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Risk of Poststroke Epilepsy Among Young Adults With Ischemic Stroke or Intracerebral Hemorrhage

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IMPORTANCE Poststroke epilepsy (PSE) is a major complication among young adults and is associated with problems with functional recovery and daily life. Although scores have been developed to predict risk of PSE, they have not been validated among patients with stroke at a young age.

OBJECTIVES To investigate both the risk of and risk factors for PSE at a young age and validate current PSE risk scores among a cohort of young adults.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from ODYSSEY (Observational Dutch Young Symptomatic Stroke Study), a prospective cohort study conducted among 17 hospitals in the Netherlands between May 27, 2013, and March 3, 2021, with follow-up until February 28, 2024. Participants included 1388 consecutive patients aged 18 to 49 years with neuroimaging-proven ischemic stroke or intracerebral hemorrhage (ICH) and without a history of epilepsy. Statistical analysis took place between June and August 2024.

EXPOSURE First-ever neuroimaging-proven ischemic stroke or ICH.

MAIN OUTCOMES AND MEASURES Poststroke epilepsy was defined as at least 1 remote symptomatic seizure (>7 days). Cumulative incidence functions were used to calculate the 5-year risk of PSE. Fine-Gray regression models were used to identify risk factors associated with PSE (age, sex, clinical stroke, and neuroimaging variables). The performances of the SeLECT (severity of stroke, large-artery atherosclerosis, early seizure, cortical involvement, and territory of middle cerebral artery) 2.0 risk score (for ischemic stroke) and the CAVE (cortical involvement, age, bleeding volume, and early seizure) risk score (for ICH) were assessed with C statistics and calibration bar plots.

RESULTS This study included 1388 patients (ischemic stroke, 1231 [88.7%]; ICH, 157 [11.3%]; median age, 44.1 years [IQR, 38.0-47.4 years]; 736 men [53.0%]; median follow-up, 5.3 years [IQR, 3.4-7.4 years]), of whom 57 (4.1%) developed PSE. The 5-year cumulative risk of PSE was 3.7% (95% CI, 0.2%-4.8%) after ischemic stroke and 7.6% (95% CI, 3.5%-11.8%) after ICH. Factors associated with PSE after ischemic stroke were an acute symptomatic seizure (<7 days) (hazard ratio [HR], 10.83 [95% CI, 2.05-57.07]; *P* = .005) and cortical involvement (HR, 5.35 [95% CI, 1.85-15.49]; *P* = .002). The only factor associated with PSE after ICH was cortical involvement (HR, 8.20 [95% CI, 2.22-30.25]; *P* = .002). The C statistic was 0.78 (95% CI, 0.71-0.84) for the SeLECT 2.0 risk score and 0.83 (95% CI, 0.76-0.90) for the CAVE risk score, and calibration was good for both scores.

CONCLUSION This study suggests that the risk of PSE among young adults is relatively low and that the factors that were associated with PSE were similar to variables included in the existing risk scores, which can therefore also be applied for young adults after stroke. Future clinical trials should investigate the optimal primary and secondary prophylaxis for patients at high risk.

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Supplemental content

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Stroke at a young age occurs during a demanding phase of life, which may result in disability, and thus poses a risk of major complications. One of these complications is poststroke epilepsy (PSE). Patients with PSE have a higher risk of mortality, worse functional outcomes, and lower quality of life.[1-6] They often need long-term treatment with antiepileptic drugs, which may cause adverse events such as fatigue, dizziness, behavioral changes, and depression.[7-9]

Only a few studies have investigated the incidence and cumulative risk of PSE specifically among young adults.[10-13] These studies reported a 5-year cumulative risk between 5.5% and 15% for patients with ischemic stroke and 21% for patients with intracerebral hemorrhage (ICH). However, these estimates are based on studies in which neuroimaging-based proof of ischemic stroke was not required, and these studies were conducted decades ago. Recently, several risk scores that predict the individual risk of PSE have been developed.[14] However, they have all been derived from the general stroke population, including mainly patients older than 65 years, with untested external validity in young adults. To accurately inform patients about the long-term risks of PSE, it is important to investigate the risk of PSE among young adults specifically and to identify which patients are at highest risk.

This study investigated the incidence of PSE among young adults aged 18 to 49 years in a large prospective cohort of patients with neuroimaging-proven strokes. In addition, we aimed to identify clinical and neuroimaging characteristics that are associated with PSE. Last, we assessed the performance of existing risk scores of PSE in a cohort of young adults.

Key Points

Question What is the risk of poststroke epilepsy (PSE) among young adults (<50 years) with ischemic stroke or intracerebral hemorrhage?

Findings In this cohort study including 1388 patients, the 5-year cumulative risk of PSE was 3.7% after ischemic stroke and 7.6% after intracerebral hemorrhage. Factors associated with PSE were similar to variables in current risk scores for PSE.

Meaning This study suggests that the risk of PSE among young adults is relatively low and that current risk scores for PSE can be applied to identify young patients at high risk.

Methods

Patients and Study Design

In this cohort study, we included patients from the Observational Dutch Young Symptomatic Stroke Study (ODYSSEY), a multicenter observational study with 17 participating hospitals in the Netherlands, which has been described in more detail previously.[15] It includes patients aged 18 to 49 years with a first-ever neuroimaging-proven ischemic stroke or ICH between May 27, 2013, and March 3, 2021. Patients with transient symptoms lasting less than 24 hours were included as having (minor) strokes according to the tissue-based definition.[16] Hemorrhagic transformation of an ischemic stroke was classified as an ischemic stroke. Exclusion criteria were transient monocular blindness or retinal infarction, a history of transient ischemic attack or stroke, traumatic ICH, subarachnoid hemorrhage, ICH due to a known ruptured aneurysm, ICH in a known cerebral malignant neoplasm, cerebral venous sinus thrombosis, and not being a permanent resident of the Netherlands. For the present study, we also excluded patients with a history of epilepsy (n = 30). The Medical Review Ethics Committee Region East-Netherlands approved this cohort study, and all participants provided written informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Outcome

The outcome was assessed using a 2-stage approach. First, information about acute symptomatic seizures was retrieved from medical files during baseline data collection by physicians. Information about the occurrence of remote symptomatic seizures was collected through contacting patients by telephone or online survey until February 28, 2024, using a standardized structured questionnaire in Dutch (translated for this article). Second, all first-reported seizures for which the patient sought medical attention, as well as the reported use of antiseizure medication, were cross-checked with medical records from the participating hospital or general practitioner. We additionally validated the self-reported method by cross-checking the medical records of 64 patients from 6 hospitals who did not report any PSE and found 100% agreement. The questionnaires are shown in the eAppendix in Supplement 1.

An acute symptomatic seizure was defined as a seizure within 7 days after the initial stroke, and a remote symptomatic seizure was defined as a seizure within 7 days or later after the initial stroke. We defined PSE as 1 or more remote acute symptomatic seizures, according to the guidelines of the International League Against Epilepsy (ILAE).[17] Seizure type was defined as focal (with or without impaired awareness) or generalized.

Risk Factors

The following cardiovascular risk factors were systematically assessed through medical files at the time of the index event: hypertension, dyslipidemia, diabetes, smoking, excessive alcohol use, illicit drug use, and obesity, and were described previously.[18] Cause of ischemic stroke was defined according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[19] Cause of ICH was defined in 4 categories: macrovascular causes, deep perforating vasculopathy, other cause determined, and undetermined. Severity of stroke was defined by the National Institutes of Health Stroke Scale (NIHSS) score at admission.[20] We stratified severity of stroke as minor stroke (NIHSS score ≤3), and major stroke (NIHSS score >3).[21]

External Validation Risk Scores

We calculated the SeLECT (severity of stroke, large-artery atherosclerosis, early seizure, cortical involvement, and ter-

ritory of middle cerebral artery) 2.0 risk score for each patient with ischemic stroke: severity of stroke (1 point for an NIHSS score of 4-10 and 2 points for an NIHSS score of ≥11), large-artery atherosclerosis (1 point), acute symptomatic seizure (3 points), acute symptomatic status epilepticus (7 points), cortical involvement (2 points), and territory of the middle cerebral artery (1 point).[22] For patients with ICH, we calculated the CAVE (cortical involvement, age, bleeding volume, and early seizure) risk score: cortical involvement (1 point), younger than 65 years of age (1 point), bleeding volume of 10 mL or more (1 point), and an early seizure (1 point).[23] Cortical involvement of the stroke was assessed on computed tomography or magnetic resonance imaging scans or based on clinical symptoms (eg, neglect, aphasia, or hemianopsia). Bleeding volume was determined by the ABC/2 formula.[24]

We assessed the performance of the SeLECT 2.0 and CAVE risk scores through discrimination and calibration. Discrimination determines how well a model can distinguish between patients with and patients without PSE and was assessed with the C statistic. Calibration shows the agreement between the predicted risk and the observed risk, which is illustrated with bar plots. The observed risk was calculated only for the risk scores with at least 30 patients.

Statistical Analysis

Statistical analysis took place between June and August 2024. Differences in baseline characteristics between patients with and patients without PSE were examined with a Mann-Whitney test for nonnormally distributed continuous variables or a χ^2 test for categorical variables. The number of patient-years was calculated until the date of first remote symptomatic seizure for patients with PSE, death, or last available follow-up. Cumulative incidence functions were used to investigate the 5-year cumulative incidence of PSE stratified per type of stroke (ischemic stroke or ICH), to account for the competing risk of death. Second, we calculated the incidence rate per 100 person-years per type of stroke, per year, by dividing the number of PSE cases by the number of person-years at risk.

Age- and sex-adjusted Fine-Gray proportional hazard models were used to investigate the association between predefined risk factors (age, sex, NIHSS score at admission, occurrence of an acute symptomatic seizure, cortical involvement, infarction in the middle cerebral artery territory, and modified TOAST classification) and PSE among patients with ischemic stroke. Second, we investigated the association between predefined risk factors (age, sex, NIHSS score at admission, occurrence of an acute symptomatic seizure, cortical involvement, and bleeding volume of ≥10 mL) and PSE among patients with ICH. Multivariable analyses were done including variables that were significant in the age- and sex-adjusted models. All *P* values were from 2-sided tests and results were deemed statistically significant at $P < .05$. Analyses were performed with RStudio, version 4.1.3 (2022-03-10; The R Project for Statistical Computing).

Results

This study included 1388 patients (median age, 44.1 years [IQR, 38.0-47.4 years]; 736 men [53.0%] and 652 women [47.0%]), of whom 1231 (88.7%) had an ischemic stroke and 157 (11.3%) had an ICH (**Table 1** and **Figure 1**). The median follow-up was 5.3 years (IQR, 3.4-7.4 years), with a total of

Table 1. Baseline Characteristics

Characteristic	All patients, No./total No. (%)	Patients without PSE, No./total No. (%)	Patients with PSE, No./total No. (%)	*P* value
Type of stroke				
Ischemic stroke	1231/1388 (88.7)	1187/1331 (89.2)	44/57 (77.2)	.01
Intracerebral hemorrhage	157/1388 (11.3)	144/1331 (10.8)	13/57 (22.8)	
Age, median (IQR), y	44.1 (38.0-47.4)	44.1 (38.2-47.4)	44.3 (35.3-47.4)	.68
Men	736/1388 (53.0)	707/1331 (53.1)	29/57 (50.9)	.84
Women	652/1388 (47.0)	624/1331 (46.9)	28/57 (49.1)	
Follow-up, median (IQR), y	5.3 (3.4-7.4)	5.3 (3.4-7.4)	5.4 (3.9-7.8)	.41
NIHSS score at admission, median (IQR)[a]	3 (1-7)	3 (1-7)	6 (2-14)	.002
Minor stroke (≤3)	776/1384 (56.1)	753/1328 (56.7)	23/56 (41.1)	.03
Major stroke (>3)	608/1384 (43.9)	575/1328 (43.3)	33/56 (58.9)	
Diabetes	130/1388 (9.4)	125/1331 (9.4)	5/57 (8.8)	<.99
Hypertension	522/1388 (37.6)	505/1331 (37.9)	17/57 (29.8)	.27
Smoking	630/1388 (45.4)	608/1331 (45.7)	2/572 (38.6)	.36
Excess alcohol use	86/1388 (6.2)	84/1331 (6.3)	2/57 (3.5)	.56
Dyslipidemia	837/1388 (60.3)	807/1331 (60.6)	30/57 (52.6)	.28
Illicit drug use[b]	90/1079 (6.5)	89/1031 (6.7)	1/48 (1.8)	.12
Acute symptomatic seizure (<7 d)	19/1388 (1.4)	13/1331 (1.0)	6/57 (10.5)	<.001
Acute status epilepticus	1/1388 (0.1)	0	1/57 (1.8)	.68
Cortical involvement[c]	659/1364 (47.5)	610/1308 (45.8)	49/56 (86.0)	<.001

(continued)

Table 1. Baseline Characteristics (continued)

Characteristic	All patients, No./total No. (%)	Patients without PSE, No./total No. (%)	Patients with PSE, No./total No. (%)	*P* value
Ischemic stroke				
TOAST classification				
Atherothrombotic	55/1231 (4.5)	52/1187 (4.4)	3/44 (6.8)	.08
Likely atherothrombotic	174/1231 (14.1)	167/1187 (14.1)	7/44 (15.9)	
Small vessel disease	161/1231 (13.1)	161/1187 (13.6)	0	
Cardioembolic	202/1231 (16.4)	194/1187 (16.3)	8/44 (18.2)	
Rare causes	280/1231 (22.7)	264/1187 (22.2)	16/44 (36.4)	
Cryptogenic	304/1231 (24.7)	295/1187 (24.9)	9/44 (20.5)	
Multiple causes	55/1231 (4.5)	54/1187 (4.5)	1/44 (2.3)	
SeLECT 2.0 score, median (IQR)[d]	2 (1-3)	2 (1-3)	4/44 (3-5)	<.001
0	215/1227 (17.5)	213/1184 (18.0)	2/43 (4.7)	
1	235/1227 (19.2)	234/1184 (19.8)	1/43 (2.3)	
2	211/1227 (17.2)	209/1184 (17.7)	2/43 (4.7)	
3	291/1227 (23.7)	277/1184 (23.4)	14/43 (32.6)	
4	147/1227 (12.0)	142/1184 (12.0)	5/43 (11.6)	
5	110/1227 (9.0)	94/1184 (7.9)	16/43 (37.2)	
6	14/1227 (1.1)	13/1184 (1.1)	1/43 (2.3)	
7	1/1227 (0.1)	0	1/43 (2.3)	
8	2/1227 (0.2)	2/1184 (0.2)	0	
9	0	0	0	
10	0	0	0	
11	0	0	0	
12	0	0	0	
13	1/1227 (0.1)	0	1/43 (2.3)	
Intracerebral hemorrhage				
Cause of stroke				
Macrovascular cause	37/157 (23.6)	31/144 (21.5)	6/13 (46.3)	.19
Deep perforating vasculopathy	57/157 (36.3)	55/144 (38.2)	2/13 (15.4)	
Other determined cause	12/157 (7.6)	11/144 (7.6)	1/13 (7.7)	
Undetermined	51/157 (32.5)	47/144 (32.6)	4/13 (30.8)	
CAVE score, median (IQR)[e]	2 (1-2)	1 (1-2)	3 (2-3)	<.001
1	70/148 (47.3)	70/135 (51.9)	0	
2	46/148 (31.1)	40/135 (29.6)	6/13 (46.2)	
3	30/148 (20.3)	24/135 (17.8)	6/13 (46.2)	
4	2/148 (1.4)	1/135 (0.7)	1/13 (7.7)	

Abbreviations: CAVE, cortical involvement, age, bleeding volume, and early seizure; NIHSS, National Institutes of Health Stroke Scale; PSE, poststroke epilepsy; SeLECT, severity of stroke, large-artery atherosclerosis, early seizure, cortical involvement, and territory of middle cerebral artery; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

[a] NIHSS score was missing for 4 patients.

[b] Illicit drug use was missing for 309 patients.

[c] Cortical involvement was missing for 24 patients.

[d] SeLECT 2.0 score was missing for 4 patients.

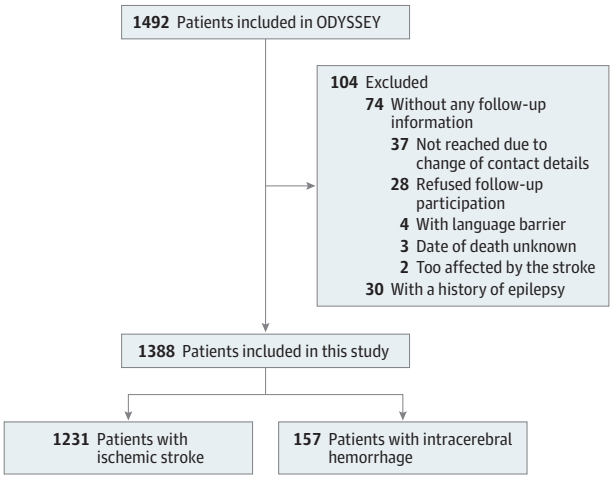
[e] CAVE score was missing for 9 patients.

7002 patient-years of follow-up. Overall, 57 patients (4.1%) developed PSE (median age, 44.3 [IQR, 35.3-47.4 years]; 29 men [50.9%] and 28 women [49.1%]). The median time to first late seizure was 7 months (IQR, 2-14 months). Table 1 shows the baseline characteristics of the included patients. The median NIHSS score at admission was 3 (IQR, 1-7) for patients without PSE and 6 (IQR, 2-14) for patient with PSE. Of 13 patients with acute symptomatic seizures who did not develop PSE, only 2 (15.4%; 1 with ischemic stroke and 1 with ICH) did not receive any antiseizure medication after the first seizure. The eTable in Supplement 1 shows the type of seizures in patients with PSE.

Ischemic Stroke and the Risk of PSE

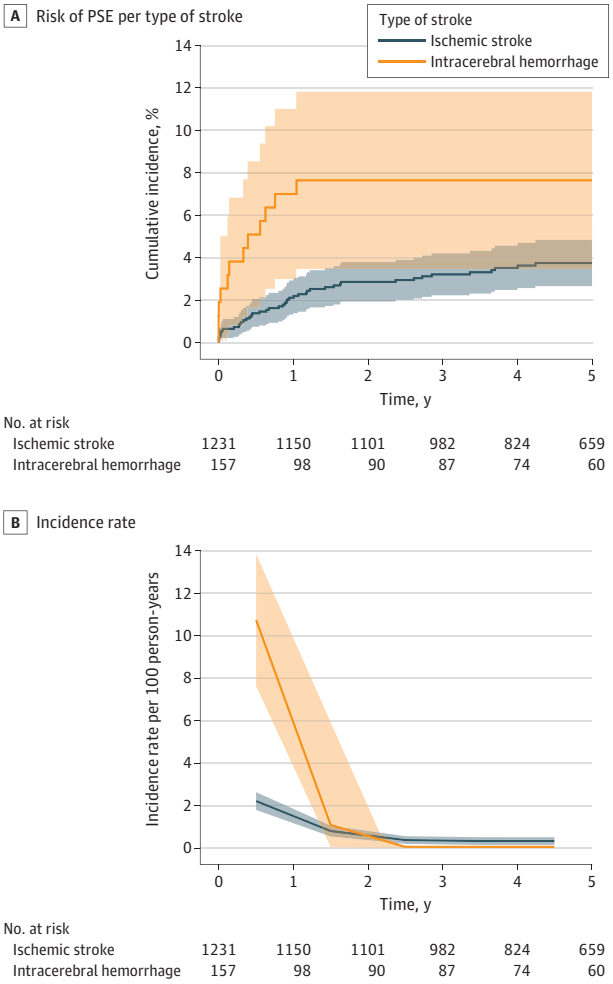
In total, 44 of 1231 patients with an ischemic stroke (3.6%) developed PSE. The 5-year cumulative risk of PSE after an ischemic stroke was 3.7% (95% CI, 0.2%-4.8%) (**Figure 2**). The incidence rate per 100 person-years was 2.2 (95% CI, 1.8-2.6) in the first year after the stroke, which decreased to 0.8 (95% CI, 0.5-1.1) in the second year. Variables that were associated with

Figure 1. Flowchart of Included Patients



ODYSSEY indicates Observational Dutch Young Symptomatic Stroke Study.

Figure 2. Five-Year Cumulative Risk and Incidence Per 100 Person-Years of Poststroke Epilepsy (PSE) After an Ischemic Stroke or Intracerebral Hemorrhage



The incidence rate per 100 person-years was calculated by dividing the number of events by the total person-years at risk per 1-year intervals. The middle of those intervals was chosen as the point estimator in the graph. The shaded areas indicate 95% CIs.

PSE in the multivariable analysis were an acute symptomatic seizure (hazard ratio [HR], 10.83 [95% CI, 2.05-57.07]; $P = .005$) and cortical involvement (HR, 5.35 [95% CI, 1.85-15.49]; $P = .002$) (**Table 2**). None of the patients with PSE had ischemic stroke caused by small vessel disease.

ICH and the Risk of PSE

A total of 13 of 157 patients with an ICH (8.3%) developed PSE during follow-up. The 5-year cumulative risk of PSE after ICH was 7.6% (95% CI, 3.5%-11.8%) (Figure 2). The incidence rate per 100 person-years was 10.8 (95% CI, 7.6-13.9) in the first year and 1.1 (95% CI, 0.0-2.1) in the second year. The only variable that was associated with PSE in multivariable analyses was cortical involvement (HR, 8.20 [95% CI, 2.22-30.25]; $P = .002$) (Table 2).

External Validation Risk Scores

The C statistic of the SeLECT 2.0 risk score was 0.78 (95% CI, 0.71-0.84). The predicted and observed risks of PSE are depicted in **Figure 3**. The observed risk of PSE according to the SeLECT 2.0 risk score in our study was lower compared with the predicted risk of the original study for all scores, however, with mostly overlapping 95% CIs between the predicted and observed risk. The C statistic of the CAVE risk score was 0.83 (95% CI, 0.76-0.90). The observed risk of PSE according to the CAVE risk score varied in overestimation and underestimation across the scores, but with wide 95% CIs.

Discussion

We showed a 5-year cumulative risk of PSE of 3.7% among patients with ischemic stroke and 7.6% among patients with ICH. For both types of stroke, the risk was highest within the first year after stroke. Variables that were associated with PSE were an acute symptomatic seizure and cortical involvement. These variables were also included in the SeLECT 2.0 and CAVE risk scores. Both risk scores showed good discrimination and reasonable calibration in this young cohort of patients with stroke.

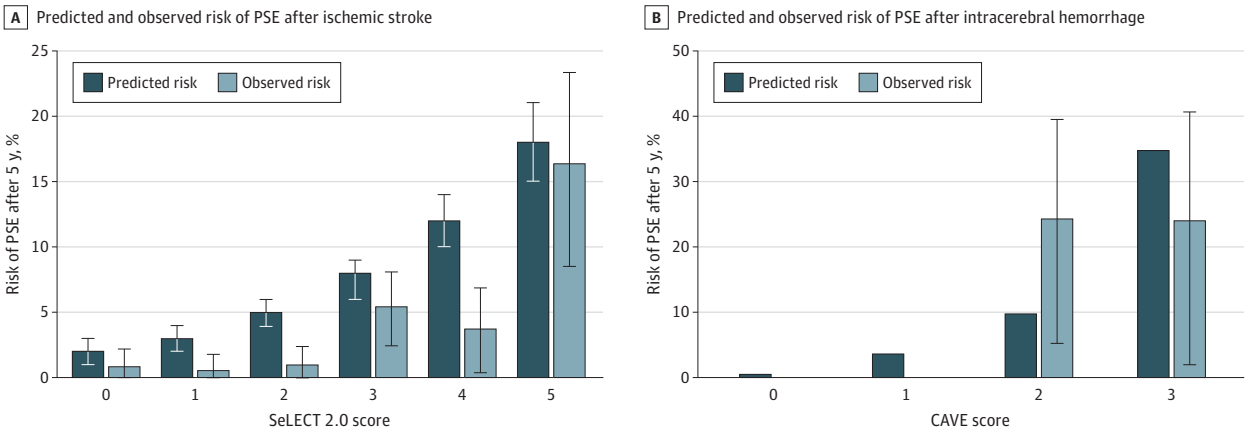
The risk of PSE in our study was lower compared with previous studies.[10-13] First, a previous Dutch cohort study reported a 5-year risk of 15% for patients with ischemic stroke and 21% for patients with ICH.[10] However, that study defined PSE by including both acute symptomatic seizures (between 1 day and 7 days) and remote symptomatic seizures based on the ILAE definitions at that time, whereas we included late seizures only due to the suggested different pathophysiological mechanisms. Although a remote symptomatic seizure is associated with chronic changes in the brain, an acute symptomatic seizure reflects acute and possibly reversible changes.[25] This difference likely resulted in an

Table 2. Age- and Sex-Adjusted and Multivariable Fine-Gray Proportional Hazard Models

	Age and sex adjusted		Multivariable	
Characteristic	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Ischemic stroke				
Age	1.01 (0.96-1.05)	.63	NA	NA
Women	1.02 (0.56-1.85)	.94	NA	NA
NIHSS score at admission				
Minor stroke (≤3)	1 [Reference]	NA	1 [Reference]	NA
Major stroke (>3)	2.26 (1.23-4.13)	.009	1.59 (0.83-3.02)	.16
Acute symptomatic seizure	12.97 (3.32-50.66)	<.001	10.83 (2.05-57.07)	.005
Cortical involvement	9.95 (3.45-28.70)	<.001	5.35 (1.85-15.49)	.002
Infarction in MCA territory	2.61 (1.21-5.67)	.01	1.61 (0.66-3.92)	.29
Cause of stroke				
Atherothrombotic	1.76 (0.45-6.84)	.17	1.13 (0.25-5.19)	.99
Likely atherothrombotic	1.33 (0.48-3.65)	.59	1.65 (0.59-4.56)	.34
Small vessel disease	NA	NA	NA	NA
Cardioembolic	1.38 (0.54-3.55)	.50	1.46 (0.55-3.90)	.45
Rare causes	2.00 (0.88-4.54)	.10	1.92 (0.77-4.78)	.16
Multiple causes	0.59 (0.08-4.61)	.61	0.75 (0.10-5.85)	.79
Cryptogenic	1 [Reference]	NA	1 [Reference]	NA
Intracerebral hemorrhage				
Age	0.94 (0.89-0.98)	.02	0.94 (0.89-1.00)	.65
Women	1.83 (0.63-5.28)	.26	NA	NA
NIHSS score at admission	1.0 (0.9-1.0)	.25	NA	NA
Minor stroke (≤3)	1 [Reference]	NA	NA	NA
Major stroke (>3)	0.60 (0.20-1.79)	.36	NA	NA
Acute symptomatic seizure	7.10 (1.40-36.31)	.02	4.02 (0.87-18.70)	.08
Cortical involvement	9.30 (2.60-33.34)	<.001	8.20 (2.22-30.25)	.002
Bleeding volume ≥10 mL	2.1 (0.7-6.9)	.21	NA	NA

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; NA, not applicable.

Figure 3. Bar Plots Showing Predicted and Observed Risk of Poststroke Epilepsy (PSE)



A, Risk after ischemic stroke according to the SeLECT (severity of stroke, large-artery atherosclerosis, early seizure, cortical involvement, and territory of middle cerebral artery) 2.0 score. B, Risk after intracerebral hemorrhage according to the CAVE (cortical involvement, age, bleeding volume, and early seizure) score. The observed risk was calculated only for risk scores with at least 30 patients. Error bars indicate 95% CIs, which were not reported for the predicted risk per CAVE score.

overestimation of the PSE risk in the previous study. Second, the previous study included ischemic strokes without neuroimaging-based proof of cerebral ischemia,[10] as was the case in another retrospective study from Helsinki that reported a cumulative 5-year risk of 9.5% (95% CI, 7.6%-11.4%) after an ischemic stroke.[12] The risk of including stroke mimics is higher without neuroimaging-based confirmation of ischemia.[25] As a consequence, previous studies might

have misclassified some seizures as transient ischemic attacks as the index event, leading to an overestimation of PSE risk. Last, a large Taiwanese retrospective cohort study showed a 5-year cumulative risk of 5.5% after ischemic stroke, which is more in line with our findings.[11] In that study, stroke and seizures were ascertained based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes, without verification of codes, which increases the risk of misclassification. We were able to confirm the relatively low risk of PSE among young adults through a well-defined cohort of patients with ischemic stroke.

We found characteristics that are associated with PSE to be similar to the variables in the SeLECT 2.0 and CAVE risk scores. These risk scores were derived from cohorts including mostly patients older than 65 years. Our study shows that these risk scores are also applicable to young adults, as is evident from the C statistics in our cohort that are similar to the original studies. We found a C statistic of 0.78 (95% CI, 0.71-0.84) for the SeLECT 2.0 score in our young cohort of patients with stroke, compared with the a C statistic of 0.77 (95% CI, 0.71-0.82) in their external validation.[22] The C statistic of the CAVE score in our study was 0.83 (95% CI, 0.76-0.90) compared with 0.81 (95% CI, 0.76-0.86) in the original derivation cohort and 0.69 (95% CI, 0.59-0.78) in an external validation cohort.[23] The CAVE score slightly underestimated the risk of PSE after ICH in our cohort, whereas the SeLECT 2.0 score slightly overestimated the observed risk. There is potential to improve discrimination of the risk scores among young adults. First, electroencephalographic (EEG) asymmetric background activity measured within the first 72 hours after stroke was a factor associated with PSE after ischemic stroke.[26] However, the clinical relevance and added value of EEG outcomes in the SeLECT 2.0 score have yet to be determined.[27] Second, cortical superficial siderosis improved the prediction of the SeLECT and CAVE scores; however, it has not been validated in a young cohort of patients with stroke.[28] Finally, it has been found that the addition of the inflammatory cytokine interleukin-1β improved the predictive value of the SeLECT score in a cohort of patients of all ages with ischemic stroke.[29] This finding could be explained by the release of an inflammatory cascade after neuronal damage.[30] Because trigger factors such as fever and flulike disease are highly prevalent among young patients with ischemic stroke, the addition of this cytokine might be of value, especially in the younger population.[31]

The present study aids neurologists in informing young patients with a stroke about the risk of PSE. In line with previous studies, we found the risk of PSE after an ICH to be higher compared with the risk after an ischemic stroke and that risk was highest in the first years after stroke. This is probably due to an increased risk of (cortical) damage in the brain after a large amount of bleeding and early processes after an ICH, such as edema and inflammation.[32] Although the risk was lower than previously described, the effect of PSE on daily life remains major, especially for young adults who have to deal with that uncertainty for decades to come (eg, not being able to drive a car, difficulties in returning to work, or starting a family). Therefore, it is important to identify which patients are at the highest risk. Our study found that the SeLECT 2.0 and CAVE risk scores can be accurately applied in this relatively young patient group as well.

Apart from informing neurologists and patients, these risk scores may also be important for stratification in future clinical trials about optimal primary and secondary prophylactic treatment of PSE. Antiseizure medication as primary prophylactic treatment for patients with ischemic stroke and ICH is currently not recommended.[25] The PEACH (Prevention of Epileptic Seizures at the Acute Phase of Intracerebral Hemorrhage) trial investigated whether levetiracetam in the acute phase of an ICH reduced the risk of acute symptomatic seizures among patients with a mean age of 77 years.[33] Because an acute symptomatic seizure is a risk factor for remote symptomatic seizures, reducing the risk of acute symptomatic seizures might reduce the risk of PSE. The PEACH trial showed that levetiracetam as the primary prophylactic drug was safe but did not have any association with the occurrence of clinical seizures and did not show differences in functional outcome. In addition, several studies have suggested a reduced risk of PSE among statin users with ischemic stroke or ICH compared with patients who do not take statins, although the evidence is conflicting.[34] Much remains uncertain regarding the prevention of PSE after stroke. Future studies should recruit patients at high risk for which risk scores can support identifying these patients.

Strengths and Limitations

Our study has some strengths. ODYSSEY is a large prospective multicenter study, with only patients with neuroimaging-proven strokes, ensuring a very small risk of misclassifying the index stroke. Second, all the variables to validate existing risk scores were available within the ODYSSEY cohort. Third, we included both patients with ischemic stroke and patients with ICH, whereas most studies included only patients with ischemic strokes.

Nevertheless, there are also some limitations. First, all seizures were self-reported by the patients, which could have resulted in an underestimation of the occurrence of PSE. However, we cross-checked this method and found perfect agreement. Second, the number of PSE cases in our study is relatively low, especially for patients with ICH. This could have hampered the validity of the association with variables. Third, the median NIHSS score in ODYSSEY was relatively low but comparable with the NIHSS score in previous studies of young patients with stroke.[10-12] This indicates that although limited generalization cannot be excluded, this risk seems limited. Our results are not generalizable to a young stroke population that is more severely affected. Fourth, data on the use and type of antiseizure medication were collected only during the first seizure. We therefore lack data to report on how many patients developed drug-resistant seizures according to the current definition of the ILAE.[35]

Conclusions

This cohort study found that the risk of PSE among young adults with ischemic stroke or ICH was relatively low and was highest in the first year after stroke. Existing risk scores may be implemented for patients experiencing a stroke at a young age and can be used to reliably inform young patients about the risk of PSE. Future clinical trials should investigate the optimal primary and secondary prophylaxis for patients at high risk.

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