FULL-LENGTH ORIGINAL RESEARCH

Seizures, electroencephalographic abnormalities, and outcome of ischemic stroke patients

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SUMMARY

Objective: Seizures and electroencephalographic (EEG) abnormalities have been associated with unfavorable stroke functional outcome. However, this association may depend on clinical and imaging stroke severity. We set out to analyze whether epileptic seizures and early EEG abnormalities are predictors of stroke outcome after adjustment for age and clinical/imaging infarct severity.

Methods: A prospective study was made on consecutive and previously independent acute stroke patients with a National Institutes of Health Stroke Scale (NIHSS) score ≥ 4 on admission and an acute anterior circulation ischemic lesion on brain imaging. All patients underwent standardized clinical and diagnostic assessment during admission and after discharge, and were followed for 12 months. Video-EEG (<60 min) was performed in the first 72 h. The Alberta Stroke Program Early CT Score quantified middle cerebral artery infarct size. The outcomes in this study were an unfavorable functional outcome (modified Rankin Scale [mRS] ≥ 3) and death (mRS = 6) at discharge and 12 months after stroke.

Results: Unfavorable outcome at discharge was independently associated with NIHSS score (p = 0.001), EEG background activity slowing (p < 0.001), and asymmetry (p < 0.001). Unfavorable outcome 1 year after stroke was independently associated with age (p = 0.001), NIHSS score (p < 0.001), remote symptomatic seizures (p = 0.046), EEG background activity slowing (p < 0.001), and asymmetry (p < 0.001). Death in the first year after stroke was independently associated with age (p = 0.028), NIHSS score (p = 0.001), acute symptomatic seizures (p = 0.015), and EEG suppression (p = 0.019).

Significance: Acute symptomatic seizures were independent predictors of vital outcome and remote symptomatic seizures of functional outcome in the first year after stroke. Therefore, their recognition and prevention strategies may be clinically relevant. Early EEG abnormalities were independent predictors and comparable to age and early clinical/imaging infarct severity in stroke functional outcome discrimination, reflecting the concept that EEG is a sensitive and robust method in the functional assessment of the brain.

KEY WORDS: Seizures, Epilepsy, EEG, Stroke, Outcome, Alberta Stroke Program Early CT Score.

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KEY POINTS

- Remote symptomatic seizures were independent predictors of unfavorable outcome 1 year after stroke
- Acute symptomatic seizures were independent predictors of vital outcome in the first year after stroke
- Early poststroke raw EEG abnormalities were independent predictors of stroke functional outcome at discharge and 1 year after stroke
- Early poststroke raw EEG abnormalities were independent predictors of stroke vital outcome 1 year after stroke
- Early poststroke EEG asymmetry had the highest odds of impacting stroke functional outcome at discharge and 12 months after stroke

Poststroke epileptic phenomena (seizures and status epilepticus)[1–6] have been associated with ischemic stroke unfavorable outcome. However, although electroencephalography (EEG) is essential for the detection of interictal and ictal epileptiform activity, it is unknown whether these EEG activities per se are also associated with stroke prognosis.

Previous work, mainly retrospective and without standardized imaging analysis, showed that raw EEG abnormalities (other than epileptiform discharges) are associated with poststroke functional outcome, essentially in the short term.[7–11] Additionally, a few small sample studies using quantitative EEG indexes showed that these might be better than a clinical scale in functional outcome prediction[12] or have a higher correlation with the residual neurological deficit after stroke than acute magnetic resonance imaging (MRI) lesion.[13]

However, it is unknown whether the association between seizures or EEG abnormalities and stroke functional outcome is independent from known cerebral infarct outcome predictors, namely age and stroke (clinical and imaging) severity.[14–17] Thus, we aimed to prospectively assess whether seizures and poststroke EEG abnormalities are outcome predictors at discharge and 12 months after stroke after adjustment for age and stroke severity.

METHODS

Study design

We performed a prospective longitudinal study of consecutive anterior circulation ischemic stroke patients admitted to the stroke unit of the neurology department of a university hospital over a period of 24 months and followed for 12 months. The ethics committee "Comissão de Ética para a Saúde" at our hospital approved this study. All subjects or their next of kin gave written informed consent for participation.

All included patients had to be previously independent (modified Rankin Scale [mRS] ≤ 1), score a value of at least 4 on the National Institutes of Health Stroke Scale (NIHSS)[18] upon admission to the emergency department, and have an acute ischemic brain lesion (noncontrast computed tomography [CT] scan or MRI) in the internal carotid artery territory and no previous history of epileptic seizures, traumatic head injury requiring hospital admission, or brain surgery.

Clinical assessment

All patients received standardized clinical and diagnostic assessment, during admission and after discharge. An investigator blinded to the neurophysiological evaluation conducted a phone interview at 6 months and a clinical appointment 12 months after stroke to access the occurrence of epileptic seizures and functional outcome.

NIHSS score at admission assessed clinical stroke severity. The functional outcome at discharge and at 12 months was assessed by the mRS.[19]

Neurophysiological evaluation

Patients underwent a neurophysiological evaluation protocol that included a 64-channel video-EEG with a maximum duration of 60 min in the first 72 h after stroke (EEG). The record included an eyes closed wake resting condition and eyes open, hyperventilation, and photic stimulation maneuvers. EEG review and classification were performed by a certified clinical neurophysiologist (C.B.) using international criteria and terminology,[20–22] blinded to clinical and imaging findings. All doubts were decided by consensus with another clinical neurophysiologist (A.R.P.).

Neuroimaging interpretation

A senior neuroradiologist (C.M. or C.C.) blinded for clinical and EEG findings analyzed all the neuroimaging studies performed during hospitalization. Doubts were decided by consensus. In patients with an isolated middle cerebral artery (MCA) stroke in the imaging study (by noncontrast-enhanced CT scan or MRI), the infarct size was quantified in the first CT performed after stroke by the Alberta Stroke Program Early CT Score (ASPECTS).[17] Whenever there was a brain CT scan performed at least 24 h after stroke onset (second CT scan), ASPECTS was also quantified in this examination in patients with an isolated MCA infarct.

Predictors and outcomes

The following predictors were registered:

1. Clinical predictors: age, gender, TOAST (Trial of Org 10172 in Acute Stroke Treatment) subgroups,[23] NIHSS on admission, occurrence of poststroke seizures[24–26] (either acute symptomatic [in the first 7 days after stroke[25]] or remote symptomatic [after that time point[26]]), and status epilepticus.[22,27,28]

2. Neuroimaging predictors: ASPECTS in the first and second CT scans and any type of hemorrhage transformation[29] in the second CT scan.
3. EEG predictors (categorical variables, dichotomized into present or absent): background activity slowing[20]; asymmetry[21]; suppression (focal, hemispheric, or diffuse)[21]; focal slow wave activity (including focal and regional concept)[20]; rhythmic slow wave activity, including rhythmic delta activity according to the definition of the American Clinical Neurophysiology Society[21] and rhythmic delta/theta (>0.5 Hz)[22]; interictal epileptiform activity[20]; and periodic discharges.[21]

The outcomes in this study were an unfavorable functional outcome (mRS ≥ 3) and death (mRS = 6) at discharge and 12 months after stroke.

Statistical analysis

A descriptive analysis was used for nominal qualitative and quantitative variables (discrete and continuous). Nominal variables are expressed in frequency, discrete variables as medians and interquartile ranges, and continuous variables as means and standard deviations (SDs).

Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate. Variables with a significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke,[14–17] namely age, clinical stroke severity (admission NIHSS), and imaging infarct size (ASPECTS), using a logistic regression model. The significance level was α ≤ 0.05. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Outcome prediction model characteristics encompassing poststroke seizures or EEG abnormalities with the highest odds of impacting outcome were compared with the model including exclusively known stroke outcome predictors. The percentage of patients correctly identified by the models was calculated. Model calibration was analyzed by Hosmer–Lemeshow test, and its discriminative capacity was measured by the area under the receiver operating characteristic (ROC) curve (95% CI).

Statistical analysis was done using the SPSS program (version 24 for Mac).

RESULTS

One hundred fifty-one patients (112 men and 39 women) were included, with a mean age of 67.4 (SD = 11.9) years. During this study, 23 patients died (seven during admission before day 7, 11 between discharge and 6 months after stroke, and five after that time point). One patient (0.66%) was lost for clinical and EEG follow-up in the last 6 months of the study. From the 127 living patients with a clinical follow-up 1 year after stroke, 117 (92.1%) had repeated EEG by that time. The study flowchart was previously

described.[30] All (151) patients had at least one acute CT scan (first CT). Furthermore, in the acute phase, a second CT scan was performed in 129 (85.4%) patients and an MRI in 63 (41.7%) patients. From the 129 patients who received a second CT scan, only 124 had an isolated MCA infarct.

Variables associated with stroke outcome at discharge

Table 1 describes clinical, imaging, and neurophysiological features of included patients, comparing unfavorable outcome (mRS ≥ 3) patients with those with a favorable outcome (mRS < 3) at discharge. In bivariate analysis, an unfavorable outcome was more frequent in older patients, and patients with a higher admission NIHSS, a lower ASPECTS, presence of hemorrhagic transformation, and an EEG with background activity slowing, asymmetry, focal slow wave activity, and periodic discharges. After adjustment of these variables for known functional outcome predictors of stroke, admission NIHSS, EEG background activity slowing, asymmetry, and periodic discharges predicted functional outcome. Second (but not first) CT ASPECTS was a discharge outcome predictor independent from age and NIHSS.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG background activity asymmetry (Table 2), the variables remaining independent predictors were NIHSS score (OR = 1.16, 95% CI = 1.07–1.27, p = 0.001) and background activity asymmetry (OR = 11.90, 95% CI = 3.73–38.46, p < 0.001). This model correctly classified 76.7% of the subjects, and the area under the ROC curve was 0.86. The prediction model including this EEG variable did not have a different discriminative capacity compared to the model encompassing the already known outcome predictors.

Clinical, imaging, and neurophysiological features of patients who died during hospitalization can be seen in Table 3. In bivariate analysis, an association was found with admission NIHSS, occurrence of acute symptomatic seizures, and EEG background activity slowing and suppression. Adjustment for known functional outcome predictors of stroke was not performed due to the low number of events (n = 7).

Variables associated with stroke outcome at 12 months

Table 4 describes clinical, imaging, and neurophysiological features of included patients, comparing those with unfavorable (mRS ≥ 3) and favorable outcome (mRS < 3). An association with unfavorable outcome was found in bivariate analysis for age, admission NIHSS, treatment with intravenous alteplase, occurrence of an acute or remote symptomatic seizure, ASPECTS, and EEG background activity slowing, asymmetry, suppression, focal and rhythmic slow wave activity, periodic discharges, and interictal epileptiform activity. After adjustment for known functional outcome predictors of stroke age, admission NIHSS, occurrence of a remote symptomatic seizure, and EEG

Table 1. Clinical, imaging, and neurophysiological features and discharge functional outcome of anterior circulation ischemic stroke patients

At discharge	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
Clinical features, n = 151	52	99		
Male	29 (55.8%)	60 (60.4%)	p = 0.566	NA
Mean age, yr (SD)	64.48 (13.20)	68.86 (10.97)	**p = 0.032**	OR = 1.02, 95% CI = 0.99–1.06, p = 0.246
Median admission NIHSS (IQR)	8 (6)	15 (10)	**p < 0.001**	OR = 1.18, 95% CI = 1.10–1.28, **p < 0.001**
IV alteplase	31 (59.6%)	70 (70.7%)	p = 0.169	NA
Stroke etiology				
Cardioembolism	21 (40.4%)	56 (56.6%)	NA	NA
Atherosclerosis	16 (30.8%)	21 (21.2%)		
Small vessels	2 (3.8%)	2 (2.0%)		
Unknown	13 (25.0%)	16 (16.2%)		
Other	0 (0%)	4 (4.0%)		
Acute symptomatic seizures	4 (7.7%)	18 (18.2%)	p = 0.094	NA
Nonconvulsive status epilepticus	0 (0%)	4 (4%)	p = 0.229	NA
Isolated MCA territory infarct patients with a first CT, n = 146	50	96		
Median ASPECTS (IQR)	10 (1)	9 (3)	**p = 0.042**	OR = 0.84, 95% CI = 0.63–1.10, p = 0.203
Isolated MCA territory infarct patients with a second CT, n = 124	35	89		
Median ASPECTS (IQR)	8 (2)	5 (4)	**p < 0.001**	OR = 0.61, 95% CI = 0.47–0.80, p < 0.001
Anterior circulation ischemic stroke patients with a second CT, n = 129	37	92		
Hemorrhagic transformation	2 (5.4%)	21 (22.8%)	**p = 0.021**	OR = 3.02, 95% CI = 0.62–14.73, p = 0.171
First EEG findings, n = 151	52	99		
Background activity slowing	6 (11.5%)	51 (51.5%)	**p < 0.001**	OR = 5.55, 95% CI = 1.89–16.33, **p = 0.002**
Background activity asymmetry	4 (7.7%)	60 (60.6%)	**p < 0.001**	OR = 11.91, 95% CI = 3.73–38.46, **p < 0.001**
EEG suppression	1 (1.9%)	11 (11.1%)	p = 0.059	NA
FSWA	42 (80.8%)	92 (92.9%)	**p = 0.025**	OR = 1.24, 95% CI = 0.36–4.24, p = 0.736
RSWA	5 (9.6%)	21 (21.2%)	p = 0.073	NA

Continued

Table 1. Continued.

At discharge	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
Periodic discharges	1 (1.9%)	26 (26.3%)	**p < 0.001**	OR = 10.39, 95% CI = 1.30–83.03, **p = 0.027**
IEA	2 (3.8%)	14 (14.1%)	p = 0.056	NA

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; EEG, electroencephalography; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RSWA, rhythmic slow wave activity; SD, standard deviation.
[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.
[b]Variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. First CT ASPECTS was used except in the model including second CT ASPECTS. The ORs for NIHSS, age, and ASPECTS are derived from multivariate logistic models including exclusively these three variables, whereas the ORs for the EEG variables are derived from models including NIHSS, age, ASPECTS, and the respective EEG variable.
Bold values indicate p ≤ 0.05.

Table 2. Comparison between stroke outcome (mRS ≥ 3) prediction model characteristics at discharge

Logistic regression models for an unfavorable outcome (mRS ≥ 3) at discharge

Model features	Omnibus test[a]	Nagelkerke R^{2}[b]	Hosmer–Lemeshow test[c]	PAC	SEN	SPE	PPV	NPV	AUC, 95%CI
Independent variables included in the model									
KP[d]	$\chi^2(3) = 34.85$, p < 0.001	29.4%	$\chi^2(8) = 4.86$, p = 0.773	73.3%	85.4%	50.0%	76.6%	64.1%	0.78, 0.70–0.86
EEG[e]	$\chi^2(1) = 44.86$, p < 0.001	35.5%	$\chi^2(0) = 0.00$, —	71.5%	60.6%	92.3%	93.8%	55.2%	0.76, 0.69–0.84
KP[d] + EEG[e]	$\chi^2(4) = 59.25$, p < 0.001	46.1%	$\chi^2(8) = 3.67$, p = 0.885	76.7%	81.3%	68.0%	83.0%	65.4%	0.86, 0.79–0.92

AUC, area under receiving operator curve; CI, confidence interval; EEG, electroencephalography; KP, known predictors; mRS, modified Rankin Scale; NPV, negative predictive value; PAC, percentage accuracy in classification (% of cases correctly classified by the model); PPV, positive predictive value; SEN, sensitivity; SPE, specificity.
[a]Omnibus test of model coefficients provides the overall statistical significance of the model, that is, how well the model predicts outcome to no independent variables.
[b]Nagelkerke R^2 is a method of calculating the explained variation, that is, how much variation of the outcome can be explained by the model.
[c]Hosmer–Lemeshow goodness of fit test analyzes how poor the model is at predicting outcome. When not significant, it indicates that the model is not a poor fit.
[d]Known stroke outcome predictors: age, admission National Institutes of Health Stroke Scale, and Alberta Stroke Program Early CT Score.
[e]EEG background activity asymmetry (EEG variable with the highest odds of impacting outcome; please refer to Table 1).

background activity slowing, asymmetry, and periodic discharges remained significant. Second (but not first) CT ASPECTS was a discharge outcome predictor independent from age and NIHSS.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG asymmetry (Table 5A), the variables remaining independent predictors were age (OR = 1.09, 95% CI = 1.09–1.04, p = 0.001), NIHSS score (OR = 1.18, 95% CI = 1.07–1.29, p = 0.001), and EEG background activity asymmetry (OR = 22.73, 95% CI = 7.30–71.43, p < 0.001). This model correctly classified 84.8% of the subjects, and the area under the ROC curve was 0.91. The prediction model including this EEG variable did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

In the logistic regression model encompassing known functional outcome predictors of stroke and remote symptomatic seizures (Table 5A), the variables remaining independent predictors were age (OR = 1.08, 95% CI = 1.04–1.14, p < 0.001), NIHSS score (OR = 1.18, 95% CI = 1.09–1.28, p < 0.001), and remote symptomatic

seizures (OR = 3.76, 95% CI = 1.02–13.83, p = 0.046). This model correctly classified 74.8% of the subjects, and the area under the ROC curve was 0.83. The prediction model including this type of poststroke seizure did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

Clinical, imaging, and neurophysiological features of patients who died in the first year after stroke are disclosed in Table 6. An association with death in the first year after stroke was found in bivariate analysis for age, admission NIHSS, occurrence of an acute symptomatic seizure, and EEG background activity slowing, asymmetry, suppression, and periodic discharges. After adjustment for known functional outcome predictors of stroke age, admission NIHSS, occurrence of an acute symptomatic seizure, and EEG suppression remained significant.

In the logistic regression model encompassing known functional outcome predictors of stroke and EEG suppression (Table 5B), the variables remaining independent predictors were age (OR = 1.06, 95% CI = 1.01–1.12, p = 0.032), NIHSS score (OR = 1.18, 95% CI = 1.07–1.31,

Table 3. Clinical, imaging, and neurophysiological features and vital outcome of anterior circulation ischemic stroke patients at discharge

At discharge	Death	Alive	Bivariate analysis[a]
Clinical features, n = 151	7	144	
Male	5 (71.4%)	84 (58.3%)	p = 0.701
Mean age, yr (SD)	71.14 (8.80)	67.17 (12.06)	p = 0.391
Median admission NIHSS (IQR)	20 (9)	12 (10)	**p = 0.032**
IV alteplase	5 (71.4%)	96 (66.7%)	p = 1.000
Stroke etiology			
Cardioembolism	1 (14.3%)	76 (52.8%)	NA
Atherosclerosis	1 (14.3%)	36 (25.0%)	
Small vessels	0 (0%)	4 (2.8%)	
Unknown	5 (71.4%)	24 (16.7%)	
Other	0 (0%)	4 (2.8%)	
Acute symptomatic seizures	6 (85.7%)	16 (11.1%)	**p < 0.001**
Nonconvulsive status epilepticus	1 (14.3%)	3 (2.1%)	p = 0.175
Isolated MCA territory infarct patients with a first CT, n = 146	6	140	
Median ASPECTS (IQR)	8.5 (5)	9 (2)	p = 0.343
Isolated MCA territory infarct patients with a second CT, n = 124	5	119	
Median ASPECTS (IQR)	3 (7)	6 (4)	p = 0.125
Anterior circulation ischemic stroke patients with a second CT, n = 129	6	123	
Hemorrhagic transformation	1 (16.7%)	22 (17.9%)	p = 1.000
First EEG findings, n = 151	7	144	
Background activity slowing	7 (100%)	50 (34.7%)	**p = 0.001**
Background activity asymmetry	5 (71.4%)	59 (41.0%)	p = 0.135
EEG suppression	4 (57.1%)	8 (5.6%)	**p = 0.001**
FSWA	6 (85.7%)	128 (88.9%)	p = 0.574
RSWA	2 (28.6%)	24 (16.7%)	p = 0.346
Periodic discharges	2 (28.6%)	25 (17.4%)	p = 0.609
IEA	1 (14.3%)	15 (10.4%)	p = 0.551

ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; RSWA, rhythmic slow wave activity; SD, standard deviation.

[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.

Bold values indicate p ≤ 0.05.

Table 4. Clinical, imaging, and neurophysiological features and functional outcome at 12 months after anterior circulation ischemic stroke

At 12 months after stroke	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
Clinical features, n = 150	73	77		
Male	40 (54.8%)	48 (62.3%)	p = 0.348	NA
Mean age, yr (SD)	63.45 (12.19)	71.23 (10.37)	**p < 0.001**	OR = 1.07, 95% CI = 1.03–1.12, **p = 0.001**
Median admission NIHSS (IQR)	9 (8)	17 (9)	**p < 0.001**	OR = 1.18, 95% CI = 1.1–1.28, **p < 0.001**
IV alteplase	43 (58.9%)	58 (75.3%)	**p = 0.032**	OR = 1.41, 95% CI = 0.59–3.74, p = 0.407
Stroke etiology			NA	NA
Cardioembolism	34 (46.6%)	43 (55.8%)		
Atherosclerosis	18 (24.7%)	18 (23.4%)		
Small vessels	3 (4.1%)	1 (1.3%)		
Unknown	16 (21.9%)	13 (16.9%)		
Other	2 (2.7%)	2 (2.6%)		
Acute symptomatic seizures	5 (6.8%)	17 (22.1%)	**p = 0.008**	OR = 2.19, 95% CI = 0.63–7.66, p = 0.220
Nonconvulsive status epilepticus	0 (0%)	4 (5.2%)	p = 0.121	NA
Remote symptomatic seizures	5 (6.8%)	18 (25.7%)	**p = 0.002**	OR = 3.76, 95% CI = 1.02–13.83, **p = 0.046**
Seizures anytime during the study	9 (12.3%)	29 (37.7%)	**p < 0.001**	OR = 2.19, 95% CI = 0.80–6.04, p = 0.128
Isolated MCA territory infarct patients with a first CT, n = 145	71	74		
Median ASPECTS (IQR)	10 (1)	9 (3)	**p = 0.029**	OR = 0.90, 95% CI = 0.61–1.04, p = 0.089
Isolated MCA territory infarct patients with a second CT, n = 124	54	70		
Median ASPECTS (IQR)	8 (3)	4.5 (5)	**p < 0.001**	OR = 0.68, 95% CI = 0.54–0.84, **p = 0.001**
Anterior circulation ischemic stroke patients with a second CT, n = 129	56	73		
Hemorrhagic transformation	7 (12.5%)	16 (21.9%)	p = 0.166	NA
First EEG findings, n = 150	73	77		
Background activity slowing	7 (9.6%)	50 (64.9%)	**p < 0.001**	OR = 14.50, 95% CI = 4.95–42.48, **p < 0.001**
Background activity asymmetry	8 (11.0%)	56 (72.7%)	**p < 0.001**	OR = 22.73, 95% CI = 7.30–71.43, **p < 0.001**

Continued

Table 4. Continued.

At 12 months after stroke	Modified Rankin Scale score < 3	Modified Rankin Scale score ≥ 3	Bivariate analysis[a]	Multivariate analysis[b]
EEG suppression	1 (1.4%)	10 (13.0%)	**p = 0.009**	OR = 8.85, 95% CI = 0.71–110.22, p = 0.09
FSWA	60 (82.2%)	73 (94.8%)	**p = 0.020**	OR = 1.60, 95% CI = 0.36–7.02, p = 0.534
RSWA	8 (11.0%)	18 (23.4%)	**p = 0.045**	OR = 2.58, 95% CI = 0.88–7.64, p = 0.086
Periodic discharges	2 (2.7%)	25 (32.5%)	**p < 0.001**	OR = 14.10, 95% CI = 2.73–72.78, **p = 0.002**
IEA	3 (4.1%)	13 (16.9%)	**p = 0.016**	OR = 3.03, 95% CI = 0.66–13.86, p = 0.153

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RSWA, rhythmic slow wave activity; SD, standard deviation.
[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.
[b]Variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. First CT ASPECTS was used except in the model including second CT ASPECTS. The ORs for NIHSS, age, and ASPECTS are derived from multivariate logistic models including exclusively these three variables, whereas the ORs for the EEG variables are derived from models including NIHSS, age, ASPECTS, and the respective EEG variable.
Bold values indicate p ≤ 0.05.

p = 0.001), and EEG suppression (OR = 7.48, 95% CI = 1.40–39.99, p = 0.019). This model correctly classified 89.0% of the subjects, and the area under the ROC curve was 0.84. The prediction model including this EEG variable did not have a significantly different discriminative capacity compared to the model encompassing the already known outcome predictors.

In the logistic regression model encompassing known functional outcome predictors of stroke and acute symptomatic seizures (Table 5A), the variables remaining independent predictors were age (OR = 1.06, 95% CI = 1.00–1.12, p = 0.039), NIHSS score (OR = 1.19, 95% CI = 1.07–1.31, p = 0.001) and acute symptomatic seizures (OR = 4.55, 95% CI = 1.34–15.47, p = 0.015). This model correctly classified 91.0% of the subjects, and the area under the ROC curve was 0.82. The prediction model including this type of poststroke seizure did not have a different discriminative capacity compared to the model encompassing the already known outcome predictors.

DISCUSSION

In this work, acute symptomatic seizures were independent predictors of death and remote symptomatic seizures were independent predictors of an unfavorable outcome in the first year after an anterior circulation ischemic stroke. We also demonstrated that EEG abnormalities extracted from visual analysis of a single, early (<72 h after stroke), and short-duration EEG are strong predictors of functional outcome, even when adjusted for previously known (early clinical and imaging) stroke outcome predictors.

We think that the strengths of this work, standing out from previous research in this area, include the sample size of consecutive anterior circulation stroke patients, the prospective nature of a multimodal (clinical, neurophysiological, and imagiological) study, and the 12 months of follow-up with only one patient lost during this period, as well as the adjustment to clinical and infarct severity.

As a limitation, we did not analyze the value of EEG as a functional outcome predictor comparatively with second CT scan or brain MRI, avoiding the inclusion of variables with a high percentage of missing data (17.9% and 58.3%, respectively) in our regression models. Sillanpaa et al.[31] showed the superiority of ASPECTS quantified at 24 h after stroke (over on-admission) noncontrast-enhanced CT in outcome prediction. In our analysis, second CT ASPECTS (but not first CT ASPECTS) was a predictor of stroke functional outcome independently from age and admission NIHSS. Nevertheless, this result must be cautiously interpreted because of the missing data. We acknowledge that our first CT ASPECTS median reflects the difficulty of estimating stroke size from early noncontrast-enhanced CT, reducing the value of this score in functional outcome assessment.

Table 5. Comparison between stroke outcome (mRS $\geq$ 3 and mRS = 6) prediction model characteristics at 12 months

A. Logistic regression models for an unfavorable outcome (mRS $\geq$ 3) at 12 months

Model features	Omnibus test[a]	Nagelkerke R²[b]	Hosmer–Lemeshow test[c]	PAC	SEN	SPE	PPV	NPV	AUC, 95%CI
Independent variables included in the model									
KP[d]	$\chi^2(3) = 52.00$, p < 0.001	40.2%	$\chi^2(8) = 3.46$, p = 0.902	71.7%	70.3%	73.2%	73.2%	70.3%	0.82, 0.75–0.88
EEG[e]	$\chi^2(1) = 64.00$, p < 0.001	46.3%	$\chi^2(0) = 0.00$, —	80.7%	72.7%	89.0%	87.5%	75.6%	0.81, 0.74–0.88
KP[d] + EEG[e]	$\chi^2(4) = 93.52$, p < 0.001	63.4%	$\chi^2(8) = 4.38$, p = 0.82	84.8%	81.1%	88.7%	88.2%	81.8%	0.91, 0.86–0.96
RSS	$\chi^2(1) = 9.88$, p = 0.002	8.9%	$\chi^2(0) = 0$, —	60.1%	25.7%	93.2%	78.3%	56.7%	0.59, 0.50–0.69
KP[d] + RSS	$\chi^2(4) = 54.62$, p < 0.001	43.3%	$\chi^2(8) = 3.74$, p = 0.88	74.8%	72.1%	77.5%	75.4%	74.3%	0.83

B. Logistic regression models for death (mRS = 6) at 12 months

Model features	Omnibus test	Nagelkerke R²	Hosmer–Lemeshow test	PAC	SEN	SPE	PPV	NPV	AUC, 95%CI
Independent variables included in the model									
KP[d]	$\chi^2(3) = 25.58$, p < 0.001	28.2%	$\chi^2(8) = 12.71$, p = 0.122	86.9%	22.7%	98.4%	71.4%	87.7%	0.81, 0.70–0.92
EEG[f]	$\chi^2(1) = 10.10$, p = 0.001	11.3%	$\chi^2(0) = 0$, —	85.3%	26.1%	96.1%	54.5%	87.8%	0.61, 0.47–0.75
KP[d] + EEG[f]	$\chi^2(4) = 31.21$, p < 0.001	33.8%	$\chi^2(8) = 15.39$, p = 0.052	89.0%	31.8%	99.2%	87.5%	89.1%	0.84, 0.74–0.93
ASS	$\chi^2(1) = 10.394$, p = 0.001	11.6%	$\chi^2(0) = 0$, —	84.7%	0%	100%	0%	84.7%	0.64, 0.51–0.78
ASS + KP[d]	$\chi^2(4) = 31.31$, p < 0.001	33.9%	$\chi^2(8) = 20.62$, p = 0.008	91.0%	40.9%	100%	100%	90.4%	0.82, 0.70–0.94

ASS, acute symptomatic seizures; AUC, area under receiving operator curve; CI, confidence interval; EEG, electroencephalography; KP, known predictor; mRS, modified Rankin Scale; NPV, negative predictive value; PAC, percentage accuracy in classification (% of cases correctly classified by the model); PPV, positive predictive value; RSS, remote symptomatic seizures; SEN, sensitivity; SPE, specificity.

[a]Omnibus test of model coefficients provides the overall statistical significance of the model, that is, how well the model predicts outcome to no independent variables.

[b]Nagelkerke R² is a method of calculating the explained variation, that is, how much variation of the outcome can be explained by the model.

[c]Hosmer–Lemeshow goodness of fit test analyzes how poor the model is at predicting outcome. When not significant, it indicates that the model is not a poor fit.

[d]Known stroke outcome predictors: age, admission National Institutes of Health Stroke Scale and Alberta Stroke Program Early CT Score.

[e]Background activity asymmetry (EEG variable with the highest odds of impacting functional outcome; please refer to Table 4).

[f]EEG suppression (EEG variable with the highest odds of impacting vital outcome; please refer to Table 6).

Table 6. Clinical, imaging, and neurophysiological features and vital outcome at 12 months after anterior circulation ischemic stroke

At 12 months	Death	Alive	Bivariate analysis[a]	Multivariate analysis[b]
Clinical features, n = 150	23	127		
Male	15 (65.2%)	73 (57.5%)	p = 0.488	NA
Mean age (SD)	73.74 (10.08)	66.31 (11.90)	**p = 0.006**	OR = 1.06, 95% CI = 1.01–1.12, **p = 0.028**
Median admission NIHSS (IQR)	18 (7)	11 (10)	**p < 0.001**	OR = 1.18, 95% CI = 0.7–1.3, **p = 0.001**
IV alteplase	18 (78.3%)	83 (65.4%)	p = 0.225	NA
Stroke etiology				
Cardioembolism	10 (43.5%)	67 (52.8%)	NA	NA
Atherosclerosis	5 (21.7%)	31 (24.4%)		
Small vessels	0 (0%)	4 (3.1%)		
Unknown	8 (34.8%)	21 (16.5%)		
Other	0 (0%)	4 (3.1%)		
Acute symptomatic seizures	9 (39.1%)	13 (10.2%)	**p < 0.001**	OR = 4.55, 95% CI = 1.34–15.47, **p = 0.015**
Nonconvulsive status epilepticus	1 (4.3%)	3 (2.4%)	p = 0.587	NA
Remote symptomatic seizures	1 (6.3%)	22 (17.3%)	p = 0.469	NA
Isolated MCA territory infarct, n = 145	22	123		
Median ASPECTS (IQR)	9 (4)	9 (2)	p = 0.295	NA
Second CT, n = 129	22	107		
Hemorrhagic transformation	2 (9.1%)	21 (19.6%)	p = 0.362	NA
First EEG findings, n = 150	23	127		
Background activity slowing	16 (69.6%)	41 (32.3%)	**p = 0.001**	OR = 1.99, 95% CI = 0.66–5.99, p = 0.219
Background activity asymmetry	16 (69.6%)	48 (37.8%)	**p = 0.005**	OR = 1.48, 95% CI = 0.48–4.50, p = 0.495
EEG suppression	6 (26.1%)	5 (3.9%)	**p < 0.001**	OR = 7.48, 95% CI = 1.40–39.99, **p < 0.019**
FSWA	22 (95.7%)	111 (87.4%)	p = 0.251	NA
RSWA	5 (21.7%)	21 (16.5%)	p = 0.544	NA
Periodic discharges	8 (34.8%)	19 (15.0%)	**p = 0.023**	OR = 1.54, 95% CI = 0.48–4.94, p = 0.464
IEA	3 (13.0%)	13 (10.2%)	p = 0.688	NA

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; EEG, electroencephalographic; FSWA, focal slow wave activity; IEA, interictal epileptiform activity; IQR, interquartile range; IV, intravenous; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RSWA, rhythmic slow wave activity; SD, standard deviation.

[a]Bivariate analysis of dichotomous data was performed by chi-square test or Fisher exact test and quantitative variables by t test or Mann–Whitney U test, as appropriate.

[b]Variables with a positive significant association in bivariate analysis were adjusted for known functional outcome predictors of stroke, namely age, clinical stroke severity (admission NIHSS), and imaging infarct severity (ASPECTS), using a logistic regression model. The ORs for NIHSS, age, and ASPECTS are derived from multivariate logistic models including exclusively these three variables, whereas the ORs for the EEG variables are derived from models including NIHSS, age, ASPECTS, and the respective EEG variable.

Bold values indicate p ≤ 0.05.

Nevertheless, in the clinical practice of a significant proportion of stroke units (such as ours), a second CT scan is not routinely performed in all patients, unless they had been treated with intravenous alteplase or had a neurological worsening. In our study, using an easy, noninvasive, short-duration, and bedside EEG examination, available in the great majority of neurological departments and intensive care units, we identified neurophysiological independent predictors of stroke outcome in models already including well-established clinical and early imaging outcome prognostic factors.

Poststroke seizures and stroke outcome

In our bivariate analysis, seizures were associated with an unfavorable functional outcome 1 year after stroke, as previously suggested in the literature.[1,3,4,32] It has been postulated in the animal model that poststroke seizures may contribute to tissue damage.[33,34] In addition, De Reuck

et al.[2] showed that remote symptomatic seizures are associated with lesion increase and worsening of disability. As a novel finding, we show that the association between remote seizures and an unfavorable functional outcome 12 months after stroke does remain significant when adjusted for age, and clinical and imaging stroke severity. Furthermore, in our work, acute symptomatic seizures remained as an independent predictor of death in the first year after an anterior circulation stroke, even after adjustment for known stroke outcome predictors. Hesdorffer et al.[1] similarly showed that patients with acute symptomatic seizures (of different etiologies) had a chance 8.9 times higher of dying within 30 days. More recently, Huang et al.[3] also found that patients with seizures during admission for stroke had a higher mortality at 30 days and 1 year. This finding was not observed in a study by Hamidou et al. study,[35] which, however, used a population-based registry and a different definition of early seizures.

EEG abnormalities and stroke outcome

EEG background activity slowing was associated with stroke clinical severity by Kayser-Gatchalian and Neundörfer[7] and, as in our study, with unfavorable stroke outcome by Cillessen et al.[9] The originality of our study resides in the definition of EEG independent predictors of stroke functional outcome, either at short or at long term, even when adjusted for age and clinical and imaging severity of stroke.

The neurophysiological feature with the highest odds of impacting functional outcome was background activity asymmetry. Quantitative EEG studies support our observation. Brain symmetry index obtained from continuous EEG records has been correlated with NIHSS score[36] and lesion volume on MRI.[37] In an easier and simpler way, we showed that background activity asymmetry in raw analysis of a single and short-duration EEG is an independent predictor of unfavorable stroke outcome. Cuspineda and collaborators, using quantitative EEG in 28 patients, showed that this is better than the Canadian Neurological Scale score in residual functional disability prediction[12] and better than the mRS in the prediction of functional outcome.[12,38] In our study, the prognostic models including raw EEG abnormalities correctly classified a higher percentage of patients than the model including exclusively the already known stroke outcome predictors. We believe that our results show that some early EEG characteristics are comparable to clinical stroke severity and better than early CT infarct severity in the determination of poststroke functional outcome, reflecting the concept that EEG is a sensitive neurological diagnosis technique in the detection of acute cerebral ischemia[39] and a robust one in the functional assessment of the brain.[40]

The association between EEG suppression and death deserves attention. Although the low number of patients who died in the hospital does not allow a multivariate analysis, this neurophysiological characteristic has been associated with larger infarcts with a higher risk of becoming malignant,[10] and may draw attention to the need for an early start of medical and/or surgical therapy. In line with our results regarding focal cerebral ischemia outcome, EEG suppression was recently ranked within malignant EEG patterns and as a poor prognostic predictor of postcardiac arrest diffuse cerebral ischemia.[41] In our study, this EEG feature was an independent predictor of the vital outcome 1 year after stroke when controlled for age and stroke severity.

CONFLICT OF INTEREST

J.M.F. reports personal fees from Boehringer Ingelheim outside the submitted work. The other authors declare no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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