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ORIGINAL COMMUNICATION

Prognostic value of early epileptic seizures on mortality and functional disability in acute stroke: the Dijon Stroke Registry (1985–2010)

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Abstract We aimed to evaluate the prognostic value of early epileptic seizures after stroke. All consecutive patients with a first-ever stroke were prospectively identified within the population of Dijon, France, thanks to a population-based registry, from 1985 to 2010. Early epileptic seizures were defined as seizures occurring within 14 days after stroke onset. Outcomes were 1-month and 1-year mortality, and severe functional handicap at discharge. Of the 4,411 stroke patients included, data about seizures were available in 4,358 (98.8, 53.5 % women, mean age, 74.1 ± 14.8 years). Among these patients, 134 (3.1 %) had early seizures. Stroke patients with early seizures differed from those without seizures, as there was a higher proportion of hemorrhagic stroke, higher blood glucose level at admission, smoking status, and more frequent impaired. Higher risks of 1-month and 1-year mortality in patients with early seizures (unadjusted HR 1.45, 95 % CI 1.00–2.10; HR = 1.59, 95 % CI 1.21–2.09, respectively) disappeared (HR 0.71, 95 % CI 0.49–1.08 and HR 0.85, 95 % CI 0.64–1.17) after adjustment for stroke severity and other confounding factors. Early seizures were associated with severe handicap in unadjusted analyses (OR 2.07, 95 % CI 1.46–2.95) but the association was no longer significant after multivariable adjustment (OR 1.12, 95 % CI 0.69–1.83). Early epileptic seizures were not associated with higher risks of mortality at 1 month and 1 year or with unfavorable functional outcome after acute stroke. The adverse effects of epileptic seizures may not be distinguishable from stroke severity, which is strongly related to epileptic seizures.

Keywords Epilepsy · Seizures · Stroke · Prognosis · Mortality · Epidemiology

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Introduction

Stroke is the most common cause of acute symptomatic seizures in the elderly population [1, 2]. Indeed, acute stroke has been reported as the leading cause of seizures in 30 % of people aged over 60 years [3–5]. Although there are different time-based definitions of stroke-associated seizures, most authors identified early seizures as those occurring within 7–14 days after acute stroke onset [6–8]. The incidence of early seizures ranged from 2 to 33 % after ischemic stroke [3], and from 4 to 16 % after intracerebral hemorrhage [9]. Previous studies demonstrated adverse consequences of early seizures on stroke outcomes, including in-hospital mortality [10], 30-day mortality [10, 11], long-term mortality [12], and functional outcome at discharge [6]. However, substantial evidence contradicted these findings, principally negative results for an impact on in-hospital mortality [1, 13, 14], 30-day mortality [7, 13], 6-month mortality [9], and functional outcomes [1, 14]. Several methodological issues may explain these conflicting results, including inconsistent uses of terminology, small sample sizes, different lengths of follow-up, ambiguities in seizure identification and classification, heterogenous designs and study populations, and confounding factors not taken into account in multivariable analyses [3].

The aim of this study was to determine the prognostic value of epileptic seizures on mortality at 1 month and

1 year, and functional outcome in first-ever stroke patients from the population-based Dijon Stroke Registry.

Methods

Study population

All patients with a first-ever stroke between January 1, 1985 and December 31, 2010 were prospectively included in the Dijon Stroke Registry. The Dijon Stroke Registry is a population-based registry that has been recording prospectively all cases of stroke and transient ischemic attack (TIA) occurring among residents of Dijon, France since 1985. According to the 2011 census, the city of Dijon has a population of 151,846 inhabitants. Multiple overlapping sources are used to ensure completeness of stroke case collection, so as to identify both fatal and nonfatal cases of hospitalized and nonhospitalized strokes [15]: (1) the emergency rooms, as well as all the clinical and radiological departments of the Dijon University Hospital, with a diagnosis of stroke made by a neurologist; (2) the three private hospitals with a diagnosis made by private neurologists; (3) the patient's home or the nursing homes of the city with a diagnosis assessed by the general practitioners with the help of either a public or a private neurologist from an outpatient clinic with; (4) the three private radiological centers to identify missed cases; (5) the ultrasound Doppler centers and (6) the death certificates mentioning stroke as the underlying cause of death obtained from the local Social Security Bureau.

Stroke definition

Stroke was defined according to World Health Organization recommendations [16]. The diagnosis of stroke subtypes was always based on clinical data and cerebral imaging (CT and/or MRI). We distinguished between ischemic stroke, hemorrhagic stroke (including spontaneous intracerebral hemorrhage and subarachnoid hemorrhage), and stroke of unknown etiology.

Definition of seizures

Seizures were defined according to International League Against Epilepsy (ILAE) criteria as paroxysmal disorders of the central nervous system, followed or not by loss of consciousness and/or with or without motor involvement [17]. In our study, only data concerning early seizures, defined as occurring within the first 2 weeks after the stroke onset [18–20], were available. Diagnostic of seizures was considered either when witnessed by health care personnel or when reported by the patient or a proxy. All suspected cases were systematically reviewed by a study doctor, so as to confirm the diagnosis.

Baseline data collected

Several baseline characteristics were recorded at stroke onset [15]: demographics, history of TIA (all focal cerebral ischemic events with symptoms lasting <24 h), known hypertension (or patients taking antihypertensive medications), atrial fibrillation, diabetes (fasting glucose $\geq$7.5 mmol/l or patients treated with oral anti-diabetic agents or insulin), hypercholesterolemia (total blood cholesterol over 6 mmol/l, or plasma cholesterol level >200 mg/dl or triglyceride plasma concentration >140 mg/dl or statin therapy), smoking status (ever smokers >1 cigarette/day vs. nonsmokers), heavy alcohol consumption ($\geq$3 units a day in men and $\geq$2 in women), myocardial infarction, and congestive heart failure. Preventive treatments before stroke, including antiplatelet agents, antihypertensive drugs, and anticoagulants were also recorded. Stroke severity on admission was assessed using proxies (motor deficit, aphasia, sensory deficit, impaired consciousness) since the National Institutes of Health Stroke Scale (NIHSS) score was only recorded in the registry from 2006.

Outcomes assessed

The first outcome was the degree of functional impairment at hospital discharge or at neurological consultations for newly diagnosed outpatients. For all patients, a self-constructed handicap scale was used to measure functional impairment; this scale has been in use since the establishment of the registry in 1985. We chose this scale because the modified Rankin scale (mRS) [21] was only introduced in the registry database in 1997. Like the mRS, the handicap scale includes six grades (1 = walking alone, 2 = walking with support, 3 = walking stick, 4 = wheelchair, 5 = bedridden, 6 = death). The level of concordance between the handicap scale and the mRS was 0.92 (95 % CI 0.91–0.93) in 1,632 patients with both measurements [22]. The functional outcome was classified as favorable when walking was possible with or without assistance (grades 1–3) and unfavorable otherwise (grades 4–6).

The second outcome was all-cause mortality at 1 month and 1 year after stroke. Vital status was systematically recorded thanks to the use of death certificates.

Statistical analysis

The characteristics of patients with seizures were compared with those without seizures using the χ^2 test or the Fisher's

exact test, when appropriate. Person-times were calculated from the date of stroke onset until death, the last contact date, or the end of follow-up at 1 month (1 year), whichever came first. Survival curves were obtained by the Kaplan–Meier test, and the logrank test was used to compare groups of patients with seizures and without seizures. The confounding effects of covariates were examined individually in unadjusted Cox models with estimations of hazard ratios (HR) and their 95 % confidence intervals (CIs). The predictors of mortality with a p value <0.20 were then selected and included in a Cox multivariate model. The association between disability and other variables was examined by bivariate logistic regression analyses. All covariates with a p value <0.20 were introduced into a multivariate logistic regression model. Variables such as seizures, age, and sex were forced into the final model. Stratum-specific analyses were performed by modifying factors with significant statistical interaction terms along with seizures. Given the a priori evidence of heterogenous effects of seizures across stroke subtypes, the results were stratified by stroke subtypes, regardless of nonsignificant interaction terms with seizures (respective p for interaction 0.08, 0.08, and 0.16 for mortality at 1 month, 1 year, and severe handicap, respectively). For potential confounders such as smoking status and blood glucose at admission with respectively 13.5 % ($n = 586$) and 18.3 % ($n = 799$) of missing information, we used dummy indicators so that patients were not discarded from the analyses. We performed sensitivity analyses to further control for NIHSS in multivariate analyses using 1,057 patients from 2006 to 2010 with NIHSS at entry. The statistical significance level was set at 5 %. Statistical analysis was performed with STATA 10.0 software (StataCorp LP, College Station, TX).

Ethics

Our registry was approved by the National Commission on Informatics and Liberties (CNIL), Public Health Surveillance (InVS), and Inserm.

Results

Baseline characteristics of patients

Of the 4,411 patients with a first-ever stroke recorded over the 26-year study period, 53 (1.2 %) were excluded because of missing information concerning early seizures. The final study population included 4,358 patients. Mean age at stroke onset was 74.13 ± 14.74 years and more than half were women. Early seizures were diagnosed in 134 patients (3.1 %; Table 1). Among these, 86 had an ischemic stroke (2.4 % of a total of 3,607 ischemic strokes) and 41 had a cerebral hemorrhage (6.6 % of a total of 620 hemorrhagic strokes). Patients excluded due to missing information concerning seizures were similar to those for whom the information was available, except that they were less likely to use antihypertensive drugs (17.0 vs. 48.9 %; $p < 0.001$).

Patients with early seizures differed significantly from those without seizures according to baseline characteristics (Table 1). They had a higher prevalence of cerebral hemorrhage and subarachnoid hemorrhage, and were less likely to have hypercholesterolemia, but more likely to be nonsmokers or have unknown smoking status, to have impaired consciousness (drowsiness, coma), high levels of blood glucose at admission or heavy alcohol consumption.

All-cause mortality at 1 month

Kaplan–Meier curves showed differences in survival rates for patients with early seizures compared to those without early seizures (78 vs. 84 %; $p = 0.046$; Fig. 1). In unadjusted analysis, early seizures were associated with a 45 % greater risk of 1-month mortality (Table 2). However, this deleterious effect of seizures on 1-month mortality disappeared in multivariate analysis (HR 0.71, 95 % CI 0.49–1.08; $p = 0.09$) (Table 2). In sensitivity analysis, further adjustment for NIHSS yielded similar results (Table 2). Statistical interaction terms along with early seizures were significant for gender ($p = 0.003$), diabetes ($p = 0.009$), smoking status ($p = 0.001$), and impaired consciousness ($p = 0.02$). Stratum-specific analyses showed 61, 38, and 44 % relative risk reductions in 1-month mortality, respectively, in women, nonsmokers, and nondiabetics with early seizures compared to patients without early seizures (Table 2). The stratum-specific effects of early seizures were homogenous in patients with impaired levels of consciousness in contrast to the nonsignificant and heterogeneous effects of early seizures across levels of stroke subtypes (Table 2).

All-cause mortality at 1 year

Kaplan–Meier curves showed lower survival rates for patients with early seizures compared to those without early seizures (58 vs. 71 %, $p < 0.001$; Fig. 2). In unadjusted analysis, patients with early seizures were 1.59 times more likely to die at 1 year than patients without seizures (Table 2). The detrimental effect of seizures at 1 year disappeared in multivariate analyses. In sensitivity analyses, early seizures were associated with a nonsignificant higher risk of 1-year mortality after further adjustment for NIHSS (Table 2). Statistical interaction terms between seizures and smoking ($p = 0.004$),

Table 1 Characteristics of the 4,358 patients according to early seizure

	Patients with seizures		Patients without seizures		Total		Fisher's exact test
	n	(%)	*n*	(%)	*n*	(%)	*p* value
Women[a]	76	56.7	2,255	53.4	2,330	53.5	0.44
Age (years)							0.63
<60	640	15.2	21	15.7	661	15.2	
60–79	1,838	43.5	63	47.0	1,901	43.6	
≥80	1,746	41.3	50	37.3	1,796	41.2	
Stroke subtypes							<0.001
Ischemic strokes	86	64.2	3,521	83.4	3,607	82.8	
Cerebral hemorrhage	31	23.1	462	10.9	493	11.3	
Subarachnoid hemorrhage	10	7.5	117	2.8	127	2.9	
Unknown	7	5.2	124	2.9	131	3.0	
Cerebral hemorrhage location							0.54
Lobar	19	61.2	221	49.0	240	49.7	
Deep	8	25.8	178	39.4	186	38.5	
Cerebellum	2	6.4	24	5.3	26	5.3	
Brainstem	1	3.2	14	3.1	15	3.1	
Pure intraventricular	0	0.0	4	0.8	4	0.8	
Unspecified	1	3.2	10	2.2	11	2.2	
Medical history							
Hypertension ($n = 4{,}334$)[a,b]	85	63.4	2,744	65.0	2,829	64.9	0.73
Diabetes ($n = 4{,}327$)[a,b]	22	16.7	625	14.9	647	15.0	0.57
Hypercholesterolemia ($n = 4{,}327$)[a,b]	18	13.6	973	23.2	991	22.9	0.01
Heart failure ($n = 4{,}331$)[a,b]	7	5.2	366	8.7	373	8.6	0.16
Smoking							0.002
Nonsmoker	72	53.7	2,363	55.9	2,435	55.9	
Smoker	31	23.1	1,306	30.9	1,337	30.7	
Unknown	31	23.1	555	13.1	586	13.5	
Heavy alcohol use ($n = 4{,}307$)[a,b]	13	10.0	232	5.5	245	5.6	0.03
Atrial fibrillation ($n = 4{,}330$)[a,b]	39	29.1	1,005	23.8	1,044	24.0	0.13
Myocardial Infarction ($n = 4{,}327$)[a,b]	22	16.7	750	17.9	772	17.8	0.51
Antiplatelet agents[a]	28	20.9	900	21.3	928	21.3	0.90
Antihypertensive drugs[a]	68	50.8	2,064	48.9	2,132	48.9	0.66
Anticoagulants[a]	14	10.5	280	6.6	294	6.8	0.08
Clinical features at admission							
Motor deficit ($n = 4{,}342$)[a,b]	105	78.4	3,155	74.7	3,260	74.8	0.29
Sensory deficit ($n = 4{,}339$)[a,b]	41	30.6	1,586	37.6	1,627	37.3	0.10
Aphasia ($n = 4{,}337$)[a,b]	59	44.0	1,330	31.5	1,389	31.9	0.002
Impaired consciousness ($n = 4{,}349$)[a,b]							<0.001
No	68	50.8	3,276	77.6	3,344	76.7	
Drowsiness	33	24.6	472	11.2	505	11.6	
Coma	33	24.6	467	11.1	500	11.5	
NIHSS ≥ 15 (period 2006–2010)[a]	4	28.6	200	19.8	204	20.0	0.41
Blood glucose ≥7.5 mmol/l ($n = 3{,}559$)[a,b]	48	35.8	985	23.3	1,033	23.7	0.003

NIHSS National Institutes of Health Stroke Scale

[a] Omitted reference category for dichotomous variables

[b] Denominator may vary due to missing information

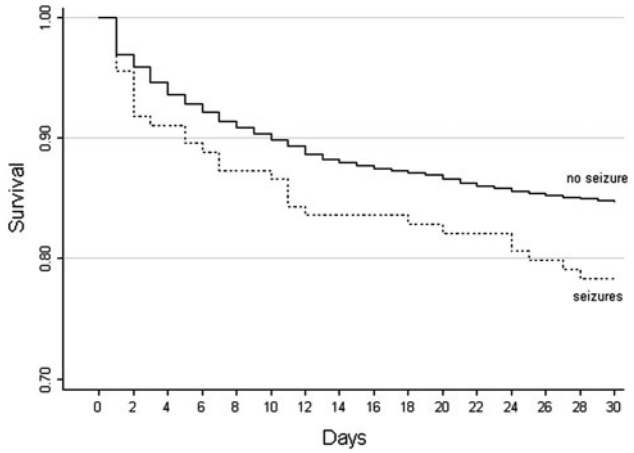

Fig. 1 Survival curves for all-cause mortality at 1 month according to seizures

diabetes ($p = 0.04$), and impaired consciousness ($p = 0.01$) were significant. Stratum-specific analyses revealed a protective effect of early seizures on 1-year mortality only in the subgroup of nonsmokers. The effects of early seizures were nonsignificant in patients with and without diabetes, impaired levels of consciousness, and stroke subtypes.

Functional outcome

Functional impairment was assessed in 4,316 patients at discharge or at outpatient consultations (99.0 % of the total sample). The number of patients affected by severe handicap was 1,242 (28.8 %), 59 (4.8 %) of whom had had seizures. There were 3,074 patients without disability (71.2 %), of whom 72 (2.3 %) had seizures. In unadjusted analysis, the risk of severe handicap in patients with early seizures was twice that in patients without seizures (Table 3). The deleterious effect of seizures was wiped out in multivariable analysis. In sensitivity analysis, early seizures were associated with a nonsignificant two-times-higher risk of severe handicap after further adjustment for NIHSS (Table 3). Statistical interaction terms between seizures and age ($p < 0.001$), heart failure ($p = 0.006$), and motor deficit ($p = 0.009$) were significant. Stratum-specific unadjusted analyses showed that patients with early seizures in subgroups aged 60–79 years, heart failure, or ischemic stroke had unfavorable functional outcomes compared to patients without seizures. However, this adverse effect disappeared in multivariate analysis. There was no modifying effect of stroke subtype on the association between early seizures and functional outcome.

We performed post hoc sequential adjustment to assess covariates that may be potential confounders of the association (Table 4). The deleterious effect of early seizures on all outcomes disappeared after adjustment for impaired consciousness. Adjustment for impaired consciousness alone or for all items of stroke severity including NIHSS yielded similar results for early seizures Adjustment for other covariates (except age and gender) erased the association between early seizures and 1-month mortality, thus contrasting with the unchanged associations for 1-year mortality and functional outcome.

Discussion

This is the largest population-based study to assess the association between post-stroke early seizures and both functional outcome and 1-month and 1-year mortality. We demonstrated that epileptic seizures were not associated with a higher risk of mortality at 1 month and 1 year, or with an unfavorable functional outcome after acute stroke, after adjustment for confounding variables, including stroke severity at onset.

In our study, 3.1 % of patients had early seizures after stroke. This proportion was within the range of 2–33 % reported by previous studies [1, 6, 7, 10–12, 14, 23, 24]. This wide range in incidence was probably due to differences in definitions of early seizures, inclusion criteria, and study design with higher incidences reported in hospital-based studies [6, 11, 24], which usually include the most severe stroke cases. Early seizures were twice as frequent in hemorrhagic stroke (either intracerebral hemorrhage (6.3 %) or subarachnoid hemorrhage (7.9 %)) as in ischemic stroke patients (2.4 %), as observed in previous studies [6, 7, 11].

Our findings were consistent with those of one population-based [7] and three hospital-based studies [1, 9, 14], which reported that early seizures were not associated with in-hospital [14] or 7-day mortality [9], 1-month [7] or 6-month mortality [9], or functional outcome at discharge [1] or at 6 months [9]. However, three hospital-based studies [6, 10, 11] and one population-based case–control study [12] suggested conflicting positive associations between early seizures and 1-month mortality [6, 11], 1-year [6] (or 5-year mortality [12] and functional outcome at 9 months [6]).

Initial stroke severity, especially impaired consciousness, erased the deleterious effect of early seizures on mortality and functional outcome after stroke. One hypothesis is that the direct effect of early seizures on poor outcomes is strongly confounded by stroke severity, a predictor of both early seizures, since early seizures are more frequent in patients with severe and disabling strokes, and of poor functional and mortality outcomes [25]. As a result, in the absence of any adjustment for initial stroke

Table 2 Associations between early seizures and 1-month and 1-year mortality

	Unadjusted analyses (Cox)			Multivariable analyses (Cox)		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
1-month mortality						
All strokes	1.45	1.00–2.10	0.04	0.71[a]	0.49–1.08	0.09
Strokes from 2006 to 2010	0.50	0.06–3.58	0.49	0.46[b]	0.06–3.38	0.44
Stratum-specific analyses						
Men	2.55	1.58–4.11	<0.001	1.17[a]	0.71–1.93	0.51
Women	0.82	0.83–1.50	0.54	0.39[a]	0.20–0.76	0.006
Nonsmokers	0.99	0.54–1.80	0.97	0.62[a]	0.40–0.95	0.03
Smokers	4.19	2.26–7.76	<0.001	1.59[a]	0.89–2.82	0.11
Unknown	0.75	0.35–1.60	0.46	0.93[a]	0.50–1.71	0.82
No diabetes	1.12	0.71–1.77	0.62	0.56[a]	0.34–0.90	0.01
Diabetes	3.66	1.83–7.29	<0.001	1.50[a]	0.69–3.25	0.30
Impaired consciousness						
No	1.92	0.94–3.90	0.07	1.10[a]	0.65–1.86	0.70
Drowsiness	0.92	0.42–1.97	0.83	1.00[a]	0.55–1.82	0.97
Coma	0.53	0.31–0.91	0.02	0.68[a]	0.43–1.09	0.11
Ischemic strokes	1.72	1.06–2.80	0.02	0.81[a]	0.49–1.34	0.41
Cerebral hemorrhage	0.71	0.35–1.45	0.35	0.59[a]	0.28–1.23	0.16
Subarachnoid hemorrhage	1.97	0.58–6.66	0.27	2.20[a]	0.17–27.05	0.53
1-year mortality						
All strokes	1.59	1.21–2.09	0.001	0.85[c]	0.64–1.17	0.31
Strokes from 2006 to 2010	1.65	0.73–3.71	0.22	1.41[d]	0.61–3.27	0.41
Stratum-specific analyses						
No diabetes	1.38	1.01–1.88	0.04	0.74[c]	0.52–1.04	0.08
Diabetes	2.85	1.58–5.13	<0.001	1.47[c]	0.78–2.76	0.23
Impaired consciousness						
No	1.49	0.93–2.38	0.09	1.10[c]	0.65–1.86	0.70
Drowsiness	1.11	0.65–1.88	0.68	0.95[c]	0.52–1.71	0.87
Coma	0.65	0.42–0.99	0.05	0.68[c]	0.43–1.09	0.11
Nonsmokers	1.25	0.85–1.86	0.24	0.61[c]	0.40–0.95	0.03
Smokers	3.38	2.04–5.60	<0.001	1.58[c]	0.89–2.81	0.11
Unknown	1.00	0.57–1.75	0.98	0.97[c]	0.53–1.78	0.82
Ischemic strokes	1.75	1.24–2.46	0.001	0.97[c]	0.68–1.39	0.89
Cerebral hemorrhage	0.86	0.49–1.52	0.62	0.66[c]	0.34–1.19	0.17
Subarachnoid hemorrhage	1.59	0.47–5.29	0.44	1.82[c]	0.16–19.86	0.62

CI confidence interval, *HR* hazard ratio, *NIHSS* National Institutes of Health Stroke Scale

[a] Adjusted for gender, age, stroke subtypes (except for stratified analysis), history of hypertension, hypercholesterolemia, heart failure, smoking status, atrial fibrillation, myocardial infarction, anticoagulants, motor deficit, sensory deficit, aphasia, impaired consciousness, and blood glucose levels at admission

[b] Adjusted for gender, age, stroke subtypes (except for stratified analysis), history of hypertension, hypercholesterolemia, heart failure, smoking status, atrial fibrillation, myocardial infarction, anticoagulants, NIHSS, and blood glucose levels at admission

[c] Adjusted for gender, age, stroke subtypes, history of hypertension, hypercholesterolemia, heart failure, smoking status, atrial fibrillation, myocardial infarction, motor deficit, sensory deficit, aphasia, impaired consciousness, blood glucose at admission, antihypertensive drugs, and anticoagulants

[d] Adjusted for gender, age, stroke subtypes, history of hypertension, hypercholesterolemia, heart failure, smoking status, atrial fibrillation, myocardial infarction, NIHSS, blood glucose at admission, antihypertensive drugs, and anticoagulants

severity, early seizures erroneously appear to be associated with poor outcomes. Another hypothesis may be an indirect effect of early seizures on poor outcomes, mediated by impaired consciousness [26]. Hence, epileptic seizures can lead to impairment of both the level and content of consciousness [27]. Adjustment for intermediate factors in

multivariable models may provide biased estimates of early seizures with attenuation to the null effect when there is unmeasured confounding for both the exposure and the intermediate factor on poor outcomes [28]. However, our data did not support this hypothesis, as almost half of the patients with seizures were suffering from long-lasting and not transient impaired consciousness (coma, drowsiness).

In patients with hyperglycemia, the incidence of seizures was twice as high as in those with normal blood glucose level (4.7 vs. 2.7 %). Blood glucose level at admission was assessed in two studies. The Copenhagen Stroke Study reported higher average values for patients with epileptic seizures (9.0 ± 3.3 mmol/l) than for those without epileptic seizures (7.7 ± 3.2; $p = 0.01$) and controlled for this factor in multivariate analyses [14]. In a recent study, hyperglycemia was an independent predictor of seizures in the first week as were a cortical location and hemorrhagic transformation [13]. Hyperglycemia has been associated with poor functional and mortality outcomes in ischemic stroke patients [29] but data are still conflicting for hemorrhagic strokes [30]. Several mechanisms have been suggested: hyperglycemia may be a marker of neuronal injury leading to a stress response with increases in levels of cortisol and catecholamines resulting in hyperglycemia; or hyperglycemia may be directly toxic to the brain by intracellular acidosis, the accumulation of extracellular glutamate, blood–brain barrier disruption leading to brain edema, and inflammation and oxidative stress [31].

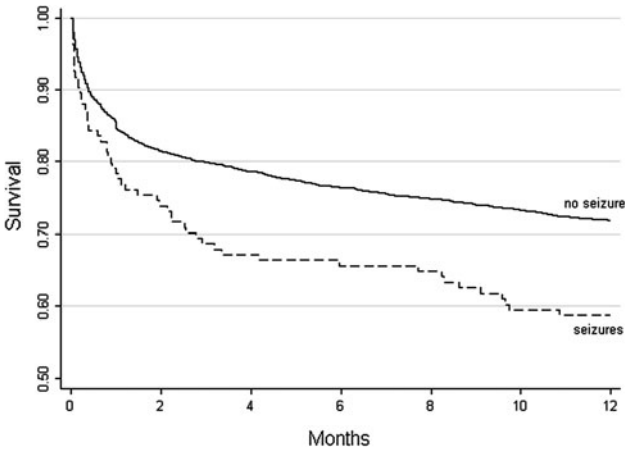

Fig. 2 Survival curves for all-cause mortality at 1 year according to seizures

This study has several strengths. It is based on a relatively large population sample with sufficient power to perform subgroup analysis. Relatively few patients were lost to follow-up at 1 month and 1 year (1.15 and 5.51 %, respectively) through active tracing of vital status in the Dijon Stroke Registry. Stroke cases were identified and validated from a population-based registry, which recruited patients from different sources, thus limiting selection biases due to incomplete inclusion. A large number of

Table 3 Associations between early seizures and post-stroke severe handicap

	Unadjusted analyses			Multivariable analyses		
	OR	95 % CI	p value	OR	95 % CI	*p* value
All strokes	2.07	1.46–2.95	<0.001	1.14[a]	0.72–1.83	0.58
Strokes from 2006 to 2010	2.63	0.98–7.10	0.054	2.21[b]	0.61–7.98	0.22
Stratum-specific analysis						
Age (years)						
<60	1.25	0.85-1.86	0.24	1.83[a]	0.49-6.87	0.36
60–79	3.38	2.04–5.60	<0.001	0.86[a]	0.41–1.80	0.69
≥80	1.00	0.57–1.75	0.98	1.31[a]	0.65–2.61	0.43
No heart failure	1.38	1.01–1.88	0.04	1.06[a]	0.65–1.73	0.79
Heart failure	2.85	1.58–5.13	<0.001	2.32[a]	0.30–17.51	0.41
No motor deficit	1.49	0.93–2.38	0.09	1.29[a]	0.33–4.90	0.70
Motor deficit	1.11	0.65–1.88	0.68	1.15[a]	0.69–1.90	0.58
Ischemic strokes	1.75	1.24–2.46	0.001	1.29[a]	0.73–2.26	0.37
Cerebral hemorrhage	0.86	0.49–1.52	0.62	0.97[a]	0.39–2.42	0.95
Subarachnoid hemorrhage	1.59	0.47–5.29	0.44	1.08[a]	0.14–7.90	0.93

CI confidence interval, *NIHSS* National Institutes of Health Stroke Scale, *OR* odds ratio

[a] Adjusted for gender, age, stroke subtypes (except for stratified analyses), history of hypertension, hypercholesterolemia, heart failure, infection, smoking status, atrial fibrillation, myocardial infarction, antiplatelet agents, anticoagulants, motor deficit, sensory deficit, aphasia, impaired consciousness, and blood glucose levels

[b] Adjusted for gender, age, stroke subtypes (except for stratified analyses), history of hypertension, hypercholesterolemia, heart failure, infection, smoking status, atrial fibrillation, myocardial infarction, antiplatelet agents, anticoagulants, NIHSS, and blood glucose levels

Table 4 Sequential multivariate models of the association between early seizures and outcomes

Model adjusted for cofactors	1-month mortality			1-year mortality			Severe handicap		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value	OR	95 % CI	*p* value
Age and gender	1.48	1.01–2.14	0.03	1.64	1.25–2.15	<0.001	2.24	1.56–3.21	<0.001
Stroke subtypes	1.23	0.84–1.81	0.27	1.37	1.03–1.83	0.02	1.83	1.27–2.64	0.001
Medical history	1.23[a]	0.84–1.80	0.28	1.38[c]	1.04–1.82	0.02	2.03[d]	1.41–2.91	<0.001
Smoking status	1.27	0.87–10.85	0.20	1.44	1.10–1.89	0.008	2.05	1.44–2.91	<0.001
Impaired consciousness	0.74	0.51–1.08	0.12	0.90	0.69–1.19	0.49	1.19	0.77–1.82	0.42
NIHSS (strokes from 2006 to 2010)	0.37	0.05–2.65	0.32	1.28	0.57–2.89	0.54	2.82	0.83–9.58	0.09
Stroke severity	0.73[b]	0.50–1.06	0.10	0.90[b]	0.69–1.19	0.49	1.19[b]	0.77–1.86	0.42
Blood glucose levels	1.19	0.82–1.74	0.33	1.39	1.06–1.82	0.01	2.08	1.46–2.95	<0.001

CI confidence interval, *HR* hazard ratio, *OR* odds ratio

[a] History of hypertension, hypercholesterolemia, heart failure, smoking status, atrial fibrillation, myocardial infarction, anticoagulants

[b] Motor deficit, sensory deficit, aphasia, impaired consciousness

[c] History of hypertension, hypercholesterolemia, heart failure, smoking status, atrial fibrillation, myocardial infarction, antihypertensive drugs, and anticoagulants

[d] History of hypertension, hypercholesterolemia, heart failure, infection, smoking status, atrial fibrillation, myocardial infarction, antiplatelet agents, anticoagulants

potential confounders or modifiers that were not studied before were evaluated in statistical analyses, ensuring the validity of our results. However, several limitations must be acknowledged. We lacked information regarding the date of seizure occurrence to calculate the time in days between the stroke and the seizures. Moreover, the high percentage of missing values for smoking and blood glucose level on admission could have introduced some selection bias by excluding a large number of patients. A dummy variable was added to account for patients with missing information, but we could not rule out residual confounding in multivariate analysis. Finally, the use of clinical data on admission to assess the initial severity of stroke may be an imperfect measurement of the NIHSS with possible residual confounding bias in the multivariate models.

To conclude, this population-based observational study showed that seizures occurring at the acute phase of stroke are not independently associated with poor early functional outcomes and mortality at 1 month and 1 year. Although, the effect of early seizures is strongly confounded by stroke severity, attention must be paid to its impact in some subgroups of patients.

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Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standard This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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