RESEARCH ARTICLE

Recurrence and Mortality After a First Status Epilepticus

A Retrospective Nationwide Study From the French National Health Data System

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Abstract

Background and Objectives

Status epilepticus (SE) is associated with high short-term mortality, but data on long-term outcomes, including recurrence and mortality, are limited. The aim of this study was to describe recurrence and postdischarge mortality rates up to 3 years after an initial SE and identify the associated risk factors.

Methods

We conducted a retrospective cohort study involving all patients, infants and adults, who survived their first hospitalization with an ICD-10 code of SE from January 1, 2011, to December 31, 2016, using the French National Health Data System, with a 3-year follow-up. Outcomes included SE recurrence, death, and cause of death from death certificates. Measures included patient characteristics, comorbidities, SE causes, intensive care unit admissions, and mechanical ventilation at the first SE. Multivariable Cox models assessed the relationships between these factors and recurrence or mortality.

Results

Among 37,930 patients (46.4% female, median age 55 years [interquartile range (IQR) 30–71]), the 3-year recurrence rate was 16.7% (95% CI 16.3–17.1) and the mortality rate was 25% (95% CI 24.5–25.4). Factors present at first SE associated with 3-year recurrence were younger age (hazard ratio [HR] 2.21, 95% CI 1.90–2.58, for age group <1 compared with 10–19 years), history of epilepsy before first SE (HR 1.73, IQR 1.63–1.84), alcohol consumption (HR 1.37, 95% CI 1.27–1.48), remote and progressive causes, comorbidities, and prolonged mechanical ventilation (HR 1.21, 95% CI 1.11–1.32). Progressive causes and higher number of comorbidities were also associated with mortality, but male sex (HR 1.24, 95% CI 1.19–1.30) and older age were specifically associated with mortality and not recurrence. Main causes of death at 3 years were tumors (32.1%), cardiovascular diseases (20.2%), and infectious or respiratory diseases (8.3%).

Discussion

Our study highlights a high risk of recurrence or death within 3 years after a first SE. We identified factors associated with increased risk of both recurrence and mortality and factors specifically associated with recurrence or mortality. A better understanding of these factors, which are mostly nonmodifiable at the time of discharge, could assist clinicians in better planning patient follow-up.

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Glossary

AP-HP = Assistance-Publique Hôpitaux de Paris; **ASM** = antiseizure medication; **ATC** = Anatomical Therapeutic Chemical; **HR** = hazard ratio; **ICD-10** = International Classification of Diseases, 10th Revision; **ICU** = intensive care unit; **ILAE** = International League Against Epilepsy; **IQR** = interquartile range; **LTD** = long-term disease; **SE** = status epilepticus; **SNDS** = Système National des Données de Santé.

Introduction

Status epilepticus (SE) is a severe neurologic emergency with a notable short-term mortality rate, ranging from 9.3% to 40% in adults. While factors such as drug refractoriness and underlying causes[1] contribute to short-term mortality, long-term outcomes of SE, including recurrence and mortality, are less studied. Few studies have examined the long-term recurrence risk after a first SE, reporting rates up to 31.7% over a 10-year follow-up period of 183 patients.[2] Nonacute causes and female sex were associated with higher risk of recurrence in 2 single-center studies.[3,4] Postdischarge mortality after SE may surpass in-hospital mortality rates,[5-7] but long-term causes of death and prognostic factors remain poorly understood and may differ from short-term mortality factors,[8,9] especially for etiologies (progressive causes exert a significant influence on prognosis at 2 years).[10] Moreover, causes of death are rarely reported in SE studies.[11]

Medicoadministrative databases represent a powerful tool for studying disease epidemiology, thanks to their large, unselected populations. Previous SE studies focused on patients hospitalized with a G41 ICD-10 code.[12-16] However, these studies primarily concentrate on hospitalization for SE without specifically examining postdischarge mortality or recurrence risk. The French National Health Data System, known as the "Système National des Données de Santé" (SNDS), covers over 99% of the French population (68 million people) since 2006 and contains individual, exhaustive, and anonymous data on health care use.[17] Leveraging this database, our study aimed to delineate (1) the long-term risk of recurrence and death after discharge for a first SE, (2) the different causes of death arising after discharge for SE, and (3) the factors associated with an increased risk of recurrence or mortality.

Methods

Study Design and Data Sources

We conducted a retrospective cohort study using data from the SNDS, including (1) discharge summaries and diagnosis codes based on ICD-10 classification for all inpatient admissions to hospitals in France, (2) procedure codes based on Common Classification of Medical Procedures, (3) out-of-hospital drugs coded based on the Anatomical Therapeutic Chemical (ATC) classification, and (4) long-term disease (LTD) codes. We only considered persons affiliated with the general scheme, corresponding to 57.5 million people in 2016 (i.e., 76% of the French population), given that their medical historical data are more exhaustive.[18]

Primary causes of death (ICD-10) are collected and analyzed by the Epidemiology Center on Medical Causes of Death and linked to the SNDS using an indirect matching procedure.

This study was reported according to the REporting of studies Conducted using Observational Routinely collected Data.

Population

We included all patients at their first hospitalization with an ICD-10 SE code (G41, including G410 for generalized convulsive SE and G411, G412, G418, and G419 for other types) as the main or associated diagnosis between January 1, 2011, and December 31, 2016. This first hospitalization constituted the index SE. Patients with a same-sex twin were excluded because of the inability to distinguish them within the database, along with outpatient encounters. In addition, patients with a history of hospitalization for SE between January 1, 2006, and December 31, 2010, were excluded. We retained only those patients who survived their first hospitalization for SE, excluding patients who died during their hospital stay or during the subsequent rehabilitation stay if transferred. Consecutive stays in different hospitals separated by 1 day or less were considered a single stay, as previously described.[19] A transfer to rehabilitation was considered if the entry date into rehabilitation fell within 7 days before or after the discharge date.

Outcomes

The primary outcome was the first recurrence of SE within 3 years after discharge for SE. SE recurrence was determined for each patient using a new hospitalization discharge with G41 ICD-10 code. The secondary outcome was the mortality within 3 years after discharge, along with a description of the primary causes of death extracted from death certificates (eTable 1).

Covariates

For each patient, we extracted, at the moment of discharge, age at entry; sex; length of stay in intensive care unit (ICU), which was classified as "no ICU" if the patient did not require ICU admission, "7 days or less," and "more than 7 days"; and length of mechanical ventilation, which was classified as "no ventilation," "1 or 2 days," and "more than 2 days." We did not have access to the reason for admission in ICU (need for anesthetic drug or complications related to SE).

A patient was considered to have epilepsy before the index SE hospitalization if she or he met any of the following criteria up

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to 5 years before the SE: (1) hospitalized with a code related to epilepsy (G40); (2) received at least 1 antiseizure medication (ASM) (ATC codes listed in eTable 2); and (3) had an LTD code for epilepsy before SE. This approach aims to be as sensitive as possible but carries the risk of overestimating the number of patients with epilepsy before the first SE.

We investigated the possible causes of index SE using the same method as in a previous study.[20] We categorized the causes of index SE into acute (vascular, infectious/inflammatory, traumatic, hypoxic, toxic, alcoholic, and metabolic), remote (vascular, infectious/inflammatory, traumatic, and hypoxic), and progressive (tumors, neurodegenerative, neurodevelopmental, neurometabolic diseases) based on the International League Against Epilepsy (ILAE)[21] classification using ICD-10 diagnostic codes (eTable 1).

The presence of toxic/metabolic causes was exclusively assessed during the index SE hospitalization while other causes (including remote and progressive causes) were scrutinized during the index SE hospitalization and in all the patient's hospitalizations up to 5 years before index SE. Medical history allowed us to distinguish acute vs remote vascular, traumatic, infectious/inflammatory, or hypoxic causes. Notably, we retained a remote cause if the patient had been previously hospitalized for a possible related cause, a remote code was found during the index SE hospitalization, or the patient had an active LTD with an acute/remote code before admission. Causes were not exclusive, and a patient could have several causes of index SE (e.g., an acute vascular cause and a metabolic cause).

If the patient had a history of epilepsy but no other identified cause for the index SE episode, we categorized the cause as "epilepsy without other causes." When no SE cause was identified by this method, we defined it as "unknown." In addition, we assessed the presence of the comorbidities proposed by Charlson[22] up to 5 years before index hospitalization for SE, using hospital discharge and LTD ICD-10 codes (eTable 1). We classified patients based on the presence of no comorbidity, 1 or 2 comorbidities, or 3 or more comorbidities. Psychiatric comorbidity was determined using either an ICD-10 diagnostic code related to psychiatric disease or at least 3 instances of psychiatric drug deliveries within 1 year up to 5 years before the index SE hospitalization, or through an active LTD with a psychiatric disease code. Detailed ICD-10 and ATC codes used are listed in eTable 2.

The selection of ICD-10 codes was based on previous studies[12] and an extensive search for potentially relevant codes. All codes underwent review by a neurologist (Q.C.) and a physician specializing in medical information (S.T.M.).

Statistical Analysis

Descriptive statistics were calculated for patient characteristics across the entire cohort and within each subgroup of interest (i.e., age groups <18 and ≥18). Categorical variables were expressed as counts and percentages while numerical variables were reported as median and interquartile range (IQR). Proportions were compared across groups using the χ^2 test.

Recurrence and Mortality in the 3 Years After Hospitalization for a First SE

We used cumulative incidence functions to estimate the risk of SE recurrence within a span of up to 3 years after the date of discharge of hospitalization or rehabilitation (if the patient was admitted to rehabilitation), considering death as a competitive event (follow-up ended at the first event of either recurrence or death). The association between each variable and the risk of recurrence was assessed using a cause-specific univariable Cox proportional hazard model (with censoring at the date of death if it occurred before the recurrence of SE).[23] Subsequently, a cause-specific multivariable Cox proportional hazard model was constructed to obtain the adjusted hazard ratios (HRs) with 95% CIs for each variable. In addition, we conducted an analysis using a subdistribution hazard model (Fine and Gray) to explore whether the results obtained with the cause-specific model were similar to the subdistribution hazards obtained by the Fine and Gray model and to capture potential differences in the risk factors influencing the subdistribution of the competing event. Visual inspection of the Schoenfeld residuals was performed for each variable to ensure compliance with the assumptions of the Cox proportional hazard model. A similar approach was applied to estimate the risk of death within a period up to 3 years after discharge and to identify factors related to mortality, using a multivariable Cox proportional hazard model.

Subgroup Analysis

We hypothesized that the risk factors of recurrence might differ between pediatric patients (<18 years) and adult patients (≥18 years), as well as among patients without a history of epilepsy. Therefore, 2 subgroup analyses were conducted based on age group (<18 years vs ≥ 18 years) and among patients without a history of epilepsy using the same methods. All analyses were performed using R version 4.2.1 (R Project for Statistical Computing), and statistical significance was defined as a 2-sided $p < 0.05$.

Data Availability

This cohort study was authorized by decree 2016-1871 from December 26, 2016, relating to the processing of personal data from the National Health Data System and French Law Art. 1461-13 and 14. The Assistance-Publique Hôpitaux de Paris (AP-HP) is an authorized permanent user of the SNDS, and the authors declared the study to the AP-HP SNDS registry, which is equivalent to an institutional review board approval. The SNDS database is property of the French health insurance system, and it is not possible to share data for legal reasons. Temporary access for studies and research is possible on request from the National Health Data Institute (Institut National des Données de Santé; health-data-hub.fr/page/faq-english).

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Results

Study Population of SE and Main Characteristics

We identified 52,775 patients with at least 1 hospitalization related to a G41 code as the main or associated diagnosis in France between January 1, 2011, and December 31, 2016. Among them, 37,930 patients survived after their first hospitalization for SE and were affiliated with the general health insurance scheme (eFigure 1). There were 46.4% of women, the median age was 55 years (IQR 30–71), and a history of epilepsy was found in 46.9% of patients (Table 1).

Acute causes were more frequent in patients without a history of epilepsy (52.3% vs 35.4%, $p < 0.001$) and in the ≥18 age group compared with the <18 age group (48.7% vs 24.9%, $p < 0.01$, eTable 3). Remote and progressive causes were more frequent in patients with a history of epilepsy (respectively, 38.3% vs 25.3%, $p < 0.001$, and 45.5% vs 30.6%, $p < 0.001$).

Patients with epilepsy had a higher number of comorbidities (37.6% of patients with epilepsy had 1 or 2 comorbidities and 18.6% 3 or more vs 33.6% and 17.2% for patients without a history of epilepsy, $p < 0.001$) and were more concerned by a history of psychiatric disease (37.8% vs 31.3%, $p < 0.001$) but were less often admitted in ICU (47.7% vs 36.1%, $p < 0.001$). Need for rehabilitation was more frequently found in patients without a history of epilepsy (22.0% vs 12.7%, $p < 0.001$) and in the ≥18 group (20.7%) compared with the <18 group (4.1%, $p < 0.01$).

Analysis of SE Recurrence

Main Analysis

Overall, 6,338 patients had a recurrence within 3 years after discharge for SE, including 1,495 patients younger than 18 years (21.7% of patients younger than 18 years).

The cumulative incidence of recurrence of SE after discharge for a first SE was 11.4% (95% CI 11.4–11.8) in the first year after discharge, 14.8% (95% CI 14.4–15.1) in the second year, and 16.7% (95% CI 16.3–17.1) at 3 years after discharge (Figure 1A). The cumulative incidence was higher at 3 years for patients younger than 18 years (21.7%, 95% CI 20.7–22.7, Figure 1B) and slightly lower for those older than 18 years (15.6%, 95% CI 15.2–16.0, Figure 1C).

Multivariable analysis revealed that factors associated with an increased rate of recurrence included younger age (HR 2.21, 95% CI 1.90–2.58, for age group <1 compared with 10–19; Figure 2, Table 2); a history of epilepsy (HR 1.73, 95% CI 1.63–1.84), alcohol consumption (HR 1.37, 95% CI 1.27–1.48); presence of a remote cause (HR 1.25, 95% CI 1.18–1.33, for remote vascular, inflammatory, or traumatic; HR 1.15, 95% CI 1.01–1.32, for remote hypoxic); presence of a progressive disease, particularly a neurodevelopmental disease (HR 1.65, 95% CI 1.53–1.77; Figure 2); a higher number of comorbidities (HR 1.29, 95% CI 1.18–1.40, for 3 or more comorbidities); and prolonged mechanical ventilation (HR 1.21, 95% CI 1.11–1.32, for more than 2 days; Figure 2). The presence of an acute cause was associated with a lower recurrence rate (HR 0.58, 95% CI 0.46–0.74, for acute hypoxic cause). Three-year recurrence rates of SE according to each variable are provided in eTable 4.

Analysis Using Subdistribution Hazard Models

Using subdistribution hazard models, we observed a slight increase in the risk of recurrence in patients with at least 7-day stay in ICU (HR 1.08, 95% CI 1.01–1.15, eTable 5) and in patients with epilepsy without any other cause of SE (HR 1.12, 95% CI 1.01–1.24). Conversely, the presence of a tumor or a remote hypoxic cause was no longer significantly associated with an increased risk of recurrence (HR 1.07, 95% CI 0.97–1.17, and HR 1.14, 95 CI 0.99–1.31, respectively).

Subgroup Analysis

Subgroup analysis by age groups revealed differences in the association between certain factors and the recurrence of SE based on the age at first SE. In patients older than 18 years, factors associated with a higher risk of recurrence included remote vascular, traumatic, or inflammatory causes (HR 1.31, 95% CI 1.22–1.40, in the ≥18 group vs HR 0.96, 95% CI 0.80–1.15, in the <18 group, eTable 6); brain tumor (HR 1.34, 95% CI 1.22–1.47, vs HR 1.02, 95% CI 0.71–1.47); a high number of comorbidities (HR 1.25, 95% CI 1.14–1.36, vs HR 0.94, 95% CI 0.47–1.91, for 3 or more comorbidities); an ICU stay of less than 7 days (HR 1.13, 95% CI 1.05–1.22, compared with no ICU admission); and prolonged mechanical ventilation (HR 1.22, 95% CI 1.11–1.34, vs HR 0.95, 95% CI 0.75–1.20, for more than 2 days of mechanical ventilation). Transfer to rehabilitation was associated with a lower recurrence risk (HR 0.81, 95% CI 0.75–0.88). In patients younger than 18 years, factors associated with a higher risk of recurrence included presence of a neurodevelopmental disease (HR 2.16, 95% CI 1.87–2.50) and the presence of a history of epilepsy without any other cause of recurrence (HR 1.46, 95% CI 1.19–1.80, vs HR 1.00, 95% CI 0.89–1.13).

Subgroup analysis based on patients with no history of epilepsy showed that very young age (HR 2.17, 95% CI 1.62–2.90, for those younger than 1 year vs 10–19) and old age (from 40 to 79 years) were associated with a greater risk of recurrence compared with the 10–19 age reference group (eTable 7). Other factors associated with a greater risk of recurrence were the same as in the main analysis, except for prolonged mechanical ventilation, where no significant association was found.

Analysis of Long-Term Mortality After SE

Overall, 9,472 patients died within 3 years after discharge for SE, including 300 patients younger than 18 years (4.4% of patients younger than 18 years). The cumulative incidence of overall death after discharge for a first SE was 14.6% (95% CI 14.3–15.0) in the first year after discharge, 20.4% (95% CI 20.0–20.8) in the second year, and 25.0% (95% CI 24.5–25.4) at 3 years after discharge (Figure 3). Overall, factors

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Table 1 Demographic and Clinical Characteristics of Patients

Clinical variable	All (n = 37,930)	Without history of epilepsy (n = 20,147)	With history of epilepsy (n = 17,783)	*p* Value[e]
Sex (female), n (%)	17,598 (46.4)	9,596 (47.6)	8,002 (45.0)	<0.001
Age, y, median (IQR)	55 (30–71)	58 (30–74)	51 (30–66)	<0.001
Age groups, n (%)				
<1	1,606 (4.2)	1,222 (6.1)	384 (2.2)	<0.001
1–4	2,733 (7.2)	1,815 (9.0)	918 (5.2)	
5–9	1,266 (3.3)	568 (2.8)	698 (3.9)	
10–19	1,612 (4.2)	613 (3.0)	999 (5.6)	
20–29	2,058 (5.4)	743 (3.7)	1,315 (7.4)	
30–39	2,502 (6.6)	916 (4.5)	1,586 (8.9)	
40–49	4,216 (11.1)	1,811 (9.0)	2,405 (13.5)	
50–59	5,878 (15.5)	2,732 (13.6)	3,146 (17.7)	
60–69	6,059 (16.0)	3,294 (16.4)	2,765 (15.5)	
70–79	4,913 (13.0)	3,028 (15.0)	1,885 (10.6)	
≥80	5,087 (13.4)	3,405 (16.9)	1,682 (9.5)	
History of epilepsy, n (%)	17,783 (46.9)	NA	NA	
Causes, n (%)[a]				
Acute[b]	16,823 (44.4)	10,533 (52.3)	6,290 (35.4)	<0.001
Vascular	2,894 (7.6)	2,354 (11.7)	540 (3.0)	<0.001
Traumatic	1,594 (4.2)	1,153 (5.7)	441 (2.5)	<0.001
Infectious/inflammatory	1,825 (4.8)	1,428 (7.1)	397 (2.2)	<0.001
Hypoxic	789 (2.1)	596 (3.0)	193 (1.1)	<0.001
Metabolic disorder	6,443 (17.0)	4,045 (20.1)	2,398 (13.5)	<0.001
Alcohol	6,300 (16.6)	3,399 (16.9)	2,901 (16.3)	<0.001
Toxic	4,224 (11.1)	2,450 (12.2)	1,774 (10.0)	<0.001
Remote[c]	11,916 (31.4)	5,104 (25.3)	6,812 (38.3)	<0.001
Vascular	7,971 (21.0)	3,520 (17.5)	4,451 (25.0)	<0.001
Traumatic	3,423 (9.0)	1,135 (5.6)	2,288 (12.9)	<0.001
Infectious/inflammatory	1,345 (3.5)	443 (2.2)	902 (5.1)	<0.001
Hypoxic	980 (2.6)	515 (2.6)	464 (2.6)	0.79
Progressive[d]	14,256 (37.6)	6,166 (30.6)	8,090 (45.5)	<0.001
Neurodegenerative disease	5,324 (14.0)	2,774 (13.8)	2,550 (14.3)	0.11
Tumor	3,772 (9.9)	1,760 (8.7)	2,012 (11.3)	<0.001
Neurodevelopmental disease	5,151 (13.6)	1,358 (6.7)	3,793 (21.3)	<0.001
Metabolic disease	1,330 (3.5)	698 (3.5)	632 (3.6)	0.66
Epilepsy without other cause, n (%)	3,252 (8.6)	NA	3,252 (18.3)	
Unknown, n (%)	3,986 (10.5)	3,986 (19.8)	NA	
No. of comorbidities, n (%)				
0	17,705 (46.7)	9,914 (49.2)	7,791 (43.8)	<0.001

Continued

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Table 1 Demographic and Clinical Characteristics of Patients *(continued)*

Clinical variable	All (n = 37,930)	Without history of epilepsy (n = 20,147)	With history of epilepsy (n = 17,783)	*p* Value[e]
1–2	13,454 (35.5)	6,766 (33.6)	6,688 (37.6)	
3+	6,771 (17.9)	3,467 (17.2)	3,304 (18.6)	
History of psychiatric disease, n (%)	13,032 (34.4)	6,306 (31.3)	6,726 (37.8)	<0.001
Length of ICU, d, n (%)				
No ICU	15,764 (42.5)	7,273 (36.1)	8,491 (47.7)	<0.001
≤7	15,301 (40.3)	8,187 (40.6)	8,114 (40.0)	
>7	6,865 (18.1)	4,687 (23.3)	2,178 (12.2)	
Mechanical ventilation, n (%)				
No ventilation	25,752 (67.9)	12,388 (61.5)	13,364 (75.2)	<0.001
1–2 d	4,385 (11.6)	2,642 (13.1)	1,743 (9.8)	
>2 d	7,793 (20.5)	5,117 (25.4)	2,676 (15.0)	
Transfer to rehabilitation, n (%)	6,692 (17.7)	4,439 (22.0)	2,253 (12.7)	<0.001
Outcomes, n (%)				
3-y recurrence	6,338 (16.7)	2,374 (11.8)	5,434 (27.0)	<0.001
3-y mortality	9,472 (25.0)	5,434 (27.0)	4,038 (22.7)	<0.001

Abbreviations: ICU = intensive care unit; IQR = interquartile range; SE = status epilepticus.
[a] Causes are not exclusive, and each patient may have 0, 1, or more causes involved in his SE.
[b] At least one of the acute causes was present during the stay for SE.
[c] At least one of the remote causes was present during the stay for SE.
[d] At least one of the progressive causes was present during the stay for SE.
[e] *p* Values were computed to compare characteristics of patients with and without history of epilepsy.

associated with mortality were male sex (HR 1.24, 95% CI 1.19–1.30); older age (HR 7.30, 95% CI 5.85–9.10, for age group ≥80 compared with 10–19; Figure 2), an acute or remote hypoxic cause (HR 1.21, 95% CI 1.04–1.41, for acute hypoxic and HR 1.41, 95% CI 1.18–1.70, for remote hypoxic); a metabolic disorder (HR 1.20, 95% CI 1.14–1.26); all progressive diseases, particularly brain tumor (HR 2.79, 95% CI 2.64–2.95; Figure 2, Table 3); and a higher number of comorbidities (HR 2.88, 95% CI 2.70–3.08, for 3 or more comorbidities). Conversely, a history of epilepsy was associated with a slight decrease in mortality (HR 0.89, 95% CI 0.85–0.93; Figure 2) as an ICU stay of less than 7 days (HR 0.82, 95% CI 0.77–0.86) and mechanical ventilation. The overall death rate at 3 years for each variable is listed in eTable 4. According to death certificates, the 3 leading causes of death were tumors (32.1%), strokes or other cardiovascular diseases (20.2%), and infectious or respiratory diseases (8.3%), but differed by age group (Figure 4). A total of 588 deaths (6.2%) were related to a recurrence of SE (in-hospital death for recurrence of SE or SE code on the death certificate).

Discussion

Using a comprehensive national database, we identified 37,930 patients with a first SE episode and observed significant rates of recurrence (16.7%) and mortality (25.0%) within 3 years after discharge. The extensive sample size enabled us to effectively identify factors associated with recurrence or mortality up to 3 years after discharge. In addition, our study offers insights into the causes of death after discharge, revealing that cancers, cardiovascular diseases, and infectious or respiratory diseases collectively constituted 60.6% of the leading causes of death at 3 years.

Our study identified young age, particularly infants younger than 1 year (compared with 10–19), as the most significant factor associated with the recurrence of SE over 3 years. This finding is consistent with a previous study on 166 patients, showing that recurrences predominantly occur in young patients, notably those younger than 4 years.[24] Because previous studies often focused exclusively on either adults or children, age as a factor for SE recurrence has been infrequently reported.[25]

The second most influential factor linked to SE recurrence was a history of epilepsy before the first SE. In our study, 46.9% of patients had a presumed epilepsy before the first SE, which remains close to the rates reported in the literature (40.7% in a recent study[26]) despite the risk of overestimation due to the identification by ASM consumption (including nonspecific ASM). This association has not been commonly

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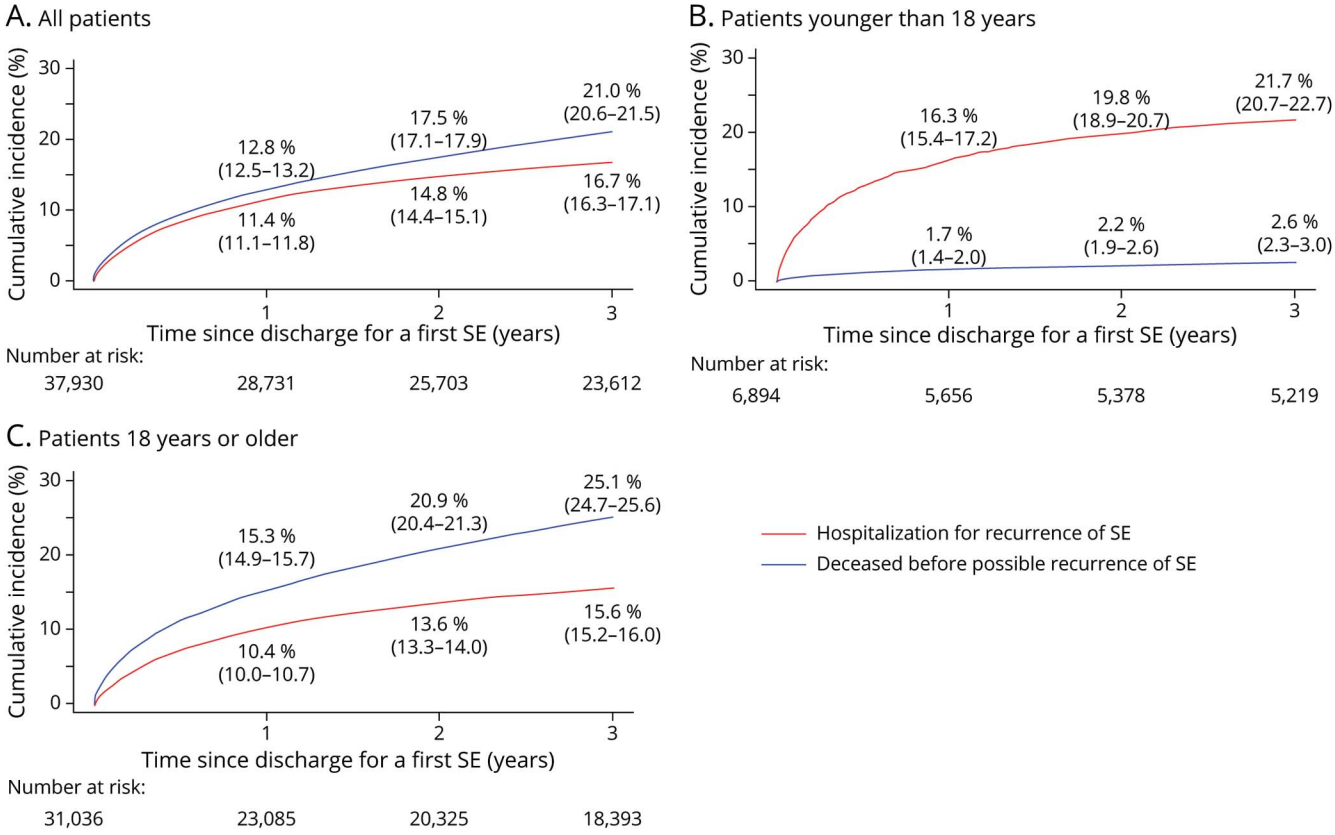
Figure 1 Cumulative Incidence of SE Recurrence After Discharge for a First SE (in Red) With Death (in Blue) as a Competing Event (Censoring at the Date of Death If It Occurred Before the Recurrence of SE)



95% CIs are shown in parentheses. The number of patients at risk, as well as the recurrence and mortality rates, is provided for each year. (A) All patients. (B) Patients younger than 18 years. (C) Patients aged 18 years or older. SE = status epilepticus.

reported, possibly because of insignificance,[3,4] omission from analysis, or focusing solely on patients already having epilepsy.[27] Our findings align with observations that not all patients develop epilepsy after their first SE episode. One study reported a 41% incidence of epilepsy after a first symptomatic SE[28] while another study found a 30.3% incidence after any initial SE.[29] Our results indicate that patients with preexisting epilepsy face a higher risk of SE recurrence, emphasizing the need for therapeutic education.

Etiology significantly influences SE recurrence risk. Previous studies suggested higher recurrence risk in patients with remote or progressive etiologies[2,4,30] while acute etiologies reveal a lower risk.[3] Our results confirm this trend in a large population and offer additional insights into specific causes associated with recurrence risk, for example, neurodevelopmental causes (HR 1.65). Our subgroup analysis revealed variations in the causes contributing to SE recurrence between adults and children. In children, neurodevelopmental and remote hypoxic causes were the most influential factors. Consistent with our results, 2 studies identified an association between remote causes and SE recurrence risk in children.[31,32] However, these studies used the 1993 ILAE definition, which encompassed vascular, inflammatory, and cerebral hypoxic factors, along with encephalopathies and cerebral malformations.[33] Our study clarifies that hypoxic sequelae and neurodevelopmental pathologies pose the highest recurrence risks.

The presence of multiple comorbidities was associated with higher recurrence risk (HR 1.28 for 3 or more comorbidities). This association could stem from conditions such as cerebrovascular disease, dementia, or hemiplegia, which may be indicative of remote or progressive causes. Other comorbidities may independently contribute to the heightened recurrence risk. Previous studies linked SE occurrence in patients with epilepsy to cardiovascular comorbidities[34] and showed an elevated risk of epilepsy development in patients with diabetes,[35] chronic renal failure,[36] or cirrhosis.[37]

Finally, our study revealed an association between prolonged mechanical ventilation (more than 2 days) and SE recurrence risk. This aligns with previous studies linking SE refractoriness to a greater risk of recurrence[4,27] because prolonged ventilation could indicate refractoriness.[14]

Advanced age was the most significant factor influencing 3-year mortality (HR 7.3 for the ≥80 years vs 10–19 years). Age consistently emerges as a pivotal prognostic factor for short-

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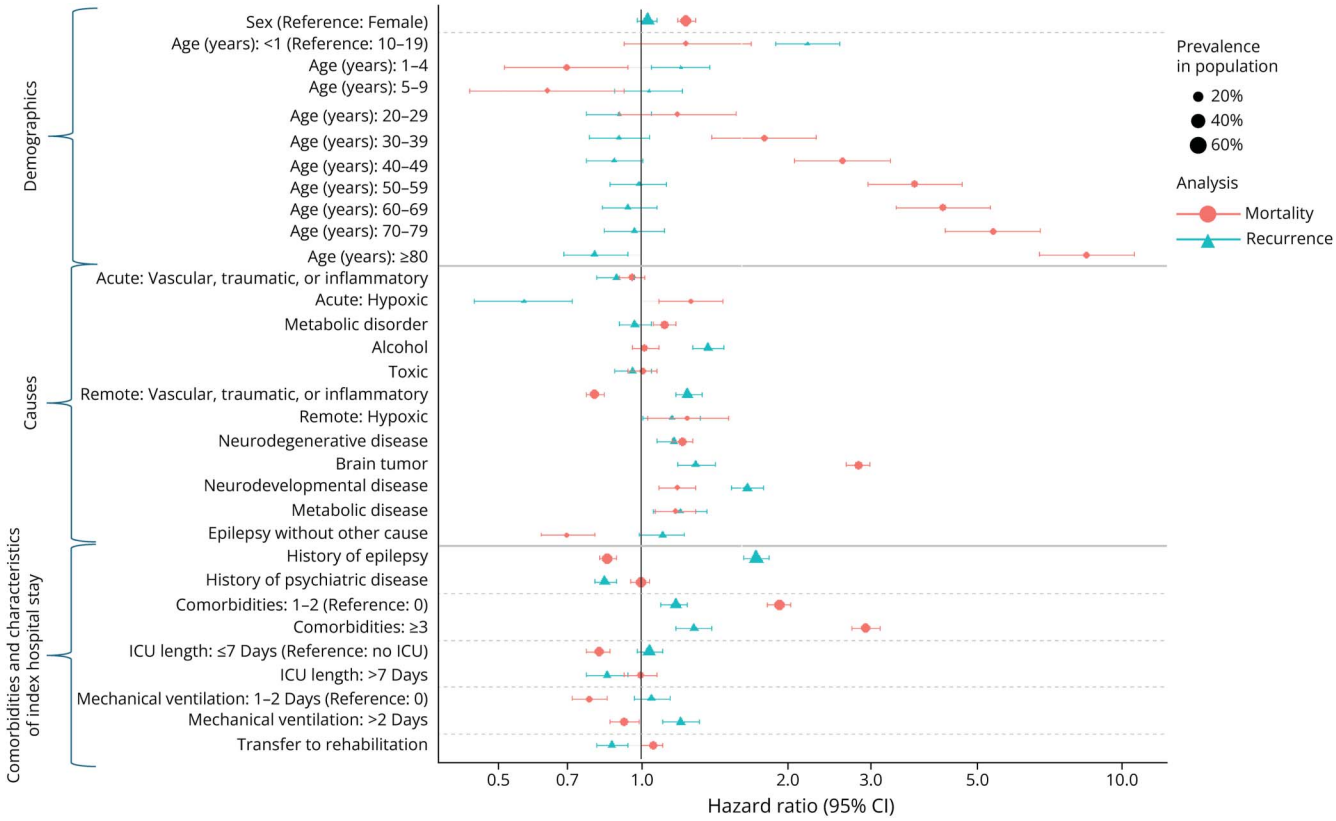
Figure 2 Risk Factors of Recurrence (Adjusted Hazard Ratio Using a Cause-Specific Multivariable Cox Regression Model, in Red) and Mortality (Adjusted Hazard Ratio Using Multivariable Cox Regression Model, in Yellow)



The size of the dot depends on the prevalence of the factor in the population of patients with a recurrence or death within 3 years. Regarding the causes, the hazard ratio corresponds to the presence of the cause compared with its absence, which is the reference. ICU = intensive care unit; SE = status epilepticus.

term mortality in SE across various studies, including those based on claims data.[12] In addition, it prominently features in long-term prognostic scoring systems such as the ACD score proposed in 2022.[5,6,10,38] Our study reaffirms age's critical role in both short-term and long-term prognostication.

Furthermore, male sex was associated with a heightened risk of postdischarge death. A higher proportion of men were reported among patients who died after hospital discharge with a minimum follow-up of 2.5 years.[7] Potential disparities in mortality rates between sexes, such as women exhibiting lower mortality rates for cancer[39] or cardiovascular diseases,[40] 2 prominent causes of death after SE, might contribute to this difference over long-term follow-up.

The cause of SE significantly influences mortality prediction.[41] Although postanoxic SE is known for its poor short-term prognosis,[1] its long-term impact remains less explored. Our study found that postanoxic SE was associated with an increased risk of death even after discharge, although lower than that previously reported for in-hospital mortality (acute hypoxic cause: OR 15.3 for in-hospital mortality vs HR 1.27 for postdischarge mortality).[20] Acute metabolic disorders, such as hyponatremia, are prevalent and linked to a substantial in-hospital mortality rate (up to 35%) in SE.[41] Our investigation revealed that metabolic disorders are associated with an elevated risk of mortality even after discharge.

Studies examining long-term mortality after SE have focused on progressive causes without distinction of the subtypes.[10,42] Our study provides a more nuanced perspective, demonstrating that all progressive causes, including tumors and neurodegenerative, neurodevelopmental, and metabolic diseases, are associated with an increased postdischarge mortality. Tumors exhibited the highest HR (HR 2.83).

A history of epilepsy, associated with reduced in-hospital mortality probability and used in the Status Epilepticus Severity Score,[43] also correlated with decreased long-term mortality risk. Of interest, the length of ICU stay did not correlate with increased mortality after discharge. A slight decrease in mortality (HR 0.82, 95 CI 0.77–0.86) was observed for ICU stays of 7 days or less compared with no stay. One of the most common reasons for refusing resuscitation is a too severe condition (37.2%).[44] This may explain why a short stay in intensive care is associated with lower long-term mortality because admitted patients could have a more favorable general condition than nonadmitted patients.

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Table 2 Factors Associated With 3-Year Recurrence of SE in All Patients

Clinical variable	HR univariable (95% CI)	HR multivariable (95% CI)
Sex (reference: female)	1.12 (1.07–1.18)	1.03 (0.98–1.08)
Age groups		
<1	1.41 (1.22–1.63)	2.21 (1.90–2.58)[a]
1–4	0.99 (0.86–1.14)	1.21 (1.05–1.39)[a]
5–9	1.05 (0.89–1.23)	1.04 (0.88–1.22)
10–19	Ref	Ref
20–29	0.87 (0.75–1.01)	0.90 (0.77–1.05)
30–39	0.88 (0.76–1.02)	0.90 (0.78–1.04)
40–49	0.87 (0.76–0.99)	0.88 (0.77–1.01)
50–59	0.98 (0.86–1.10)	0.99 (0.86–1.13)
60–69	0.88 (0.78–1.00)	0.94 (0.83–1.08)
70–79	0.82 (0.72–0.94)	0.97 (0.84–1.12)
≥80	0.65 (0.57–0.75)	0.80 (0.69–0.94)[a]
History of epilepsy	1.94 (1.84–2.04)	1.73 (1.63–1.84)[a]
Causes[b]		
Acute		
Vascular, traumatic, or inflammatory	0.69 (0.64–0.74)	0.90 (0.82–0.97)[a]
Hypoxic	0.55 (0.44–0.69)	0.58 (0.46–0.74)[a]
Metabolic disorder	0.87 (0.81–0.93)	0.97 (0.90–1.04)
Alcohol	1.16 (1.09–1.23)	1.37 (1.27–1.48)[a]
Toxic	0.89 (0.82–0.97)	0.96 (0.88–1.04)
Remote		
Vascular, traumatic, or inflammatory	1.33 (1.26–1.40)	1.25 (1.18–1.33)[a]
Hypoxic	1.59 (1.41–1.81)	1.15 (1.01–1.32)[a]
Progressive		
Neurodegenerative disease	1.06 (0.98–1.14)	1.16 (1.07–1.27)[a]
Tumor	1.20 (1.10–1.31)	1.30 (1.19–1.43)[a]
Neurodevelopmental disease	1.80 (1.70–1.91)	1.65 (1.53–1.77)[a]
Metabolic disease	1.30 (1.15–1.47)	1.21 (1.07–1.36)[a]
Epilepsy without other cause	1.07 (0.98–1.16)	1.11 (0.99–1.23)
Clinical variable	**OR univariable (95% CI)**	**OR multivariable (95% CI)**
No. of comorbidities		
0	Ref	Ref
1–2	1.14 (1.08–1.20)	1.18 (1.10–1.25)[a]
3+	1.22 (1.13–1.30)	1.29 (1.18–1.40)[a]
History of psychiatric disease	0.86 (0.82–0.91)	0.84 (0.80–0.89)[a]
Length of ICU (d)		
No ICU	Ref	Ref

Continued

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Table 2 Factors Associated With 3-Year Recurrence of SE in All Patients *(continued)*

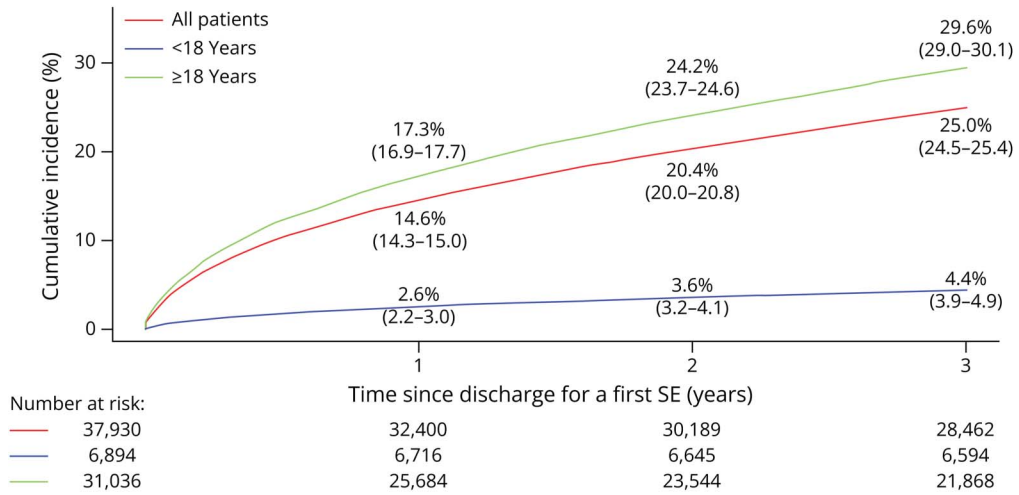
Clinical variable	OR univariable (95% CI)	OR multivariable (95% CI)
≤7	1.03 (0.98–1.09)	1.04 (0.98–1.11)
>7	0.81 (0.75–0.87)	0.85 (0.77–0.94)[a]
Mechanical ventilation		
0	Ref	Ref
1–2 d	0.94 (0.87–1.01)	1.05 (0.97–1.15)
>2 d	0.91 (0.86–0.97)	1.21 (1.11–1.32)[a]
Transfer to rehabilitation	0.75 (0.68–0.79)	0.87 (0.81–0.94)[a]

Abbreviations: HR univariable = hazard ratio with 95% CI found using the univariable Cox regression model; HR multivariable = hazard ratio with 95% CI found using the multivariable Cox regression model; ICU = intensive care unit; OR = odds ratio; Ref = reference class; SE = status epilepticus.
[a] For HRs associated with *p* values less than 0.05 in the multivariable Cox regression model.
[b] Causes are not exclusive, and each patient may have 0, 1, or more causes involved in his SE. The HR presented, therefore, corresponds to the risk associated with the presence of the cause vs its absence.

The leading causes of death 3 years after SE were cancer (32.1%) and cardiovascular diseases (20.2%), according to our study. Few studies previously focused on long-term mortality causes after a first SE. One study reported cardiovascular disease as the most frequent cause of death after a first seizure or SE without an underlying cause.[45] Another found that gliomas or systematic tumors accounted for 28.3% of deaths after a first unprovoked seizure or SE and vascular cause (stroke or cardiac events) for 20.6% of deaths.[46] These findings align with our results in a larger cohort, suggesting a similar pattern of mortality causes.

Our study unveiled variations in mortality causes among pediatric populations. Neurologic pathologies other than stroke, epilepsy, and neurodegenerative diseases were the primary cause (33.3%), followed by cancers (17%) and epilepsy (13%). Only few studies have explored mortality causes after a first SE in children. One study monitoring 228 children for 8 years after a first generalized SE identified an underlying neurologic pathology on the death certificate among all the 23 patients who died, such as developmental encephalopathy or Dravet syndrome.[47] Our study shows significant differences in mortality causes between adults and children, with specific neurologic conditions, such as brain malformations and chromosomal abnormalities, being the leading causes in children. Finally, we found only few differences between overall mortality causes and the main causes of death after SE, in France between 2011 and 2019 (28.7% of deaths related to cancer in the general population vs 32.1% after a SE and 18.2% related to cardiovascular diseases vs 20.6% after a SE).

Figure 3 Cumulative Incidence of Overall Deaths After Discharge for a First SE



For all patients (red) and by age group (younger than 18 years, blue; 18 years and older, green), 95% CIs are shown in parentheses. SE = status epilepticus.

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Table 3 Factors Associated With 3-Year Mortality in All Patients

Clinical variable	HR univariable (95% CI)	HR multivariable (95% CI)
Sex (reference: female)	1.00 (0.96–1.04)	1.24 (1.19–1.30)[a]
Age groups		
<1	1.16 (0.86–1.55)	1.24 (0.92–1.68)
1–4	0.66 (0.49–0.88)	0.70 (0.52–0.94)[a]
5–9	0.64 (0.44–0.93)	0.64 (0.44–0.92)[a]
10–19	Ref	Ref
20–29	1.15 (0.87–1.53)	1.19 (0.90–1.58)
30–39	2.04 (1.59–2.61)	1.80 (1.40–2.31)[a]
40–49	3.37 (2.68–4.23)	2.62 (2.08–3.30)[a]
50–59	5.51 (4.42–6.87)	3.71 (2.96–4.65)[a]
60–69	7.09 (5.69–8.84)	4.24 (3.38–5.31)[a]
70–79	9.47 (7.60–11.8)	5.38 (4.29–6.75)[a]
≥80	15.0 (12.0–18.6)	8.44 (6.73–10.6)[a]
History of epilepsy	0.84 (0.81–0.88)	0.85 (0.82–0.89)[a]
Causes[b]		
Acute		
Vascular, traumatic, or inflammatory	0.94 (0.88–0.99)	0.96 (0.90–1.02)
Hypoxic	0.93 (0.80–1.08)	1.27 (1.09–1.48)[a]
Metabolic disorder	1.31 (1.24–1.37)	1.13 (1.07–1.19)[a]
Alcohol	0.95 (0.90–1.00)	1.01 (0.95–1.08)
Toxic	0.89 (0.83–0.95)	1.00 (0.93–1.08)
Remote		
Vascular, traumatic, or inflammatory	1.45 (1.39–1.52)	0.80 (0.76–0.84)[a]
Hypoxic	0.43 (0.36–0.51)	1.27 (1.05–1.53)[a]
Progressive		
Neurodegenerative disease	2.62 (2.51–2.75)	1.22 (1.16–1.29)[a]
Tumor	3.28 (3.12–3.44)	2.83 (2.68–2.98)[a]
Neurodevelopmental disease	0.42 (0.38–0.45)	1.19 (1.09–1.30)[a]
Metabolic disease	1.36 (1.23–1.50)	1.19 (1.07–1.31)[a]
Epilepsy without other cause	0.31 (0.27–0.35)	0.70 (0.62–0.80)[a]
Clinical variable	**OR univariable (95% CI)**	**OR multivariable (95% CI)**
No. of comorbidities		
0	Ref	Ref
1–2	3.40 (3.22–3.59)	1.93 (1.82–2.04)[a]
3+	6.15 (5.81–6.51)	2.93 (2.74–3.13)[a]
History of psychiatric disease	1.40 (1.34–1.46)	1.00 (0.95–1.04)
Length of ICU (d)		
No ICU	Ref	Ref

Continued

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Table 3 Factors Associated With 3-Year Mortality in All Patients *(continued)*

Clinical variable	OR univariable (95% CI)	OR multivariable (95% CI)
≤7	0.60 (0.57–0.63)	0.82 (0.77–0.86)[a]
>7	0.86 (0.81–0.90)	1.00 (0.92–1.08)
Mechanical ventilation		
0	Ref	Ref
1–2 d	0.61 (0.57–0.66)	0.78 (0.72–0.85)[a]
>2 d	0.91 (0.87–0.96)	0.92 (0.86–0.99)[a]
Transfer to rehabilitation	1.71 (1.63–1.79)	1.06 (1.00–1.11)[a]

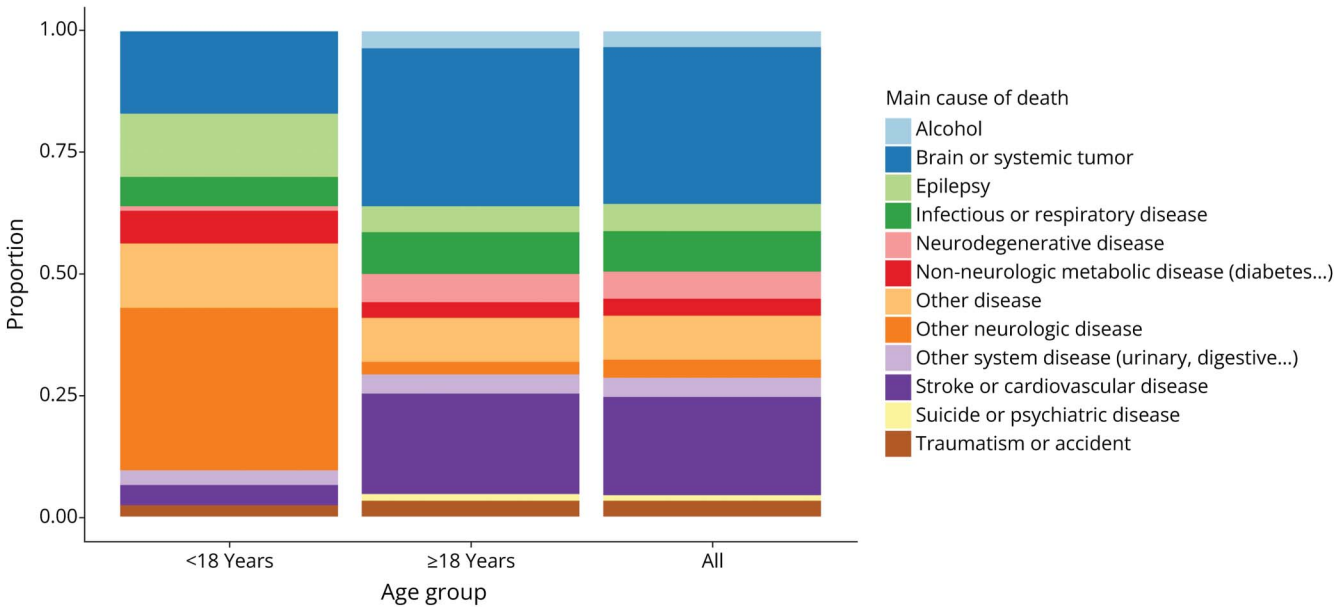
Abbreviations: HR univariable = hazard ratio with 95% CI found using the univariable Cox regression model; HR multivariable = hazard ratio with 95% CI found using the multivariable Cox regression model; ICU = intensive care unit; OR = odds ratio; Ref = reference class; SE = status epilepticus.
[a] For HRs associated with *p* values less than 0.05 in the multivariable Cox regression model.
[b] Causes are not exclusive, and each patient may have 0, 1, or more causes involved in his SE. The HR presented, therefore, corresponds to the risk associated with the presence of the cause vs its absence.

In the French pediatric population, deaths related to neurologic conditions (excluding stroke, epilepsy, or neurodegenerative disease) accounted for 2.2% (vs 33.3% in our cohort), tumors for 7.6% (vs 17%), and epilepsy for 1.0% (vs 13%).

A major strength of this study is the use of a large, nationwide cohort to examine both recurrence and mortality after discharge for a first episode of SE within the same population. Leveraging the extensive historical data of the SNDS spanning from 2006 to 2019, we obtained comprehensive insights and minimized selection bias, typical in specialized center studies.

However, certain limitations should be acknowledged. First, the SNDS lacks detailed clinical information, imaging results, biological data, and functional outcome scores, potentially affecting the precision of our findings. We also lack precise socioeconomic data, although a more disadvantaged socioeconomic status could be associated with higher mortality.[48] Although distinct ICD-10 codes theoretically differentiate between generalized (G41.0) and focal (G41.2) SE, their validation remains uncertain. Hence, we opted to include all G41 codes, aligning with previous epidemiologic studies of SE.[12-14] In addition, it was possible to neither

Figure 4 Proportion of Main Causes of Death for All Patients Who Died Within 3 Years After Discharge and According to Age Group (<18 or ≥18)



Other pathologies include all conditions not covered by the other categories, such as ICD-10 codes starting with "R," which correspond to symptoms, or cases where the primary cause of death is listed as unknown on the certificate.

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distinguish between SE with and without motor signs, nor evaluate their duration, which is nevertheless a major prognostic factor: a generalized convulsive SE could cause long-term damage after 30 minutes and a focal SE with impaired consciousness after 60 minutes.[21] In addition, the reliability of the coding system in identifying patients with epilepsy varies across studies and countries, and some cases may have been misclassified as epilepsy or convulsion instead of SE.[49] Finally, the coding system may not consistently differentiate acute causes from SE-related consequences, such as metabolic disorders, which poses challenges in interpreting primary causality.

In this study, we conducted an extensive population-based investigation into the long-term prognosis after hospitalization for a first SE. Our findings highlight key factors influencing mortality and recurrence rates, emphasizing the importance of several factors. Progressive causes were linked to higher mortality and increased SE recurrence rates while a history of epilepsy correlated with lower mortality but higher recurrence risk. In addition, advancing age was associated with elevated mortality but reduced recurrence rates. This study provides valuable insights for physicians to assess the risk of recurrence or mortality after discharge for a first SE, facilitating more effective management of underlying conditions and comorbidities.

Author Contributions

Q. Calonge: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. O. Guinebretiere: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. T. Nedelec: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. A. Hanin: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. F. Le Gac: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Chavez: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. F. Tubach: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S. Tezenas Du Montcel: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. V. Navarro: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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