ 80 years, vs. 114 [34-302] in patients younger than 65 years ($P=0.01$); iv) the proportion of encephalitis due to *L. monocytogenes*, and VZV increased with age ($P<0.001$), the latter becoming the primary cause of infectious encephalitis after 80 years. The proportion of TBE and *M. tuberculosis* encephalitis decreased with age ($P<0.05$). Overall, about one third of cases remained undocumented whatever the age group; v) In-hospital mortality was 6/234 (3%) in patients younger than 65 years, 18/183 (10%) in 65-79 year-old, and 13/73 (18%) in patients older than 80 years ($P<0.001$). Not surprisingly, age was also associated with increased 6-month CFR, and higher risk of sequelae, for GOS as well as mRS ($P<0.001$ for all criteria); vi) age ≥ 80 years, coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis were independently predictive of 6-month CFR.

To the best of our knowledge, this is the first prospective study focusing on encephalitis in the elderlies. Our findings are in line with previous retrospective cohorts, in terms of clinical presentation, more often incomplete in the elderlies [16][22]. Indeed, fever is absent in 44-77% of cases in recent studies [3][6][7], particularly in the elderly [16][17]. Of note, we observed striking differences regarding the prevalence of fever on admission: 146/236 (62%) of encephalitis cases in patients younger than 65 years, vs. 73/184 (40%) in 65-79 years, and 14/74 (19%) in patients older than 80 years ($P<0.001$). Lower CSF white cells count in encephalitis in the elderlies has been documented by others [22][23][24]. Age has repeatedly been identified as an independent risk factor for fatal outcome in encephalitis [4][5][8][22][25][26][27][28]. This may be largely driven by immuno-senescence [29], and comorbidities. Interestingly, only age ≥ 80 years remained associated with mortality in our multivariate analysis, while the age group 65-79 years was not independently predictive of death. This confirms that age by itself should not be considered as a criteria for limitation of care in most cases: Indeed, this tricky decision must be individualized,

184 taking into account comorbidities, frailty, neurological status on admission, and quality of life
185 before the onset of encephalitis. Whenever possible, the patient, the closest relatives, and the
186 general practitioner must be involved in this complex decision process.

187 The third most common pathogen responsible for encephalitis in patients older than 65
188 years, after HSV and VZV, was *L. monocytogenes*. Although rarely reported in encephalitis cohorts
189 from other countries [3][6][7], listeriosis was the fourth pathogen of all ages in the previous large
190 cohort study in France, in 2007 [8], and the third in the population aged over 65 years. This outlines
191 the importance of local epidemiological studies to monitor the epidemiology of encephalitis, as it
192 informs the selection of empirical treatment: Indeed, French guidelines are unique in their
193 recommendation to add amoxicillin to aciclovir as the first-line empirical treatment for acute
194 encephalitis [1]. This combination seems appropriate in the elderlies, as it covers 94% (44/47) of
195 the pathogens identified in the subgroup of encephalitis in patients ≥ 80 years. The ENCEIF study
196 also allowed to detect the emergence of TBE [30], as in neighbouring countries [31] but as it is
197 mostly associated with outdoor activities [32], the elderlies are not the primary target, with no case
198 diagnosed in patients older than 80 years in our study.

199 Our findings outline the difficulties to diagnose encephalitis in elderly patients, as i)
200 cardinal signs, such as fever, are usually absent; ii) confusion or delirium in the elderlies may be
201 triggered by many other mechanisms, including metabolic, neoplastic, vascular, septic, or toxic
202 pathways. Central nervous system infections, including encephalitis, may be mistaken for many
203 other diseases, and this is especially true in the elderlies, for whom the diagnosis of encephalitis is
204 particularly challenging [33][34]. Nevertheless, in our study, time from symptoms onset to
205 aciclovir treatment start was similar across all age groups.

206 Our study has limitations. First, as this was performed in one single country, with
207 epidemiological particularities, our findings not necessarily apply to other countries. Second, given

the rapid evolution of infectious diseases in the XXIst century, the repartition of pathogens may change rapidly, which would require iterative surveillance studies to remain informed on the primary pathogens encountered in each age groups. Third, we used the threshold of 65 years to define the elderlies, in line with most other scientific publications, and the WHO, although this represents a very heterogeneous group. Although we dichotomized the elderlies in two groups (65-79, and ≥ 80 years), we did not use a comorbidity or frailty score, which may have allowed a better stratification of patients. However, our study also has strengths, including the prospective and standardized collection of data, the multicentre design, and the involvement of a collaborative network of experts in the field, which allowed the enrolment of the largest sample size of encephalitis in the elderlies to date.

In conclusion, we found that $>50\%$ of adult patients with encephalitis are ≥ 65 years, with higher proportion of *L. monocytogenes* and VZV, and lower proportion of TBE virus and *M. tuberculosis* encephalitis. Current recommendations for empirical treatment with aciclovir and amoxicillin seem appropriate given the current epidemiology in France. In-hospital CFR increases from 3% in patients <65 years to 18% in patients ≥ 80 years, with higher risk of sequelae in the elderlies. Age ≥ 80 years, coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis are independently predictive of 6-month CFR.

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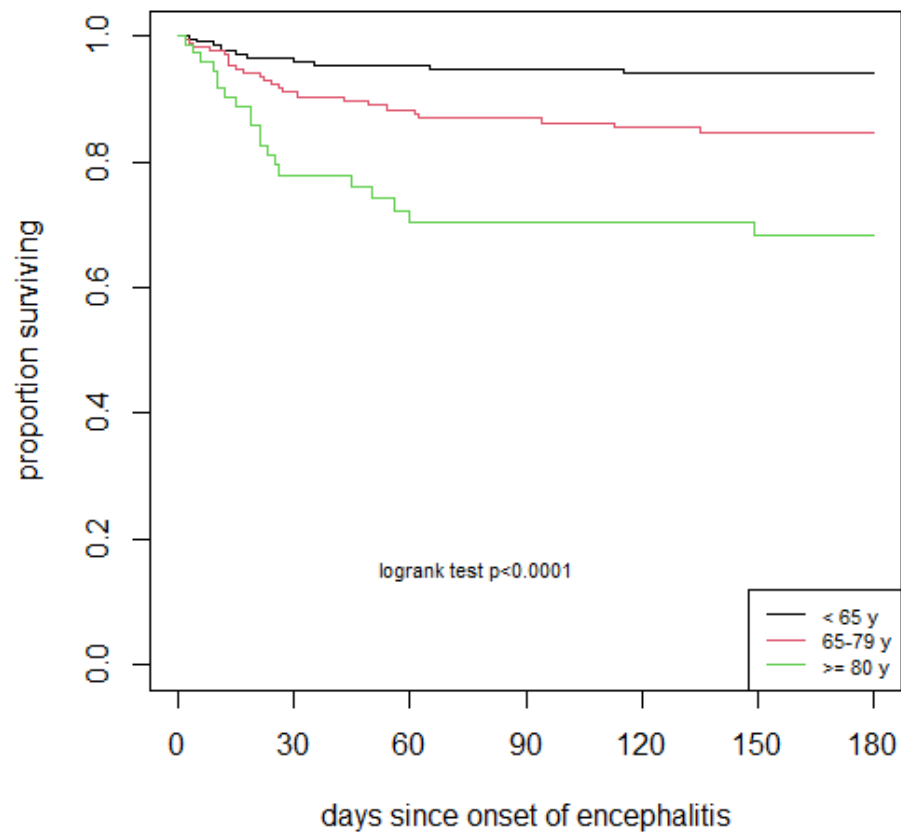
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Conflict of interest

None to declare

Figure 1. Survival of patients with encephalitis according to age (<65, 65-69, ≥80 years)



	number at risk						
< 65 y	234	162	151	145	142	138	128
65-79 y	183	138	127	121	117	114	104
≥ 80 y	73	44	39	38	37	35	33

1 **Table 1.** Patients characteristics

	<65 years (n= 236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
Male gender	153/236 (65)	109/184 (59)	41/73 (56)	0.304
Diabetes	19/233 (8)	33/184 (18)	15/74 (20)	0.003
Cancer	3/236 (1)	21/183 (11)	15/73 (21)	<0.001
Haematological malignancies	3/235 (1)	19/183 (10)	5/73 (7)	<0.001
Immunodeficiency	9/236 (4)	39/184 (21)	11/74 (15)	<0.001
Autoimmune diseases	3/233 (1)	14/183 (8)	6/71 (8)	<0.001
Neurological diseases	8/236 (3)	14/184 (8)	7/74 (9)	0.054
International travel within the last 6 months	54/225 (24)	22/173 (13)	5/69 (7)	<0.001
Coma	18 (8)	9 (5)	11 (15)	0.025
Impaired consciousness	84 (36)	74 (41)	39 (53)	0.032
Confusion	127 (54)	126 (69)	53 (72)	0.002
Seizure	33 (14)	30 (16)	11 (15)	0.803
Headache	146 (62)	73 (40)	14 (19)	<0.0001
Infratentorial neurological signs	46 (20)	37 (20)	9 (12)	0.298
- Cerebellar syndrome	19 (8)	22 (12)	3 (4)	0.107
- Cranial nerve palsy(ies)	29 (12)	20 (11)	6 (8)	0.602
Supratentorial neurological signs	84 (36)	90 (49)	32 (43)	0.022
- Deficit (motor/sensitive)	32 (14)	18 (10)	9 (12)	0.495
- Aphasia	63 (27)	79 (43)	28 (38)	0.002
Fever	146 (62)	73 (40)	14 (19)	<0.001
Skin rash	16 (7)	18 (10)	17 (23)	<0.001
Respiratory symptoms	29 (12)	20 (11)	6 (8)	0.602
Digestive symptoms	50 (21)	33 (18)	11 (15)	0.430
Rheumatological symptoms	11 (5)	7 (4)	0 (0)	0.173

2 Data are presented as numbers (%)

3 **Table 2.** Investigations

	<65 years (n= 236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
CSF white blood cells count, /mm³	114 [34-302]	61 [13-220]	62 [17-180]	0.010
CSF glucose, mmol/L	3.2 [1.8-4.1]	3.2 [0.8-4.3]	3.4 [2.5-4.6]	0.197
CSF protein, g/L	0.9 [0.6-1.4]	0.9 [0.6-1.4]	0.9 [0.6-1.6]	0.666
CSF lactates, mmol/L	2.8 [2.2-3.4]	2.6 [2.2-3.3]	3.3 [2.2-4.5]	0.211
Electroencephalogram				
- performed	181/232 (78)	135/183 (74)	59/73 (81)	0.407
- abnormal	125/173 (72)	106/134 (79)	44/59 (75)	0.385
Brain imaging (CT scan or MRI)				
- performed	231/236 (98)	182/184 (99)	73/74 (98)	0.796
- abnormal	132/230 (57)	115/180 (64)	35/73 (48)	0.060

4 Quantitative data are presented as median [interquartile range], qualitative data are presented as numbers (%)

5 CSF, cerebrospinal fluid

6

7 **Table 3.** Aetiologies of infectious encephalitis

	<65 years (n=236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
Causative agent identified	152 (64)	125 (68)	47 (64)	0.692
Herpes simplex virus	64 (27)	53 (29)	15 (20)	0.368
Varicella-zona virus	16 (7)	27 (15)	22 (30)	<0.001
<i>Mycobacterium tuberculosis</i>	10 (4)	1 (0.5)	0 (0.0)	0.023
<i>Listeria monocytogenes</i>	3 (1)	13 (7)	7 (9)	<0.001
Arboviruses ¹	20 (8)	14 (8)	1 (1)	0.107
- Tick-borne encephalitis	17 (7)	9 (5)	0 (0)	0.032
Enterovirus	5 (2)	1 (0.5)	0 (0)	0.317
<i>Cryptococcus neoformans</i>	1 (0.4)	3 (2)	0 (0)	0.373
Influenza virus	8 (3)	3 (2)	0 (0)	0.210
Epstein-Barr virus	4 (2)	1 (0.5)	1 (1)	0.534
JC virus	1 (0.4)	2 (1)	0 (0)	0.744
<i>Borrelia burgdorferi</i>	1 (0.4)	2 (1)	0 (0)	0.744
Measles virus	3 (1)	0 (0)	0 (0)	0.385
<i>Mycoplasma pneumoniae</i>	4 (1.7)	0 (0.0)	0 (0.0)	0.210
Miscellaneous ²	12 (5)	5 (3)	1 (1)	0.276
Unknown	84 (36)	59 (32)	27 (36)	0.692

8 Data are presented as numbers (%)

9 ¹**Other arboviruses:** Chikungunya (n=1), Japanese Encephalitis (n=2), Toscana virus (n=1), West-Nile virus (n=4),
10 Zika (n=1).

11 ²**Miscellaneous:** CMV (n=1), HHV6 (n=2), Parvovirus B19 (n=1), VIH (n=1), *Anaplasma spp.* (n=1), *Bartonella spp.*
12 (n=1), *Capnocytophaga spp.* (n=2), *Coxiella spp.* (n=1), *Francisella tularensis* (n=1), *Legionella spp.* (n=1),
13 *Leptospira spp.* (n=2), *Rickettsia spp.* (n=1), *Treponema pallidum* (n=1), *Tropheryma whipplei.* (n=2).

14 **Table 4.** Management and outcome

	<65 years (n=236)	65-79 years (n=184)	≥80 years (n=74)	<i>P</i>
Management				
Intravenous aciclovir	200/229 (87)	156/179 (87)	71/73 (97)	0.045
Time from symptoms onset to aciclovir start, days	3 [1-6]	2 [1-6]	2 [1-4]	0.848
Corticosteroids	54/221 (24)	30/173 (17)	9/70 (13)	0.058
Antibacterial treatment	163/229 (71)	119/181 (66)	47/73 (64)	0.382
Outcome				
Shock	10/235 (4)	9/183 (5)	5/74 (7)	0.633
Intensive Care Unit (ICU) admission	109/235 (46)	69/184 (38)	27/74 (36)	0.117
ICU length of stay, days	6 [2-13]	5 [4-12]	4 [2-10]	0.648
Hospital length of stay, days	15 [9 - 25]	19 [12 - 31]	20 [12 - 26]	0.005
Glasgow outcome scale on discharge				<0.001
- 1	6/230 (3)	18/180 (10)	13/72 (18)	
- 2	0/230 (0)	2/180 (1)	0/72 (0)	
- 3	19/230 (8)	20/180 (11)	12/72 (17)	
- 4	58/230 (25)	45/180 (25)	17/72 (24)	
- 5	147/230 (64)	95/180 (53)	30/72 (42)	
Modified Rankin scale on discharge				<0.001
- 0	56/212 (26)	26/165 (16)	11/66 (17)	
- 1	62/212 (29)	39/165 (24)	7/66 (11)	
- 2	40/212 (19)	24/165 (15)	10/66 (15)	
- 3	27/212 (13)	32/165 (20)	6/66 (9)	
- 4	15/212 (7)	20/165 (12)	17/66 (26)	
- 5	6/212 (3)	6/165 (4)	2/66 (3)	
- 6	6/212 (3)	18/165 (11)	13/66 (20)	
In-hospital mortality	6/234 (3)	18/183 (10)	13/73 (18)	<0.001

15

16 Quantitative data are presented as median [interquartile range], qualitative data are presented as numbers (%)

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18

19 **Table 5.** Univariate and multivariate analysis of risk factors for six-month mortality (Cox model)

	Univariate analysis			Multivariate analysis ¹		
	HR	CI 95%	P	HR	CI 95%	P
Age (ref < 65 years)						
- 65-79 years	2.6	[1.3 – 5.3]	0.0084	1.9	[0.9-4.1]	0.1124
- ≥80 years	6.1	[2.9 – 12.7]	<0.0001	5.2	[2.3-11.7]	<0.0001
Male gender	0.8	[0.5 – 1.4]	0.4160	-	-	-
Diabetes	1.1	[0.5 – 2.2]	0.8814	-	-	-
Immunodeficiency	3.1	[1.7 – 5.5]	<0.0001	-	-	-
Coma on admission	3.8	[1.9 – 7.3]	<0.0001	3.4	[1.6-6.9]	0.0011
Confusion on admission	1.1	[0.6 – 2.0]	0.6313	-	-	-
Seizure on admission	1.2	[0.6 – 2.5]	0.5967	-	-	-
Fever on admission	0.7	[0.4 – 1.2]	0.1873	0.8	[0.4-1.6]	0.5931
Headache on admission	0.3	[0.2 – 0.6]	0.0006	0.8	[0.4-1.7]	0.5827
Skin rash on admission	1.2	[0.6 – 2.7]	0.6230	-	-	-
Infratentorial neurological signs on admission	0.4	[0.2 – 1.0]	0.051	0.7	[0.3-1.8]	0.4377
Supratentorial neurological signs on admission	0.9	[0.5 – 1.5]	0.696	-	-	-
Abnormal EEG	1.6	[0.7 - 3.6]	0.2470	-	-	-
Abnormal brain imaging	1.6	[0.9 – 3.0]	0.1060	-	-	-
CSF Protein ≥0.8 g/L	1.9	[1.1 – 3.4]	0.0313	2.6	[1.4-5.0]	0.0028
CSF white cells ≥80/mm³	0.6	[0.3 – 0.9]	0.0467	0.6	[0.3-1.1]	0.0926
Viral encephalitis	1.7	[0.9 – 3.0]	0.0690	1.9	[1.0-3.7]	0.0418
Bacterial encephalitis	1.1	[0.4 – 2.8]	0.8090	-	-	-
Parasitic encephalitis	3.1	[0.4 – 22.8]	0.2580			

¹ Stratified on immunodeficiency, and brain imaging

CSF, cerebrospinal fluid; EEG, electroencephalogram; CI 95%, confidence interval 95%