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Outcomes in Patients With Poststroke Seizures
A Systematic Review and Meta-Analysis

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IMPORTANCE Published data about the impact of poststroke seizures (PSSs) on the outcomes of patients with stroke are inconsistent and have not been systematically evaluated, to the authors' knowledge.

OBJECTIVE To investigate outcomes in people with PSS compared with people without PSS.

DATA SOURCES MEDLINE, Embase, PsycInfo, Cochrane, LILACS, LIPECS, and Web of Science, with years searched from 1951 to January 30, 2023.

STUDY SELECTION Observational studies that reported PSS outcomes.

DATA EXTRACTION AND SYNTHESIS The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was used for abstracting data, and the Joanna Briggs Institute tool was used for risk-of-bias assessment. Data were reported as odds ratio (OR) and standardized mean difference (SMD) with a 95% CI using a random-effects meta-analysis. Publication bias was assessed using funnel plots and the Egger test. Outlier and meta-regression analyses were performed to explore the source of heterogeneity. Data were analyzed from November 2022 to January 2023.

MAIN OUTCOMES AND MEASURES Measured outcomes were mortality, poor functional outcome (modified Rankin scale [mRS] score 3-6), disability (mean mRS score), recurrent stroke, and dementia at patient follow-up.

RESULTS The search yielded 71 eligible articles, including 20 110 patients with PSS and 1 166 085 patients without PSS. Of the participants with PSS, 1967 (9.8%) had early seizures, and 10 605 (52.7%) had late seizures. The risk of bias was high in 5 studies (7.0%), moderate in 35 (49.3%), and low in 31 (43.7%). PSSs were associated with mortality risk (OR, 2.1; 95% CI, 1.8-2.4), poor functional outcome (OR, 2.2; 95% CI, 1.8-2.8), greater disability (SMD, 0.6; 95% CI, 0.4-0.7), and increased dementia risk (OR, 3.1; 95% CI, 1.3-7.7) compared with patients without PSS. In subgroup analyses, early seizures but not late seizures were associated with mortality (OR, 2.4; 95% CI, 1.9-2.9 vs OR, 1.2; 95% CI, 0.8-2.0) and both ischemic and hemorrhagic stroke subtypes were associated with mortality (OR, 2.2; 95% CI, 1.8-2.7 vs OR, 1.4; 95% CI, 1.0-1.8). In addition, early and late seizures (OR, 2.4; 95% CI, 1.6-3.4 vs OR, 2.7; 95% CI, 1.8-4.1) and stroke subtypes were associated with poor outcomes (OR, 2.6; 95% CI, 1.9-3.7 vs OR, 1.9; 95% CI, 1.0-3.6).

CONCLUSIONS AND RELEVANCE Results of this systematic review and meta-analysis suggest that PSSs were associated with significantly increased mortality and severe disability in patients with history of stroke. Unraveling these associations is a high clinical and research priority. Trials of interventions to prevent seizures may be warranted.

Supplemental content

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Cerebrovascular disease is the leading cause of new-onset epilepsy in older adults, accounting for nearly 50% of cases.[1] Stroke mortality rates have decreased owing to advances in hyperacute stroke treatments, including intravenous thrombolysis or endovascular thrombectomy, patient care in a stroke unit, and risk management.[2] As a result, these patients are living longer. The older adult population is expanding as well, resulting in an increase in stroke survivors.[3] As stroke is the most common cause of new-onset epilepsy in older individuals, the burden of poststroke seizures (PSSs) is also likely to expand. PSSs impair quality of life because they require that patients take antiseizure medications with associated cognitive and other adverse effects, carry the risk of injury and sudden death from unexpected seizures, and impose restrictions on work, driving, and other aspects of daily life. Previous studies have indicated that epileptic seizures adversely affect the functional, neurologic, and cognitive outcomes of patients with stroke. However, the published data are inconsistent and have not, to our knowledge, been systematically evaluated. We therefore undertook a comprehensive systematic review and meta-analysis to investigate the association of outcomes, including mortality, poor functional outcome, disability, recurrent stroke, and dementia in patients with PSS compared with patients without PSS.

Key Points

Question Are patients with poststroke seizures (PSSs) at a greater risk of mortality, poor functional outcomes, recurrent stroke, and dementia compared with patients without PSSs?

Findings This systematic review and meta-analysis of 71 studies and 20 110 patients with PSS suggests that PSSs are associated with increased mortality risk, poor functional outcomes, disability, and dementia. This study also identifies limitations in existing PSS research, eg, the lack of common data elements, definitions of relevant outcomes, and reporting standards.

Meaning The findings highlight that PSSs are a public health concern and warrant significant research efforts to prevent poststroke epileptogenesis.

Methods

Search Strategy and Study Selection

We searched MEDLINE, Embase, PsycInfo, Cochrane, LILACS, LIPECS, and Web of Science databases for eligible studies from 1951 until January 30, 2023 (eAppendix in Supplement 1).

Our inclusion criteria included patients with history of stroke (ischemic, hemorrhagic, or both) and those aged 18 years or older presenting with either early or late PSS, which included desired outcome data in patients with and without PSS. We did not impose restrictions based on publication date, language, gender, or ethnicity. We included published patient data irrespective of their race and ethnicity. We, however, did not include information on race and ethnicity in our analyses as these data were not consistently available from all the studies.

Our study exclusion criteria included patients with a prior history of seizures before the index stroke, studies not in full text, studies without outcome data, duplicate publications, narrative or systematic reviews, conference proceedings, dissertations, ongoing research, and preprints. The protocol was preregistered on PROSPERO.[4]

Definition and Outcomes

The definition of seizures and poststroke epilepsy have varied over time. Until 2014, 2 or more seizures were termed poststroke epilepsy; however, after 2014, the International League Against Epilepsy updated the criteria for seizure classification. One seizure after stroke was enough to lead to the diagnosis of poststroke epilepsy.[5] However, considering the lack of uniformity and reporting regarding the classification and definition of early and late-onset seizures, we accepted the definitions reported by individual studies. We provide the breakdown of early and late seizures in eTable 1 in Supplement 1.

Study outcomes were mortality, poor functional outcome (modified Rankin Scale [mRS] score 3-6), disability (mean mRS score), recurrent stroke, and dementia at patient follow-up.

Data Extraction

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guidelines.[6] We used Covidence software for the review and management of articles. We first assessed the titles and abstracts of the retrieved articles for eligibility. We carefully reviewed multiple publications from the same group to prevent duplicate data entry and included the most updated article in our meta-analysis. Seven reviewers (S. Misra, E.E., J.V., L.S.S., L.B.H., E.I.K., and S. Mohidat) independently screened the title and abstract. Subsequently, we screened the full-text articles for inclusion. We resolved conflicts via discussion with the corresponding author (N.K.M.). We extracted the following from each eligible study: first author; publication year; country; study design; sample size; patient age and sex; stroke subtype (ischemic and hemorrhagic); early and late seizures; disability on mRS; follow-up duration; the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes; vascular risk factors; thrombolysis; and hemorrhagic transformation.

Risk-of-Bias (Quality) Assessment

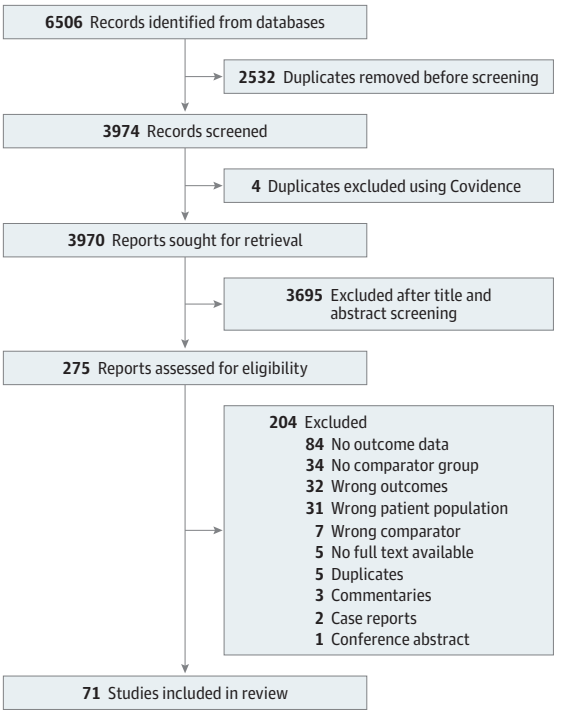
Two authors (S. Misra and E.E.) assessed the studies' methodological quality using the Joanna Briggs Institute tool for cohort studies.[7] The 11-item tool scored each item as No (0 point), Unclear (1 point), and Yes (2 points). Scores ranged from 0 (minimum) to 22 (maximum), and the studies were classified into high risk of bias (0-12), some concerns/moderate risk of bias (13-18), and low risk of bias (19-22).

Statistical Analysis

Dichotomous variables were reported as percentages, and continuous variables as mean and SD. A random-effects meta-analysis was performed if 2 or more studies were pooled. We

determined the association of different outcome measures with the prognosis of PSS using pooled odds ratio (OR) or pooled standardized mean difference (SMD) along with 95% CIs. Heterogeneity was assessed using I^2 and Cochrane Q values and categorized as low (I^2 < 25%), moderate (I^2 = 25%-75%), and high (I^2 > 75%).[8] We used the Sidik-Jonkman estimator for binary outcome data and the restricted maximum-likelihood estimator for continuous outcome data. We applied Knapp-Hartung adjustments to calculate the CI around the pooled effect. Publication bias was assessed using a funnel plot and quantitatively analyzed using the Egger regression test. We conducted a limit meta-analysis[9] to adjust for small-study effects and provided adjusted-pooled OR and SMD. We further explored the source of heterogeneity by conducting meta-regression analysis (predictor variables: risk of bias, publication year, mean age, study design, and follow-up duration), outlier analysis, and sensitivity analysis using the leave-one-out method. Subgroup analyses were performed for stroke subtypes, early and late-onset seizures, and risk of bias. The meta-analysis was conducted using the meta, metafor, and dmetar packages in R, version 4.2.0 (R Project for Statistical Computing). All *P* values were 2-sided, and *P* values < .05 were considered significant. Data were analyzed from November 2022 to January 2023.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram



Results

Our search yielded 71 studies (**Figure 1**).[10-80] There was 1 ambispective,[35] 20 prospective,[13,18,24,28,29,36,42,43,45,47,50,53,54,56,57,63,65-67,75] 47 retrospective[10-12,14,16,17,19-23,25-27,30-34,37-39,41,44,46,48,49,51,52,55,58-62,64,68-74,76-78,80] cohort studies, and 3 case-control[15,40,79] studies. All studies were published in English, and we identified no studies in other languages. The follow-up duration ranged from hospital discharge to 26 years (eTable 2 in Supplement 1). The studies included patients from 31 countries (eFigure 1 in Supplement 1).

The studies included 20 110 patients with PSS and 1 166 085 patients without PSS. The articles included 1967 patients (9.8%) with early seizures and 10 605 patients (52.7%) with late seizures after stroke; 7538 seizures (37.5%) were not classified as early or late. PSS were diagnosed according to clinical or medical chart data in 59 studies[10-13,15-20,22-32,34,36-45,47,49-54,56-59,61-67,69-73,75,76,78,79] and using the *ICD-10* codes in 12 studies[14,21,33,35,46,48,55,60,68,74,77,80] (including 15 033 patients [74.8%]). Patients with PSS had a significantly higher history of ischemic heart disease (OR, 1.3; 95% CI, 1.1-1.6), prior cerebrovascular disease (OR, 1.3; 95% CI, 1.0-1.6), atrial fibrillation (OR, 1.2; 95% CI, 1.1-1.4), and the presence of hemorrhagic transformation (OR, 2.2; 95% CI, 1.6-3.0) than patients without PSS (eTable 3 in Supplement 1).

Risk-of-Bias (Quality) Assessment

Five studies (7.0%)[17,19,40,49,64] had a high risk of bias, 35 studies (49.3%)[10,12-15,22,23,25,27,29,31,33,34,36-38,42,47,48,50-53,55,57,66,68,69,72-75,77,79,80] presented a moderate risk of bias, and 31 studies (43.7%)[12,16,18,20,21,24,26,28,30,32,35,39,41,43-46,54,56,58-63,65,67,70,71,76,78] had a low risk of bias (eTable 4 in Supplement 1).

Statistical analyses were appropriate in 44 studies (62%).[11,13,14,16,18,20,21,24-30,32-35,38,39,43,46-48,50,53,54,56,58-60,62,63,65,67-69,71,72,74,76-78,80] Confounding factors were identified in 58 studies (81.7%)[11,13-16,18,20,21,24-36,38,39,41,43-50,52-63,65-72,74-78,80] and were adjusted in the statistical analysis in 53 studies (74.6%).[11,13-16,18,20,21,24-29,32-35,38,39,41,43-50,52-63,65,67-72,74,76-78,80] Only 37 studies (52.1%)[10-12,16,19,21,22,25,28-33,35,37,41,42,44,46,50,52,53,56,59,64,68,70-78,80] provided complete follow-up data. The outcomes were measured validly and reliably in 53 studies (74.6%).[10,11,13,14,16-18,20-24,26,27,29,32,34,37-41,43-46,49-57,59,61-64,67-73,75-80]

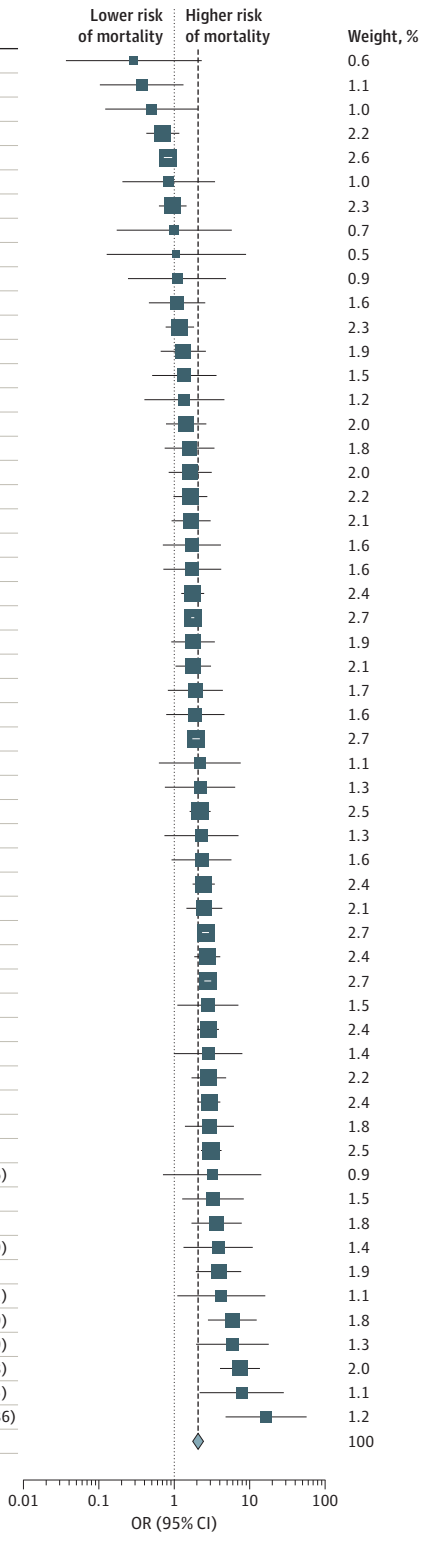
Mortality (mRS 6)

In 57 studies,[10-66] patients with PSS had approximately double the risk of death (OR, 2.1; 95% CI, 1.8 to 2.4; I^2 = 86%) with substantial heterogeneity (**Figure 2**). The funnel plot was symmetric, and no publication bias was observed (Egger *P* value = 0.4) (eFigure 2A in Supplement 1). The association remained significant when adjusting for the small-study effect using limit meta-analysis (**Table 1**). We identified 8 outlier studies using the outlier analysis,[11,13,14,16,48,62,64,66] and the significant association persisted after removing these studies with reduced heterogeneity (I^2 = 59%) (Table 1). We conducted a sensitivity analysis using the leave-one-out method. We observed that the overall effect size remained unchanged, and heterogeneity reduced to I^2 = 76% after removing the study by Mullen et al[14] (eFigure 3 in Supplement 1). Meta-regression analyses showed that follow-up duration accounted for 5.5% heterogeneity, but this was not statistically significant.

Figure 2. Association of Poststroke Seizures With Mortality

Source	Participants, No.	OR (95% CI)	Weight, %
Lin et al,[10] 2008	137	0.29 (0.04-2.31)	0.6
Brondani et al,[11] 2020	153	0.37 (0.10-1.33)	1.1
Brondani et al,[12] 2017	36	0.50 (0.12-2.06)	1.0
De Herdt et al,[13] 2011	508	0.71 (0.43-1.17)	2.2
Mullen et al,[14] 2013	13033	0.83 (0.73-0.94)	2.6
Devuyst et al,[15] 2003	111	0.84 (0.21-3.47)	1.0
Claessens et al,[16] 2017	747	0.96 (0.63-1.46)	2.3
Mohamed et al,[17] 2023	90	1.00 (0.17-5.79)	0.7
Turaga et al,[18] 2021	279	1.07 (0.13-8.96)	0.5
Franco et al,[19] 2022	56	1.09 (0.24-4.86)	0.9
Ba et al,[20] 2021	1638	1.09 (0.46-2.58)	1.6
Huttunen et al,[21] 2017	779	1.19 (0.77-1.83)	2.3
Ahangar et al,[22] 2008	243	1.32 (0.66-2.63)	1.9
Scoppettuolo et al,[23] 2019	81	1.36 (0.51-3.63)	1.5
van Tuijl et al,[24] 2018	444	1.36 (0.40-4.63)	1.2
Knake et al,[25] 2006	166	1.44 (0.78-2.66)	2.0
Tabaeizadeh et al,[26] 2020	143	1.60 (0.75-3.41)	1.8
Jung et al,[27] 2012	789	1.63 (0.84-3.14)	2.0
Arntz et al,[28] 2015	631	1.64 (0.97-2.74)	2.2
Merlino et al,[29] 2019	635	1.67 (0.92-3.04)	2.1
Alemany et al,[30] 2021	344	1.71 (0.71-4.16)	1.6
Chen et al,[31] 2017	348	1.73 (0.72-4.20)	1.6
Hamidou et al,[32] 2013	4358	1.76 (1.24-2.49)	2.4
Zelano et al,[33] 2016	104000	1.76 (1.68-1.84)	2.7
De Marchis et al,[34] 2016	308	1.78 (0.91-3.45)	1.9
Lahti et al,[35] 2021	611	1.79 (1.04-3.07)	2.1
Aiwansoba and Chukwuyem,[36] 2014	251	1.90 (0.82-4.41)	1.7
Zelano et al,[37] 2015	91	1.90 (0.78-4.64)	1.6
Zöllner et al,[38] 2020	135117	1.95 (1.74-2.19)	2.7
Anadani et al,[39] 2019	459	2.18 (0.63-7.61)	1.1
Mushannen et al,[40] 2021	1009	2.20 (0.75-6.42)	1.3
Huang et al,[41] 2014	10261	2.20 (1.60-3.04)	2.5
Shinton et al,[42] 1988	230	2.30 (0.74-7.11)	1.3
Beghi et al,[43] 2011	714	2.30 (0.92-5.73)	1.6
Burneo et al,[44] 2010	5027	2.46 (1.75-3.45)	2.4
Procaccianti et al,[45] 2012	2053	2.51 (1.45-4.33)	2.1
Harnod et al,[46] 2019	13603	2.60 (2.34-2.88)	2.7
Law et al,[47] 2020	2101	2.74 (1.84-4.07)	2.4
Bateman et al,[48] 2007	821294	2.78 (2.50-3.09)	2.7
Alsaad et al,[49] 2022	665	2.79 (1.10-7.09)	1.5
Bladin et al,[50] 2000	1897	2.81 (2.01-3.91)	2.4
Couillard et al,[51] 2012	397	2.81 (0.99-8.00)	1.4
Leung et al,[52] 2017	2532	2.87 (1.69-4.87)	2.2
Li et al,[53] 2015	3216	2.90 (2.06-4.08)	2.4
Xu et al,[54] 2017	3139	2.93 (1.39-6.18)	1.8
Szaflarski et al,[55] 2008	6044	3.09 (2.26-4.23)	2.5
Lossius et al,[56] 2005	484	3.18 (0.71-14.26)	0.9
Dávalos et al,[57] 1988	412	3.26 (1.27-8.35)	1.5
Arboix et al,[58] 1997	1220	3.65 (1.69-7.85)	1.8
Matsubara et al,[59] 2018	228	3.82 (1.33-10.99)	1.4
Labovitz et al,[60] 2001	904	3.86 (1.93-7.72)	1.9
Liao et al,[61] 2019	297	4.20 (1.10-16.11)	1.1
Alme et al,[62] 2017	2593	5.89 (2.80-12.39)	1.8
Zhang et al,[63] 2022	80	5.90 (1.95-17.89)	1.3
Panitchote and Tiamkao,[64] 2010	372	7.44 (4.04-13.68)	2.0
Shehta et al,[65] 2018	150	7.84 (2.17-28.35)	1.1
Guekht et al,[66] 2015	100	16.50 (4.79-56.86)	1.2
Random effects model		2.07 (1.76-2.44)	100

Heterogeneity: : I^2 = 86%; 95% CI, 83-89; τ^2 = 0.3026; P < .01



The vertical dashed line represents the overall meta-analyzed measure of effect, ie, the pooled odds ratio.

A subgroup analysis based on seizure subtypes identified that early seizures were associated with an increased mortality risk but not late seizures (OR, 2.4; 95% CI, 1.9-2.9 vs OR, 1.2; 95% CI, 0.8-2.0) (eFigure 4 in Supplement 1). The findings were the same in patients with ischemic and hemorrhagic stroke who subsequently developed seizures; both subtypes were associated with mortality (OR, 2.2; 95% CI, 1.8-2.7 vs OR, 1.4; 95% CI, 1.0-1.8) (eFigure 5 in Supplement 1). We also

Table 1. Association of Mortality With Poststroke Seizures

Serial No.	Outcome measures	PSS (event/total)	No PSS (event/total)	No. of studies	OR (95% CI)	I^2, %
Main analysis						
1	Primary analysis					
	PSS vs no PSS	7556/17 252	181 227/1 130 356	57	2.07 (1.76-2.44)[a]	86
	Limit analysis by adjusting for small study effect					
	PSS vs no PSS	7556/17 252	181 227/1 130 356	57	2.19 (1.71-2.82)[a]	86
	Outlier analysis (by removing eight outlier studies)					
	PSS vs no PSS	6560/13 789	70 779/295 019	49	2.11 (1.87-2.39)[a]	59
Subgroup analyses						
2	Seizure types					
	Early seizure	474/1524	7862/42 910	30	2.35 (1.88-2.92)[a]	53
	Late seizure	4461/8136	41 275/99 884	9	1.24 (0.76-2.00)	58
3	Risk of bias					
	Low	1541/3101	12 402/48 238	26	2.18 (1.72-2.77)[a]	63
	Moderate	5969/13 951	168 753/1 080 126	26	1.89 (1.47-2.43)[a]	91
	High	46/200	122/1992	5	2.70 (0.97-7.57)	64
4	*ICD-10* codes					
	No *ICD-10* codes	1320/4319	26 499/183 021	49	2.09 (1.74-2.52)[a]	60
	ICD-10 codes	6236/12 933	154 778/947 335	8	1.97 (1.28-3.03)[a]	97
5	Stroke subtypes					
	Ischemic stroke	1138/4227	93 426/879 801	23	2.23 (1.82-2.74)[a]	76
	Hemorrhagic stroke	817/2548	40 659/123 464	15	1.35 (1.01-1.82)[a]	85
	Early and late seizures after ischemic stroke					
	Early PISS vs no PISS	172/564	4090/22 828	12	2.41 (1.81-3.20)[a]	34
	Late PISS vs no PISS	32/49	404/528	2	0.66 (0.27-1.61)	0
	Early and late seizures after hemorrhagic stroke					
	Early PHSS vs no PHSS	95/251	938/3328	4	1.55 (0.71-3.40)	86
	Late PHSS vs no PHSS	143/278	908/1827	3	1.23 (0.88-1.73)	34
6	Status epilepticus					
	PSSE vs no PSSE	589/1879	106 786/821 302	7	2.54 (1.67-3.84)[a]	34

Abbreviations: *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition*; OR, odds ratio; PHSS, posthemorrhagic stroke seizure; PISS, postischemic stroke seizure; PSS, poststroke seizure; PSSE, poststroke status epilepticus.

[a] $P < .05$.

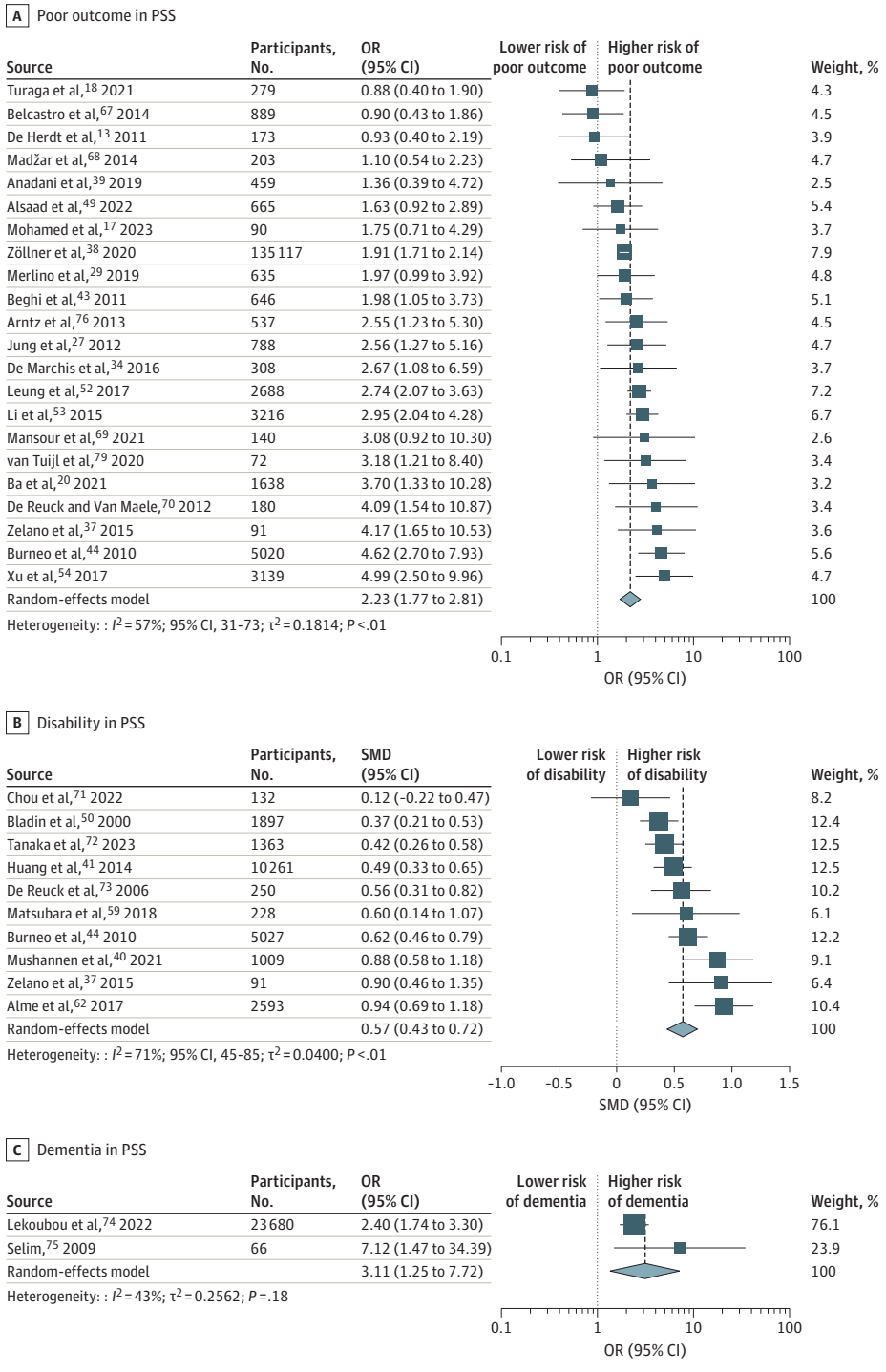
observed that early seizures after ischemic stroke were associated with mortality but not late seizures (OR, 2.4; 95% CI, 1.8-3.2 vs OR, 0.7; 95% CI, 0.3-1.6) (eFigure 6A in Supplement 1). We did not identify any significant association between early or late seizures and increased mortality risk after hemorrhagic stroke (eFigure 6B in Supplement 1). Additionally, the subgroup of patients with poststroke status epilepticus presented with increased mortality (OR, 2.5; 95% CI, 1.7-3.8) (eFigure 7 in Supplement 1 and Table 1). There was no significant difference in the subgroups for risk of bias.

Poor Functional Outcome (mRS 3-6)

In 22 studies, patients with PSS had poorer outcomes than those without PSS (OR, 2.2; 95% CI, 1.8-2.8; I^2 = 57%) (**Figure 3**A).[13,17,18,20,27,29,34,37-39,43,44,49,52-54,67-70,76,79] The funnel plot was symmetric, and no publication bias was observed using the Egger test (eFigure 2B in Supplement 1). There were no variations in the pooled effect size after conducting a limit meta-analysis and the leave-one-out sensitivity analysis (eFigure 8 in Supplement 1). Meta-regression could not identify any predictor that significantly contributed to increased heterogeneity.

We conducted subgroup analyses based on seizure subtypes (eFigure 9 in Supplement 1) and stroke subtypes (eFigure 10 in Supplement 1). We observed that early and late-onset seizures after stroke (OR, 2.4; 95% CI, 1.6-3.4 vs OR, 2.7; 95% CI, 1.8-4.1) and seizures after ischemic and hemorrhagic stroke (OR, 2.6; 95% CI, 1.9-3.7 vs OR, 1.9; 95% CI, 1.0-3.6) were significantly associated with poor outcomes. In patients with ischemic stroke, early seizures were associated with poor outcomes (eFigure 11A in Supplement 1), whereas neither early nor late seizures were associated with poor outcomes after hemorrhagic stroke (eFigure 11B in Supplement 1 and **Table 2**). A significant difference in heterogeneity was observed after performing a subgroup analysis by risk of bias (low, I^2 = 70%; moderate, I^2 = 50%; high, I^2 = 0%; P for subgroup differences =.02).

Figure 3. Association of Poststroke Seizures With Poor Functional Outcome, Disability, and Dementia



Association of poststroke seizures with poor functional outcome (A), disability (B), and dementia (C).

Disability (Mean mRS Score)

The mean mRS disability at follow-up was significantly higher in 10 studies[37,40,41,44,50,59,62,71-73] in patients with PSS than in patients without PSS (SMD, 0.6; 95% CI, 0.4-0.7; I^2 = 71%) (Figure 3B). No publication bias was detected (eFigure 2C in Supplement 1), and findings remained consistent in a sensitivity analysis using the leave-one-out method (eFigure 12 in Supplement 1). Meta-regression identified that age significantly accounted for 45.1% heterogeneity (estimate, −0.02; 95% CI, −0.04 to −0.003; P = .03). In subgroup analyses, early and late seizures were associated with higher disability (eFigure 13 in Supplement 1). Seizures after ischemic stroke were associated with a higher disability but not after hemorrhagic stroke (eFigure 14 in Supplement 1). No significant difference

Table 2. Association of Poor Outcome (Modified Rankin Scale Score 3-6) With Poststroke Seizures

Serial No.	Outcome measures	PSS (event/total)	No PSS (event/total)	No. of studies	OR (95% CI)	I^2, %
Main analysis						
1	Primary analysis					
	PSS vs no PSS	2167/2952	96 967/154 021	22	2.23 (1.77-2.81)[a]	57
	Limit analysis by adjusting for small study effect					
	PSS vs no PSS	2167/2952	96 967/154 021	22	2.25 (1.43-3.53)[a]	57
Subgroup analyses						
2	Seizure types					
	Early seizure	276/424	4646/10 468	11	2.36 (1.64-3.39)[a]	43
	Late seizure	154/273	1403/3940	6	2.73 (1.83-4.09)[a]	0
3	Risk of bias					
	Low	304/436	6607/12 351	9	2.35 (1.38-4)[a]	70
	Moderate	1822/2435	90 089/140 996	11	2.25 (1.71-2.96)[a]	50
	High	41/81	271/674	2	1.66 (1.09-2.53)[a]	0
4	*ICD-10* codes					
	No *ICD-10* codes	2143/2912	96 873/153 858	21	2.31 (1.84-2.91)[a]	56
	ICD-10 codes	24/40	94/163	1	1.10 (0.54-2.23)	NA
5	Stroke subtypes					
	PISS vs no PISS	1788/2383	93 644/147 608	12	2.60 (1.85-3.67)[a]	64
	PHSS vs no PHSS	218/302	2397/4494	6	1.91 (1-3.63)[a]	42
	Early and late seizures after ischemic stroke					
	Early PISS vs no PISS	279/439	4146/9266	8	2.97 (2.05-4.31)[a]	11
	Late PISS vs no PISS	28/41	462/901	2	2.27 (0-4048.73)	64
	Early and late seizures after hemorrhagic stroke					
	Early PHSS vs no PHSS	12/17	41/74	1	1.93 (0.62-6.04)	NA
	Late PHSS vs no PHSS	0/10	5/29	1	0.21 (0.01-4.19)	NA

Abbreviations: *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition*; NA, not applicable; OR, odds ratio; PHSS, posthemorrhagic stroke seizure; PISS, postischemic stroke seizure; PSS, poststroke seizure.

[a] $P < .05$.

in heterogeneity was observed when stratified by risk of bias (eTable 5 in Supplement 1).

Recurrent Stroke and Dementia

Five studies[49,71,77,78,80] found no association of recurrent stroke with PSS (OR, 1.3; 95% CI, 0.6-3.0) (eFigure 15 in Supplement 1). Two studies[74,75] identified an increased dementia risk in patients with PSS (OR, 3.1; 95% CI, 1.3-7.7) (Figure 3c) (eTable 6 in Supplement 1).

Discussion

This was a comprehensive analysis of PSS outcome data obtained from 71 studies published through January 2023. In this systematic review and meta-analysis, results suggest that in patients with history of stroke, PSSs were associated with significantly increased risk of mortality, poor functional outcomes, higher disability, and increased risk of dementia compared with patients without PSS.

The main reason for death in PSS is known to be cardiovascular death, not seizure related.[81] However, chronic epilepsy is associated with abnormal cardiac functions, including greater cardiovascular risk.[82] The increased cardiovascular risk has been attributed to the interactions of antiseizure medications or cardiopathies due to chronic seizures, ie, "epileptic heart."[83-85]

On the contrary, stroke severity is strongly related to early seizures; therefore, the mortality rate from the stroke itself may be higher in the early seizure group.[86] We conducted subgroup analyses to determine outcomes in patients with early and late seizures. We found that patients with early seizures had a greater mortality risk. Because the studies did not consistently report stroke severity and raw data for cardiovascular risks, we could not test the interaction of these variables with PSS on influencing mortality risk.

We found that patients with late seizures also had a greater mortality risk; however, the CI for this subgroup failed to reach statistical significance. We speculate that this was probably because of a smaller sample size or other unknown mechanisms, eg, bias in the data (Table 1). We, therefore, classified patients based on the risk of bias in the included studies. We found that patients in the studies with high risk of bias were at statistically significant risk of poor outcomes and disability. Even though the point estimate suggested greater mortality risk in this subgroup, the 95% CI failed to reach statistical

significance (Table 1). In contrast, patients in the studies with a low or moderate risk of bias had a significantly increased risk of mortality, poor outcome, and disability.

We conducted additional subgroup analyses examining outcomes in patients with ischemic and hemorrhagic strokes separately. We found that early but not late seizures were associated with mortality in the ischemic stroke subtype. We found no association of mortality for hemorrhagic stroke subtype with any seizure type (Table 1). Mortality in patients with stroke and late seizures may be determined by age, stroke severity, and vascular risk factors rather than by seizure development. Both seizure types and stroke subtypes were associated with poor outcomes. Early seizures after ischemic stroke subtype were associated with poor outcomes but not late seizures. Neither early nor late seizures were associated with poor outcomes in patients with the hemorrhagic stroke subtype (Table 2).

In addition to examining mortality and functional outcomes in patients with PSS, we decided to examine a priori the dementia risk and the risk of recurrent stroke in patients with PSS. We observed a 3-fold increased dementia risk in patients with PSS than in those without PSS (Figure 3C). This finding, however, was based on data pooled from only 2 studies (45 patients with PSS and dementia[74] and 5 patients with PSS and dementia[75]). Patients with cerebrovascular disease are at an increased risk of vascular cognitive impairment and dementia.[87] Chronic seizure activity may contribute to the dementia risk.[88,89] To characterize the PSS-associated cognitive impairment and dementia as outcomes in these patients, longitudinally collected data are needed.

Patients with PSS may be at greater risk of recurrent stroke. This could be due to poor compliance with secondary stroke prevention medications and interaction of antiseizure medications with efficacy of secondary stroke prevention drugs. Risk factor management is crucial in patients with PSS to reduce the frequency and severity of seizures.[90] Although due to a limited number of studies we found no association between recurrent stroke and PSS, some data indicate that people with epilepsy have a higher prevalence of cardiovascular risk factors, independent of stroke.[91] Thus, patients with PSS may be at higher risk of recurrent stroke, which requires close monitoring of vascular risk factors in patients with PSS.

Our systematic review identified that 15 033 patients with PSS (74.8%) from 12 studies were diagnosed using *ICD-10* codes. *ICD-10* code–based research is prone to misclassification and may lead to errors in hospital admissions.[92] However, when we stratified the data based on *ICD-10* and no *ICD-10* codes, the results were consistent for studies with no *ICD-10* codes (Table 1, Table 2, and eTables 5 and 6 in Supplement 1).

Mechanisms of early and late seizures are very different and, not surprisingly, have very different clinical significance[93]; therefore, early and late seizures must be treated separately in future studies, including meta-analyses. Early seizures reflect acute reversible metabolic defects that might be life-threatening. In contrast, late seizures reflect structural changes that require time to develop and are not due to life-threatening underlying pathology.[94] Also, efforts to reduce the mortality associated with early seizures involve efforts to prevent or correct acute metabolic defects than efforts to prevent seizures, which are just a symptom of the problem. Collaborative efforts to predict and prevent the structural and associated biological changes that lead to late seizures (ie, poststroke epileptogenesis and ictogenesis) can address the disability and mortality of these events.[95]

Strengths and Limitations

The strengths of our meta-analysis include its robust methodology on a large international sample of patients with PSS. This is the largest meta-analysis to date, to our knowledge, which allowed us to assess outcomes in relation to seizure subtypes, stroke subtypes, and study quality. We collected raw data and adjusted for multiple confounders using meta-regression analyses. We rigorously tested for publication bias. Furthermore, we conducted a limit analysis to account for bias due to small-study effects and provided adjusted estimates for each outcome measure. Our methods allowed us to include a larger number of studies (N = 71 vs N = 10[96] and N = 13[97]) and avoid the confounder imbalance,[98] which can be introduced by pooling adjusted ORs as was done in the 2 previous systematic reviews.[96,97] We compared and contrasted our systematic review with these 2 previous systematic reviews in eTable 7 in Supplement 1.[96,97]

Despite adopting robust methods, we observed several challenges in pooling data in this meta-analysis. eTable 8 in Supplement 1 contains a list of challenges and our recommendations to tackle them.

The results of our meta-analysis must be considered in light of the following limitations. First, there are scarce data from prospective studies; most data came from retrospective cohorts. Second, few studies did not provide outcome data segregated by seizure type and stroke subtype. Third, due to a lack of consistent reporting of National Institutes of Health Stroke Scale data, we could not examine the effect of stroke severity on clinical outcomes after PSS, which is very likely a potential confounder. Fourth, we could not determine the effect of concurrent medications. Fifth, data on the cause of mortality were unavailable. Sixth, the authors of some studies used disparate definitions for seizures that might introduce some misclassification in our subgroup analyses (eTable 1 in Supplement 1). Seventh, outcomes were measured at variable time points ranging from hospital discharge to 26 years after stroke (eTable 2 in Supplement 1). We suggest that within-study comparisons should be valid if follow-up was the same for patients with and without PSS, but absolute values are not readily interpretable. An individual patient data analysis project is under way in which we will collect original, raw data from eligible studies and conduct meta-analysis by standardizing the common data elements, patient outcomes, and the duration of patient follow-up.[99]

Conclusions

Results of this systematic review and meta-analysis suggest that PSSs were associated with a doubled risk of death and severe disability and were thus an important burden of disease.

PSS prevention is a high clinical and research priority. We also observed a significant variation in reporting standards in the published literature and propose future directions for PSS research. Collaborative scientific efforts should be directed toward addressing these challenges.[95] The role of stroke severity and lesion location or volume also requires further investigation.

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