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The associations of post-stroke delirium with outcomes: a systematic review and meta-analysis

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Abstract

Background Published data on whether post-stroke delirium (PSD) is an independent predictor of outcomes in patients with acute stroke are inconsistent and have not yet been synthesized and quantified via meta-analyses.

Methods This systematic review and meta-analysis followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The study protocol involved a search of the PubMed, Embase, PsycINFO, and Medline databases from 1946 to November 1, 2023, of which prospective observational and case–control studies were included. The quality of the included studies was rated using the Newcastle Ottawa Scale. Pooled effect estimates calculated using a random-effects model were expressed as the odds ratios (ORs), hazard ratios (HRs), and standardized mean differences (SMDs) with 95% confidence intervals (CIs). The protocol was registered in PROSPERO (CRD42023472551).

Results The search yielded 39 eligible articles comprising 3295 and 9643 patients with and without PSD, respectively. Thirty studies were high quality, while 9 had moderate quality. The primary analyses, adequately adjusting for predefined confounders, showed that PSD was significantly associated with mortality risk (average follow-up of 19.50 months; OR, 3.47; 95% CI, 2.35–5.12; I^2, 26.0%) and poor neurological function (average follow-up of 21.75 months; OR, 3.62; 95% CI, 2.15–6.09; I^2, 0). Secondary analyses, with or without inadequate adjustment, showed that PSD was significantly associated with prolonged hospital length of stay, increased risk of institutionalization, poor cognitive outcomes, and quality of life after discharge.

Conclusions This systematic review and meta-analysis provides evidence that PSD was independently associated with mortality and poor neurological function after controlling for pre-specified confounders. The prevention of PSD remains a high clinical and research priority.

Keywords Delirium, Post-stroke, Outcomes, Meta-analysis

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Background

Delirium, a neuropsychiatric syndrome characterized by acute and fluctuating disturbances in consciousness and cognition, is the most common complication in elderly hospitalized patients [1, 2]. Numerous studies have shown that delirium is associated with increased morbidity and mortality, placing a considerable burden on healthcare services and expenditures [3, 4].

Delirium is usually associated with acute physical stressors, such as acute stroke [5]. Previous meta-analyses have shown that post-stroke delirium (PSD) affects approximately 25% of acute stroke patients [6] and is associated with higher mortality, longer hospitalization, and dependency post-discharge [7]. However, the potential fragility of PSD-outcomes association may depend on the choice of confounders included in adjusted models [3, 4]. To date, no meta-analyses have yet examined whether PSD is an independent predictor of adverse outcomes. Further, while functional and cognitive outcomes, as well as quality of life in patients with PSD, have attracted increasing attention [7], quantitative estimates of the associations between PSD and these outcomes have not yet been synthesized via meta-analysis.

These above-mentioned issues preclude drawing reliable conclusions regarding the prognosis of PSD, which may allow clinicians, policymakers, and researchers to pay more attention to PSD. Therefore, in the present study, we systematically reviewed and summarized data on the risk of various outcomes (mortality, length of stay [LOS], institutionalization, functional and cognitive outcomes, and quality of life) after delirium in acute stroke patients. Our primary objective was to explore the association between PSD and adverse outcomes, while controlling for important confounders.

Methods

Data sources and study selection

This study followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [8] (Additional file 1) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [9] (Additional file 2) reporting guidelines for systematic reviews and meta-analyses. The protocol has been registered in PROSPERO (CRD42023472551) [10].

The following databases were searched for eligible studies: PubMed from 2006 to 2023, Embase from 1988 to 2023, PsycINFO from 1968 to 2023, and Medline from 1946 to 2023. The search keywords for delirium were combined with stroke-specific and outcome keywords (Additional file 3: eAppendix 1). The primary study outcome was the association between PSD and various outcomes (mortality, hospital LoS, institutionalization, functional outcomes, cognitive outcomes, and QoL) after adequate adjustment for important confounders during the follow-up period. The secondary outcome was the association between PSD and each outcome based on inadequate adjustment and non-adjustment.

Research articles examining the outcome of delirium in patients with acute stroke were included if they met the following criteria: (1) prospective observational cohort studies of acute stroke patients aged 18 years or older, and (2) studies using a definition of stroke based on the World Health Organization definition, including ischemic, hemorrhagic, transient ischemic attack, or subarachnoid hemorrhage [11]. Acute stroke was defined as the period from ictus to 6 weeks post-event [6]; (3) delirium was prospectively identified using any edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [12] or the diagnostic tool validated against DSM, e.g., confusion assessment method (CAM) [13], confusion assessment method for the intensive care unit (CAM-ICU) [14], and intensive care delirium screening checklist (ICDSC) [15], Delirium Rating Scale (DRS) [16], DRS-R-98 [17], Delirium Observation Screening (DOS) [18], and 4A's Test (4AT) [19]; (4) at least one of the following outcomes was reported: mortality, hospital LoS, institutionalization, neurological functional outcome, cognitive outcome and quality of life. Specifically, institutionalization was defined as admission to a care or nursing home following hospital discharge; neurological functional outcome was required to be measured after hospital discharge by the modified Rankin Scale score (mRS) [20]; the cognitive outcome was required to be measured after hospital discharge using validated cognition assessment scales, such as the Mini-Metal State Examination (MMSE) [21] or the Montreal Cognitive Assessment (MoCA) [22] score; and the quality of life was required to be measured using validated scales, such as the Barthel Index (BI) [23], the Functional Independence Measure (FIM) [24], and the Instrumental Activities of Daily Living (ADL) Scale [25]. (5) The manuscript was written in English. The exclusion criteria were: studies with designs other than case–control, case studies or case series, studies without available raw data, and duplicate publications.

Data extraction

Three reviewers (H. W. H., J. M. L., and W. J. Y.) independently extracted data from each study. Initial data extraction was performed on 1 November 2023. The following information was recorded: study characteristics (country, publication year, setting, sample size, and delirium assessment tools), patient characteristics (age, sex, stroke subtype, stroke severity, comorbidity, baseline cognitive impairment, and baseline institutionalization), and any reported endpoints. For longitudinal studies, data from

the last follow-up for each outcome were selected for our analysis. Disagreements were resolved through discussion with the corresponding author (G. B. Z.).

Quality assessment

The quality of the included studies was rated using the modified Newcastle–Ottawa Scale [26] (Additional file 3: eAppendix 2 and 3), which contains separate quality assessment instruments for cohort studies [27] (Additional file 3: eAppendix 2)and case–control(Additional file 3: eAppendix 3). The NOS comprises three sections: study population selection, comparability, and outcome measures. A maximum of nine scores was awarded to each study: four for selection, three for outcome, and two for comparability. The specific items and their scores are detailed in Additional file 3: eAppendix 2. Points were scored for each "yes" answer. Given the sum of the scores for each individual item, studies with a score of 7–9 points were classified as high quality, studies with scores of 3–5 points were classified as moderate quality, and studies with scores of less than 2 were classified as low quality.

Statistical analysis

All statistical analyses were conducted using the Comprehensive Meta-Analysis software (version 3.0). Dichotomous variables are presented as percentages, while continuous variables are presented as means with standard deviations. We determined the association between different outcome measures and PSD using pooled odds ratios (ORs), hazard ratios (HRs), and pooled standardized mean differences (SMD) with 95% confidence intervals (CIs). In keeping with previous studies [3, 4], our primary analysis included only studies adjusted for age and comorbidity. Given that the severity of stroke has been reported to be a predictor of post-stroke outcomes and PSD [6, 28], it was also included in our list of required adjusted variables for primary analysis. Control for confounding factors was determined to be inadequate if the aforementioned key variables were not included in the final adjusted model [29, 30]. Therefore, we further conducted secondary and tertiary analyses, in which we included estimates of associations that were inadequately adjusted and unadjusted. A random-effects meta-analysis was performed when two or more studies were pooled. Heterogeneity was measured using the chi-squared Cochran's Q-test and I^2 statistics; $I^2 > 50\%$ indicated significant heterogeneity [31]. We further conducted a meta-regression to explore whether the a priori defined covariates explained the source of heterogeneity. Subgroup analyses were performed for stroke subtypes (Table 1). Publication bias was assessed by inspecting funnel plots, Egger's test, and Duval and Tweedie's trim-and-fill method [32]. Sensitivity analyses were performed to examine: (1) whether the pooled estimates between PSD and mortality were more conservative after excluding studies that reported hospitalized mortality, (2) whether the strength of the association between PSD and hospital LoS was affected after excluding studies that involved incident cases of ICU admission, (3) whether the association between PSD and institutionalization was affected after excluding studies that included incident cases who had resided in an institution at baseline, and (4) whether the association between PSD and cognitive outcome was affected after excluding studies that included patients with cognitive impairment at baseline. Outliers were identified if the CI did not overlap with that of the pooled effect [33]. All tests were 2-sided. Statistical significance was set at $P < 0.05$.

Results

Study selection and study characteristics

Initially, 3682 articles were identified through the primary search. Following the removal of duplicate articles, 1178 articles were reviewed in the title and abstract screening stage. Subsequently, 66 articles underwent full-text screening, of which 27 were excluded as they were deemed ineligible for inclusion. Ultimately, 39 studies were eligible for inclusion in the analysis (Fig. 1) [34–72]. The main characteristics of the selected studies are summarized in Table 2. There were 35 prospective cohort [34–42, 44–69] and 4 case–control studies [43, 70–72]. The sample size ranged from 50 to 1487. The follow-up period ranged from hospital discharge to 5 years.

The studies included 3295 (25.5%) patients with PSD and 9643 patients without PSD. For PSD screening, 16 studies [39–42, 46, 48, 51–53, 57, 58, 62, 64, 65, 70] used the CAM, 11 [45, 47, 50, 54, 55, 57, 58, 61, 62, 67, 69] used the CAM-ICU, while 25 [34–41, 44–49, 54–60, 62, 63, 69, 71] used DSM. Ten studies [41, 42, 47, 57, 59–62, 67, 69] used multivariate approaches to adjust for the association between PSD and the outcomes. Three studies provided separate data on the risk of hemorrhagic stroke [47, 50, 59], 8 provided separate risk data for ischemic stroke[44, 49, 51, 53–55, 62, 65], and 28 provided risk data for hemorrhagic and ischemic stroke[34–43, 45, 46, 48, 52, 56–58, 60, 61, 63, 64, 66–72].

Quality assessment

According to the NOS score, 31 studies [35, 37, 39–48, 50–55, 57–63, 67–72] were rated as high-quality and eight [34, 36, 38, 49, 56, 64–66] as moderate-quality (Additional file 3: Table S1). Of the 35 cohort studies, the majority were observational cohort studies ($n = 27$) considered to have an overall high quality [73], while the remaining cohort studies ($n = 8$) were only of moderate

Table 1 Unadjusted meta-analysis of outcomes for post-stroke delirium

Outcomes	No. of studies	Pooled effect size (95% CI)	*p*-value	*Q*-value, *p*-value, I^2 (%)	*p*-value for Egger's regression
Mortality					
Main analysis, OR	26	4.69 (3.55 to 6.20)	< **0.001**	65.47, < **0.001**, 61.82	0.82
Subgroup analyses					
ICH	1	29.67 (7.19 to 1222.33)	< **0.001**	0.00, 1.000, 0.00	
IS	5	5.45 (4.39 to 6.77)	< **0.001**	2.41, 0.661, 0.00	
LOS					
Main analysis, SMD	20	1.21 (0.54 to 1.89) *	< **0.001**	1588.27, < **0.001**, 98.81	< **0.001**
Subgroup analyses					
ICH	2	2.56 (2.16 to 2.97)	< **0.001**	2.20, 0.13, 54.61	
IS	5	0.69 (− 0.03 to 1.43)	0.06	118.65, < **0.001**, 96.62	
Institutionalization					
Main analysis, OR	11	4.14 (2.68 to 6.38)	< **0.001**	60.75, < **0.001**, 83.53	0.34
Subgroup analyses					
ICH	1	27.04 (6.55 to 111.63)	< **0.001**	0.00, 1.000, 0.00	
IS	2	1.59 (1.16 to 2.16)	**0.003**	1.39, 0.23, 28.34	
Cognitive decline					
Main analysis					
Dichotomized, OR	5	5.68 (3.24 to 9.93)	< **0.001**	10.76, 0.096, 44.23	0.79
Continuous, SMD	4	− 2.43 (− 3.92 to 0.93)	**0.001**	73.21, < **0.001**, 95.90	0.14
Dementia					
Main analysis, OR	4	4.74 (2.08 to 10.79)	< **0.001**	6.80, 0.078, 55.89	0.82
Neurological functional outcomes					
Main analysis					
Dichotomized, OR	7	8.13 (5.74 to 11.50)	< **0.001**	10.97, 0.089, 45.34	0.49
Continuous, SMD	10	3.36 (1.57 to 5.15)	< **0.001**	2136.14, < **0.001**, 99.58	0.40
Subgroup analyses					
ICH	2	5.34 (2.05 to 12.75)	0.157	415.78, < **0.001**, 99.75	
IS	4	2.23 (0.60 to 5.08)	0.123	903.77, < **0.001**, 99.66	
Poor quality of life					
Dichotomized, OR	1	4.97 (2.26 to 10.94)	< **0.001**	-	-
Continuous, SMD	8	-2.56 (-4.44 to 0.68)	**0.007**	1068.74, < **0.001**, 99.34	0.46

Boldface type indicates statistical significance with two-sided $p < 0.05$

* Pooled effect size was adjusted by the trim-and-filled method

Abbreviations: CI confidence interval, *LOS* length of stay, *OR* odds ratio, *SMD* standardized mean difference, *ICH* intracerebral hemorrhage, *IS* ischemic stroke

quality [34, 36, 38, 49, 56, 64–66] due to controlling for insufficient covariates [34, 36, 38, 49, 56, 64–66], experiencing more than 20% loss to follow-up [34, 36, 38, 49, 56, 64–66], inadequate follow-up [34, 36, 38, 49, 56, 65, 66], and insufficient follow-up length to allow outcomes to occur [34, 36, 38, 56, 64–66]. The four case–control studies were of high quality [43, 70–72].

Mortality

Twenty-six studies ($n = 10{,}421$) [34, 35, 37–39, 42, 43, 45, 46, 48, 51, 53–55, 70, 71] examined the association between PSD and mortality. Four studies ($n = 2187$) [57, 60, 67, 69] were included in the primary analysis, and 30.1% ($n = 663$) of the patients developed PSD. The overall adequately adjusted ORs showed a significant association between PSD and mortality following a mean (SD) follow-up of 19.50 (27.30) months (range, 3–60 months) (OR, 3.47 [95% CI, 2.35–5.12]; I^2, 26.0%) (Fig. 2B). No publication bias (Additional file 3: Fig. S1) or outliers were identified.

The secondary analysis of inadequately adjusted ORs included 6 studies [41, 42, 57, 60, 67, 69], with results indicating that PSD was associated with a threefold increase in the odds of mortality (OR, 3.35 [95% CI,

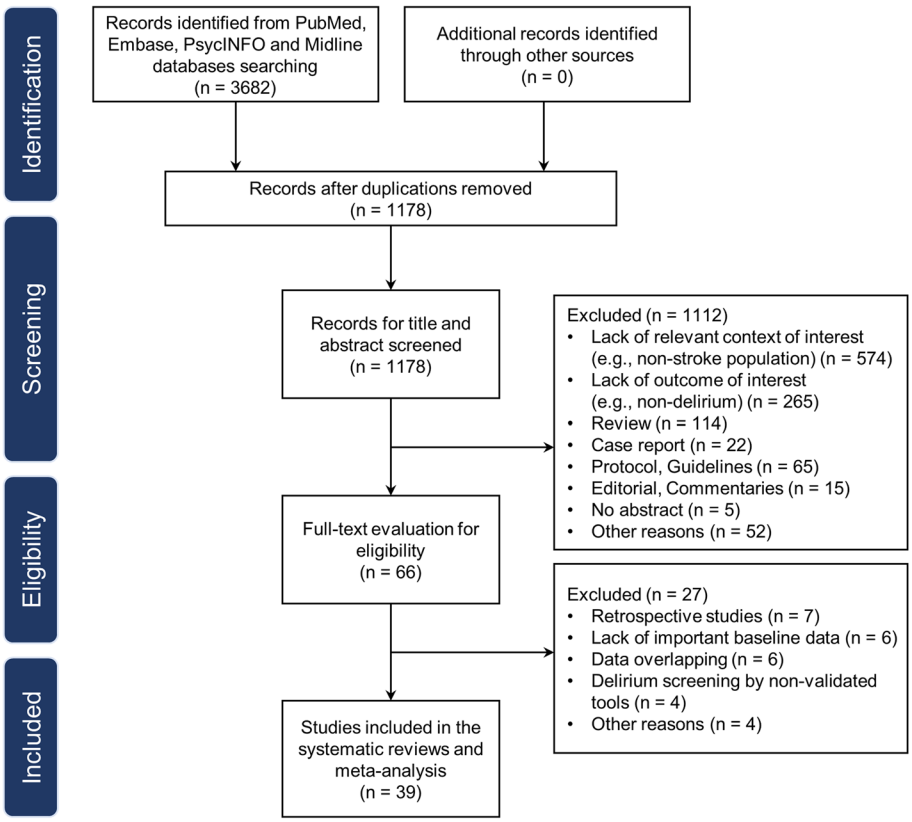

Fig. 1 PRISMA flowchart of the study

1.78–6.32]; I^2, 54.0%) after a mean (SD) follow-up of 17.16 (22.67) months (range, 1–60 months). Significant publication bias was observed using the Egger test ($P=0.030$), and the trim-and-filled method simulated 1 missing study (OR, 2.92 [95% CI, 1.51–5.64]) (Additional file 3: Fig. S1). No outliers were identified.

The tertiary analysis included 26 studies [34, 35, 37–39, 42, 43, 45, 46, 48, 51, 53–55, 70, 71], and yielded results showing that the overall unadjusted OR for mortality in patients with PSD was 4.69 (OR, 4.69 [95% CI, 3.55–6.20]; I^2, 61.8%) after a mean (SD) follow-up of 11.09 (12.93) months (range, 1–60 months) (Table 3). No publication bias was detected (Additional file 3: Fig. S1). We identified 3 outlier studies [35, 57, 59], and the significant association was retained after removing studies with reduced heterogeneity (I^2, 34.2%) (Additional file 3: Table S3). Meta-regression analysis showed that the stroke type and follow-up duration accounted for 16% of the heterogeneity (Table 4). We conducted subgroup analysis based on stroke types and observed that both delirium after ischemic and hemorrhagic stroke (OR, 5.45; 95% CI, 4.39–6.77, $P<0.001$ vs OR, 29.67; 95% CI, 7.19–122.33) were significantly associated with mortality (Table 3). Finally, we conducted sensitivity analyses, which showed that the direction and strength of the results of all ORs remained the same when excluding the studies which reported hospitalized mortality (Additional file 3: Table S5).

Hospital LoS

Twenty-one studies [34, 35, 37, 39, 42, 45–47, 49, 51, 54–57, 59–61, 65–67, 70] assessed the association between PSD and hospital LOS. Only 1 study [45] adequately adjusted for prespecified confounders, with results showing that the PSD was significantly associated with longer hospital LoS (HR, 1.63 [95% CI, 1.11–2.39]) (Fig. 2C).

Twenty studies [34, 35, 37, 39, 42, 46, 47, 49, 51, 54–57, 59–61, 65–67, 70] were used for pooled unadjusted analysis, which revealed that patients with PSD had significantly increased hospital LoS compared to those without (SMD, 1.03, 95% CI, 0.65 to 1.40; I^2, 98.8%). We further identified a significant publication bias (Egger test $P<0.001$), while the trim-and-filled method simulated 3 missing studies (SMD, 1.21 [95% CI, 0.54–1.89]) (Additional file 3: Table S2, Fig. S2). We identified eight outlier studies [35, 39, 47, 54, 55, 59, 61, 67], and the results remained the same after removing studies with reduced heterogeneity ($I^2=57.7\%$) (Additional file 3: Table S2).

Table 2 Characteristics of included studies

Author	Country	Setting	Center	Stroke type	Total sample, n	Delirium cases, *n*	Average age, mean (SD)	Gender (M/F)	Delirium assessment	Quality assessment
Gustafson et al., 1991	Sweden	Stroke Unit	Single	Acute IS or ICH	145	69	73.0 (10.2)	90/55	DSM-III	5
Henon et al., 1999	France	Stroke Unit	Single	Acute IS or ICH	202	49	75.0 (10.7)	97/105	DSM-IV	8
Caeiro et al., 2004	Portugal	Stroke Unit	Single	All stroke	218	29	NA	130/88	DSM-IV/DRS	5
Sheng et al., 2006	Australia	Stroke Unit	Single	Acute IS or ICH	156	39	79.2 (6.7)	83/73	DSM-IV	8
Dostovic et al., 2009	Bosnia and Herzegovina	Neurology	Single	Acute IS or ICH and SAH	233	59	NA	NA	DSM-IV/DRS-98	5
Manus et al., 2009	UK	Stroke Unit	Single	Acute IS or ICH excluding SAH	82	23	66.4 (15.9)	51/31	DSM-III/CAM	7
Dahl MH, 2010	Norway	Stroke Unit	Single	All stroke	178	18	73.0	102/76	DSM-IV/CAM	7
Mcmanus et al., 2011	UK	Stroke Unit	Single	Acute IS or ICH excluding SAH	82	23	66.4 (15.9)	51/31	DSM-III/CAM	9
Rijsbergen et al., 2011	Netherlands	Stroke Unit	Multi-center	Acute IS or ICH excluding SAH	122	61	75.1 (10.7)	29/21	CAM	9
Oldenbeuving et al., 2011	Netherlands	Stroke Unit	Multi-center	Acute IS or ICH excluding SAH and TIA	527	62	72 (11.2)	288/239	CAM/DRS	9
Miu et al., 2012	China	Stroke Unit	Single	Acute IS excluding TIA or ICH	314	86	72.9 (10.3)	163/151	DSM-III/CAM	8
Melkas et al., 2012	Finland	Helsinki Stroke Aging Memory Cohort	Single	Acute IS	263	50	70.8 (7.4)	135/128	DSM-IV	9
Mitasova et al., 2012	Czech Republic	Stroke Unit	Single	Acute IS excluding TIA or ICH excluding SAH	129	55	71.2 (11.5)	72/57	DSM-IV/ CAM-ICU	8
Naidech et al., 2013	USA	ICU and Stroke Unit	Single	Acute ICH	114	31	62.4 (13.8)	62/52	DSM-IV/ CAM-ICU	8
Kozak et al., 2016	Turkey	Stroke Unit	Single	Acute IS excluding TIA	60	11	66.2 (12.5)	29/31	DSM-IV/DRS	6
Chan et al., 2017	Australia	Stroke Unit	Single	Acute IS excluding TIA or ICH excluding SAH	156	39	79.2 (6.7)	83/73	DSM-IV	8
Rosenthal et al., 2017	USA	Neuro/Spine ICU	Single	Acute ICH	174	53	63.5	92/82	CAM-ICU	7
Lim et al., 2017	Korea	Stroke Unit	Single	Acute IS	576	38	65.2 (11.7)	368/208	CAM/ DRS-R-98	8
Nydahl et al., 2017	Germany	Stroke Unit	Single	Acute IS and ICH including TIA	309	33	73.4 (4.7)	NA	CAM	8
Ojagbemi et al., 2017	Nigeria	Neurology Department	Single	Acute IS or ICH	99	33	61.1 (12.9)	52/47	CAM/DRS	7

Table 2 (continued)

Author	Country	Setting	Center	Stroke type	Total sample, n	Delirium cases, *n*	Average age, mean (SD)	Gender (M/F)	Delirium assessment	Quality assessment
Qu et al., 2018	China	Neurology Department	Single	Acute IS	261	38	61.3 (12.0)	184/77	CAM/DRS	8
Dostovic et al., 2018	Bosnia and Herzegovina	Neurology Department	Single	Acute IS or ICH	200	100	NA	NA	DSM-IV/DRS-98	7
Kotfis et al., 2019	Poland	Stroke Unit	Single	Acute IS	760	121	71.6 (12.5)	393/367	DSM-V/CAM-ICU	8
Kotfis et al., 2019	Poland	Neurology Department	Single	Acute IS	1001	172	71.0 (3.0)	523/478	DSM-V/ CAM-ICU	8
Zipser et al., 2019	Switzerland	Neurology Department	Single	All stroke	1487	356	71.2 (13.3)	836/651	DSM-V/DOS	5
Pasinska et al., 2019	Poland	Stroke Unit	Single	Acute IS or ICH including TIA	750	203	71.8 (13.1)	352/398	DSM-V/CAM/CAM-ICU	9
Zaitoun et al., 2019	Egypt	ICU, Stroke Unit and Neurology	Single	All stroke excluding TIA	74	15	60.7 (11.5)	40/34	DSM-IV	7
Aizen et al., 2019	Israel	Rehabilitation	Single	All stroke	110	30	80.2 (8.0)	53/57	CAM/ DRS-R-98	6
Kowalska et al., 2020	Poland	Stroke Unit	Single	Acute IS or ICH including TIA	750	203	71.8 (13.1)	352/398	DSM-V/CAM/CAM-ICU	8
Reznik et al., 2021	USA	Neurocritical Care and Stroke Unit	Single	Acute ICH	590	348	70.5 (15.5)	309/281	DSM-V	9
Zipser et al., 2021	Switzerland	Neurology Department	Single	All stroke	567	221	72.3 (4.2)	331/236	DSM-V/DOS	9
Silva et al., 2021	Brazil	Stroke Unit	Single	Acute IS or ICH	227	71	62.5 (13.5)	121/106	CAM-ICU	9
Czyzycki et al., 2021	Poland	Neurology Department	Single	Acute IS or ICH including TIA	688	169	72.4 (5.1)	318/370	CAM/CAM-ICU/ DSM-V/DRS-R-98	8
Stokholm et al., 2021	Denmark	Neurology Department	Single	Acute IS	64	8	70 (9.8)	42/22	CAM	5
Dostovic et al., 2021	Croatia	Neurology Department	Single	Acute IS or ICH	200	100	NA	NA	DRS-R-98	6
Mansutti et al., 2022	Italy	Stroke Unit	Multi-center	Acute IS or ICH	78	27	73.1 (11.5)	46/32	4AT	5
Rollo et al.,2022	Italy	Stroke Unit	Single	Acute IS or ICH	103	36	75 (3.0)	62/41	RASS / CAM-ICU	8
Nerdal et al., 2022	Norway	Stroke Unit	Multi-center	Acute IS or ICH	139	13	71.4 (13.4)	73/68	CAM	8
Droś et al., 2023	Poland	Stroke Unit	Single	Acute IS or ICH including TIA	750	203	74 (3.16)	352/398	bCAM/CAM-ICU/ DSM-V	9

Abbreviations: 4AT 4 A's Test, *bCAM* abbreviated version of the Confusion Assessment Method, *CAM* Confusion Assessment Method, *CAM-ICU* Confusion Assessment Method of the Intensive Care Unit, *CAM-S* Confusion Assessment Method of Severity, *DOS* Delirium Observation Screening, *DRS* Delirium Rating Scale, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *ICH* intracranial cerebral hemorrhage, *ICU* Intensive Care Unit, *IS* ischemic stroke, *NA* not available, *RASS* Richmond Agitation Sedation Scale, *SAH* subarachnoid hemorrhage, *TIA* transient ischemic attack, *USA* United States of America, *UK* United Kingdom

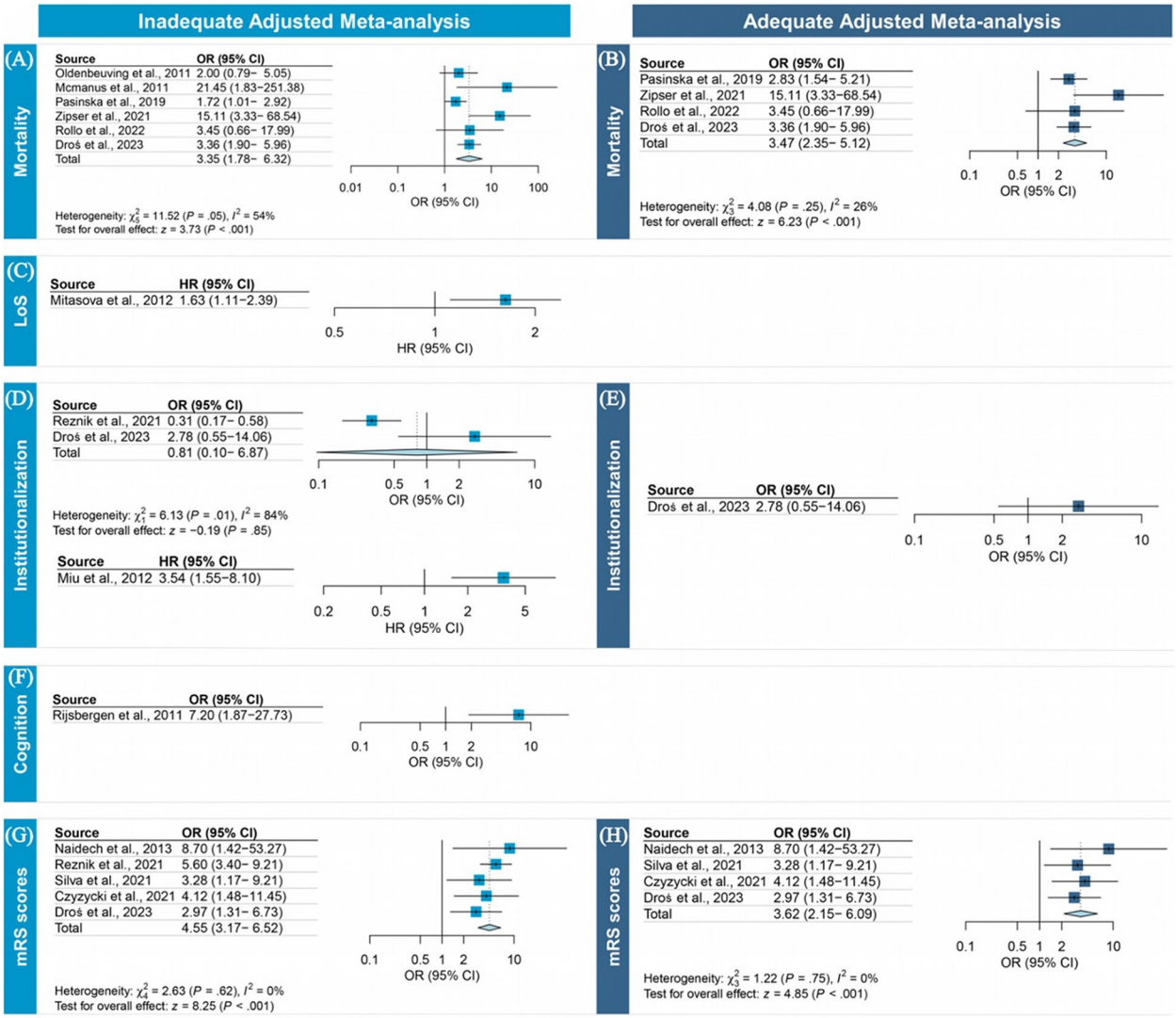

Fig. 2 Forest plots of the associations of post-stroke delirium with outcomes

Sensitivity analysis showed that the association between PSD and hospital LOS remained when patients admitted to the ICU at baseline were excluded (Additional file 3: Table S3). The meta-regression analysis showed that stroke type, history of neuropsychiatric disorders, and quality assessment together accounted for 41% of the heterogeneity (Table 4). Subgroup analysis by stroke type showed risks of 0.69 (95% CI, − 0.03–1.43, $P = 0.06$) and 2.56 (95% CI, 2.16–2.97, $P < 0.001$) for ischemic and hemorrhagic stroke, respectively, indicating that stroke type may be an important source of heterogeneity (Table 3).

Institutionalization

Eleven studies [35, 37, 39, 46, 54–56, 59, 60, 66, 69] examined the association between PSD and institutionalization. However, only one [69] adequately adjusted for key confounders, with this study suggesting that PSD was not significantly associated with the risk of institutionalization (OR, 2.78 [95% CI, 0.55–14.06], $P = 0.2$) (Fig. 2D). Two studies were inadequately adjusted for prespecified confounders. A pooled analysis of these three studies was not possible, as one study [46] reported the results as adjusted HRs (HR, 3.54 [95% CI, 1.55–8.10]) (Fig. 2D), while two [59, 69] reported the adjusted ORs. The pooled inadequately adjusted OR suggested PSD was not associated with an increased institutionalization risk (OR, 0.81 [95% CI, 0.10–6.87]) (Fig. 2D). Eleven studies [35, 37, 39, 46, 54–56, 59, 60, 66, 69] presented unadjusted event rates, and the pooled OR indicated that PSD was associated with a fourfold increased

Table 3 Unadjusted meta-analysis of outcomes for post-stroke delirium

Outcomes	No. of studies	Pooled effect size (95% CI)	*p*-value	*Q*-value, *p*-value, I^2 (%)	*p*-value for Egger's regression
Mortality					
Main analysis, OR	26	4.69 (3.55 to 6.20)	< **0.001**	65.47, < **0.001**, 61.82	0.82
Subgroup analyses					
ICH	1	29.67 (7.19 to 1222.33)	< **0.001**	0.00, 1.000, 0.00	
IS	5	5.45 (4.39 to 6.77)	< **0.001**	2.41, 0.661, 0.00	
LOS					
Main analysis, SMD	20	1.21 (0.54 to 1.89)*	< **0.001**	1588.27, < **0.001**, 98.81	< **0.001**
Subgroup analyses					
ICH	2	2.56 (2.16 to 2.97)	< **0.001**	2.20, 0.13, 54.61	
IS	5	0.69 (− 0.03 to 1.43)	0.06	118.65, < **0.001**, 96.62	
Institutionalization					
Main analysis, OR	11	4.14 (2.68 to 6.38)	< **0.001**	60.75, < **0.001**, 83.53	0.34
Subgroup analyses					
ICH	1	27.04 (6.55 to 111.63)	< **0.001**	0.00, 1.000, 0.00	
IS	2	1.59 (1.16 to 2.16)	**0.003**	1.39, 0.23, 28.34	
Cognitive decline					
Main analysis					
Dichotomized, OR	5	5.68 (3.24 to 9.93)	< **0.001**	10.76, 0.096, 44.23	0.79
Continuous, SMD	4	− 2.43 (− 3.92 to 0.93)	**0.001**	73.21, < **0.001**, 95.90	0.14
Dementia					
Main analysis, OR	4	4.74 (2.08 to 10.79)	< **0.001**	6.80, 0.078, 55.89	0.82
Neurological functional outcomes					
Main analysis					
Dichotomized, OR	7	8.13 (5.74 to 11.50)	< **0.001**	10.97, 0.089, 45.34	0.49
Continuous, SMD	10	3.36 (1.57 to 5.15)	< **0.001**	2136.14, < **0.001**, 99.58	0.40
Subgroup analyses					
ICH	2	5.34 (− 2.05 to 12.75)	0.157	415.78, < **0.001**, 99.75	
IS	4	2.23 (0.60 to 5.08)	0.123	903.77, < **0.001**, 99.66	
Poor quality of life					
Dichotomized, OR	1	4.97 (2.26 to 10.94)	< **0.001**	-	-
Continuous, SMD	8	− 2.56 (− 4.44 to 0.68)	**0.007**	1068.74, < **0.001**, 99.34	0.46

Boldface type indicates statistical significance with two-sided $p < 0.05$

* Pooled effect size was adjusted by the trim-and-filled method

Abbreviations: CI confidence interval, *LOS*length of stay, *OR* odds ratio, *SMD* standardized mean difference, *ICH* intracerebral hemorrhage, *IS*ischemic stroke

institutionalization risk (OR, 4.14 [95% CI, 2.68–6.38]; I^2, 83.5%) after a mean (SD) follow-up of 13.44 (18.04) months (range, 1–60 months) (Table 3). No publication bias was identified (Additional file 3: Fig. S3). We identified two outlier studies [55, 59], and the significant association persisted after removing these studies with reduced heterogeneity ($I^2 = 63.8\%$) (Additional file 3: Table S2). Sensitivity analysis showed that the association between PSD and institutionalization remained when only patients who had not resided in an institution at baseline were considered (Additional file 3: Table S3). Meta-regression analysis showed that the stroke type accounted for 100% of the heterogeneity (Table 4). Subgroup analysis by types of stroke showed a risk of 1.59 (95% CI, 1.16–2.16, $P = 0.003$) and 27.04 (95% CI, 6.55–111.63, $P < 0.001$) for ischemic and hemorrhagic stroke, respectively (Table 3).

Cognitive outcomes

Eight studies [35, 37, 43, 44, 48, 52, 68, 72] investigated the association between PSD and cognitive outcomes, including 4 on dementia and 5 on cognitive decline. However, 1 study [43], which suggested that PSD was significantly associated the risk of dementia at 24 months (OR,

Table 4 Uni- and multivariable meta-regression for heterogeneity-originated covariates of outcomes

Outcomes	Univariable						Multivariable			
	β	SE	95% CI	*z*-value	*p*-value	R^2 (%)	*β*	*z*-value	*p*-value	R^2 (%)
Mortality										
Age at baseline, year	−0.03	0.03	−0.10 to 0.03	−1.09	0.276	0				16
NIHSS	−0.03	0.07	−0.18 to 0.10	−0.52	0.606	0				
Measure of delirium					0.557	0				
CAM	Ref	-	-	-	-					
DSM	−0.28	0.57	−1.42 to 0.84	−0.49	0.621					
Other	1.25	1.66	−2.01 to 4.53	0.75	0.450					
Mix	0.20	0.47	−0.73 to 1.13	0.42	0.676					
Stroke type						10.0				
ICH	Ref	-	-	-	-		Ref	-	-	
IS	−1.69	0.90	−3.47 to −0.08	−1.87	0.061		−1.01	−1.07	0.284	
IS and ICH	−1.95	0.87	−3.67 to −0.24	−2.24	**0.025**		−1.51	−1.70	0.089	
Neuropsychiatric disorders excluded						0				
No	Ref	-	-	-	-					
Yes	−0.07	0.29	−0.65 to 0.51	−0.24	0.808					
Duration of follow-up, m						1.0				
< 3	Ref	-	-	-	-		Ref	-	-	
≥ 3	−0.69	0.30	−1.29 to −0.09	−2.26	**0.023**		−0.69	−2.18	**0.029**	
NOS scores	−0.10	0.11	−0.33 to 0.13	−0.86	0.390	0				
LoS										
Age at baseline, years	−0.03	0.04	−0.11 to 0.05	−0.74	0.458	0				41
NIHSS	−0.08	0.08	−0.25 to 0.08	−0.99	0.324	0				
Measure of delirium					0.218	0				
CAM	Ref	-	-	-	-					
DSM	−0.98	0.70	−2.36 to 0.39	−1.40	0.161					
Other	−1.40	0.99	−3.36 to 0.55	−1.41	0.159					
Mix	−0.14	0.55	−1.23 to 0.95	−0.25	0.801					
Stroke type					**0.004**	37			**0.012**	
ICH	Ref	-	-	-	-		Ref	-	-	
IS	−1.81	0.57	−2.94 to −0.68	−3.14	**0.001**		−1.62	−2.79	**0.005**	
IS and ICH	−1.60	0.52	−2.62 to −0.58	−3.09	**0.002**		−1.48	−2.83	**0.004**	
Neuropsychiatric disorders excluded						5				
No	Ref	-	-	-	-		Ref	-	-	
Yes	0.50	0.53	−0.53 to 1.54	0.95	0.340		0.96	2.18	**0.029**	
NOS scores	0.27	0.13	0.01 to 0.53	2.11	**0.035**	4	0.25	2.29	**0.022**	

7.20 [95% CI, 1.87–27.73]), was inadequately adjusted for the prespecified confounders (Fig. 2F). Five studies reported unadjusted dichotomous cognitive outcomes, while the pooled unadjusted OR for poorer cognitive outcomes in patients with PSD was 5.68 (95% CI, 3.24–9.93; I^2, 44.23%) after a mean (SD) follow-up of 33 (34.20) months (range, 3–90 months) (Table 3). No publication bias (Additional file 3: Fig. S4) or outliers were identified. Four studies reported continuous cognitive outcomes, revealing significantly worse outcomes in patients with PSD (SMD − 2.43, 95% CI − 3.92 to − 0.93; I^2, 95.9%) compared with those without (Table 3). No publication bias was identified (Additional file 3, Fig. S4). We identified one outlier study, and the results remained the same after removing studies with reduced heterogeneity (I^2 = 46.8%) (Additional file 3: Table S2). Meta-regression analysis revealed that delirium accounted for 97% of the heterogeneity (Table 4). Four studies reported dementia as an outcome, and the pooled unadjusted OR in patients with PSD was 4.74 (95% CI, 2.08–10.79; I^2, 55.9%) after a mean (SD) follow-up of 32.25 (39.45) months (range, 3–90 months) (Table 3). No publication biases or outliers were identified (Additional file 3: Fig. S5). We further conducted sensitivity analyses of the unadjusted ORs of

Table 4 (continued)

Outcomes	Univariable						Multivariable			
	β	SE	95% CI	*z*-value	*p*-value	R^2 (%)	*β*	*z*-value	*p*-value	R^2 (%)
Institutionalization										
Age at baseline, years	−0.01	0.06	−0.13 to 0.10	−0.30	0.760	0				100
NIHSS	−0.01	0.15	−0.31 to 0.28	−0.10	0.920	0				
Measure of delirium					0.830	0				
DSM	Ref	-	-	-	-					
Other	−0.59	0.98	−2.52 to 1.34	−0.60	0.550					
Mix	−0.12	0.62	−1.34 to 1.09	−0.21	0.836					
Stroke type					**< 0.001**	100			**< 0.001**	
ICH	Ref	-	-	-	-		Ref	-	-	
IS	−2.84	0.73	−4.28 to −1.39	−3.86	**< 0.001**		−2.84	−3.86	**< 0.001**	
IS and ICH	−1.75	0.72	−3.18 to −0.32	−2.40	**0.016**		−1.75	−2.40	**0.016**	
Neuropsychiatric disorders excluded						0				
No	Ref	-	-	-						
Yes	0.43	0.45	−0.46 to 1.33	0.95	0.340					
NOS scores	0.06	0.17	−0.28 to 0.41	0.34	0.732	0				
Cognitive decline										
Measure of delirium						97				97
CAM	Ref	-	-	-	-		Ref	-	-	
DSM	6.00	0.77	4.48 to 7.51	7.75	**< 0.001**		6.00	7.75	**< 0.001**	
Functional outcome										
Age at baseline, years	0.21	0.23	−0.24 to 0.66	0.90	0.367	0				14
NIHSS	−0.13	0.34	−0.81 to 0.55	−0.37	0.709	0				
Measure of delirium					0.613	0				
CAM	Ref	-	-	-	-					
DSM	−0.14	4.39	−8.75 to 8.45	−0.03	0.972					
Other	0.54	4.39	−8.06 to 9.16	0.12	0.900					
Mix	2.98	3.32	−3.53 to 9.50	0.90	0.368					
Stroke type					0.482	0				
ICH	Ref	-	-	-	-					
IS	−3.10	2.58	−8.16 to 1.95	−1.20	0.229					
IS and ICH	−1.84	2.58	−6.90 to −3.21	−0.72	0.474					
Neuropsychiatric disorders excluded						0				
No	Ref	-	-	-	-					
Yes	0.42	2.06	−3.61 to −4.46	0.21	0.836					
Duration of follow-up, m						0				
< 3	Ref	-	-	-	-					
≥ 3	−0.26	2.43	−5.04 to 4.51	−0.11	0.913					
NOS scores	1.06	0.59	−0.11 to 2.23	1.77	0.076	14	1.06	1.77	0.076	

poorer cognitive outcomes and dementia, finding that the associations remained when patients with cognitive impairment at baseline were excluded (Additional file 3: Table S3).

Functional outcome

Fifteen studies [35, 36, 47, 48, 51, 53–55, 57, 59, 60, 65, 66] investigated the association between PSD and functional outcomes (i.e., modified Rankin Scale [mRS] scores). The aggregated analysis of adequately adjusted ORs in 4 studies revealed that PSD was associated with poorer functional outcome after a mean (SD) follow-up of 21.75 (25.85) months (range, 3–60 months) (OR, 3.62 [95% CI, 2.15–6.09]; I^2, 0%) (Fig. 2H). The pooled inadequately adjusted OR in 5 studies indicated that PSD was associated with a 4.5-fold increase in the odds

Table 4 (continued)

Outcomes	Univariable						Multivariable			
	β	SE	95% CI	*z*-value	*p*-value	R^2 (%)	*β*	*z*-value	*p*-value	R^2 (%)
Quality of life										
Age at baseline, y	−0.00	0.17	−0.34 to 0.32	−0.05	0.961	0				79
NIHSS	−1.23	1.20	−3.58 to 1.12	−0.10	0.306	0				
Measure of delirium					0.548	0				
DSM	Ref	-	-	-	-					
Other	−0.14	3.48	−6.97 to 6.67	−0.04	0.966					
Mix	−2.36	2.30	−6.88 to 2.14	−1.03	0.303					
Stroke type						0				
IS										
IS and ICH	−2.46	3.03	−8.41 to 3.48	−0.81	0.417					
Measure tools					< **0.001**	79			< **0.001**	
BI	Ref	-	-	-	-		Ref	-	-	
FIM	0.63	1.06	−1.44 to 2.70	0.59	0.551		0.53	0.48	0.629	
IADL	−8.15	1.39	−10.89 to −5.41	−5.84	< **0.001**		−7.77	−4.97	< **0.001**	
NOS scores	−1.10	0.69	−2.47 to 0.25	−1.60	0.110	8	−0.24	−0.62	0.534	

Boldface type indicates statistical significance with two-sided $p < 0.05$

Abbreviations: BI Barthel Index, *CAM* Confusion Assessment Method, *CAM* Confusion Assessment Method, *CI* confidence interval, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *FIM* Functional Independence Measure, *IADL* Instrumental Activities of Daily Living, *ICH* intracranial cerebral hemorrhage, *IS* ischemic stroke, *LoS* length of stay, *NA* not available, *NIHSS*, National Institute of Health stroke scale, *m* month, *RASS*, Richmond Agitation Sedation Scale, *Ref.*, reference, *SAH* subarachnoid hemorrhage, *TIA* transient ischemic attack, *USA* United States of America, *UK* United Kingdom, *y* year

of poor functional outcome (OR, 4.55 [95% CI, 3.17–6.52]; I^2, 0%) after a mean (SD) follow-up of 18 (23.90) months (range, 3–60 months) (Fig. 2G). The pooled unadjusted OR in 7 studies indicated PSD was associated with an eightfold increased risk of poor functional outcomes (OR, 8.13 [95% CI, 5.74–11.50]; I^2, 45.3%) after a mean (SD) follow-up of 14.50 (22.56) months (range, 3–60 months) (Table 3). In the above meta-analyses, no publication biases (Additional file 3: Fig. S6) or outlier studies were identified. Sensitivity analyses indicated that the direction and strength of all the results remained the same when patients with higher baseline mRS scores were excluded (Additional file 3: Table S3).

Ten studies reported on continuous functional outcomes, presenting results that indicated poorer functional outcomes in patients with delirium (SMD 3.36, 95% CI 1.57 to 5.15; $p < 0.001$; I^2, 99.6%) compared with those without (Table 3). No publication bias or outliers were identified (Additional file 3: Fig. S6). Meta-regression analysis revealed that the quality assessment accounted for 14% of the heterogeneity (Table 4). Subgroup analysis further showed that both delirium after ischemic and hemorrhagic stroke (OR, 2.23; 95% CI, 0.60–5.08, $P = 0.123$ vs. OR, 5.34; 95% CI, −2.05–12.75, $P = 0.157$) was numerically associated with neurological functional outcomes (Table 3). Sensitivity analyses revealed that the direction and strength of the results remained the same when patients with higher baseline mRS scores were excluded (Additional file 3: Table S3).

Quality of life

Nine studies [35, 37, 42, 51, 53, 57, 63, 64, 66] examined the association between PSD and quality of life. One that presented unadjusted event rates indicated that PSD was associated with an unadjusted fourfold increase in the odds of poor quality of life (OR, 4.97 [95% CI, 2.26–10.94]) (Table 3). Eight studies that reported continuous outcomes reported significantly worse outcomes in patients with PSD (SMD −2.56, 95% CI −4.44 to −0.68; $p = 0.007$; I^2, 99.3%) compared with those without (Table 3). No publication bias was identified (Additional file 3, Fig. S7). We identified one outlier study, in which the association persisted after removing this study with reduced heterogeneity (Additional file 3: Table S2). Meta-regression analysis showed that the measures of quality of life and study quality accounted for 79% of the heterogeneity (Table 4). Sensitivity analyses revealed that the direction and strength of the results remained the same when only patients with poor quality of life at baseline were excluded (Additional file 3: Fig. S3).

Discussion

This study comprised a comprehensive review of PSD outcome data obtained from 39 studies, including 35 prospective observational studies and 4 case–control

studies. Overall, the results suggested that delirium identified in acute stroke patients is strongly associated with mortality and functional outcomes, even after adjusting for age, comorbid illnesses, and stroke severity. On an inadequately adjusted and unadjusted basis, PSD was found to be associated with a significantly increased risk of death, longer LoS, institutionalization, poor function, cognition, and quality of life. Compared with a previous meta-analysis [7], our investigation included a larger number of studies and patients (10 vs. 39 studies; 2004 vs 12,938 patients) and included more comprehensive endpoints. More importantly, this is the first meta-analysis to quantify the association between PSD and outcomes after controlling for key confounders that may have influenced the association between delirium and poor outcomes.

Our meta-analysis has several practical clinical implications. Delirium has been suggested to reflect the quality of inpatient care [74]; however, it is frequently overlooked and poorly documented among patients with neurological symptoms [75]. Although no intervention has been found to improve long-term outcomes of delirium, our results indicate that PSD is a potentially modifiable risk factor for adverse outcomes. Therefore, delirium may be a promising target for outcome optimization. For example, multicomponent interventions aimed at addressing the risk factors for delirium could diminish the risk of delirium and improve outcomes associated with delirium (i.e., a trend toward reduced LOS and institutionalization) [76]. Identifying high-risk populations and implementing strategies to prevent delirium may improve PSD-associated adverse outcomes in patients with acute stroke.

This study highlights several directions for future clinical studies on PSD. First, patients with acute stroke who develop delirium tend to differ substantially from patients without delirium at baseline, and these differences (e.g., age, comorbidity, and severity of stroke) are closely associated with adverse outcomes. Therefore, any attempt to identify the association between PSD and its outcomes requires careful control of these variables. One prior meta-analysis by Salluh et al. demonstrated a significant increase in the risk of mortality associated with delirium in critically ill patients, after controlling for age, sex, and illness [4]. Another meta-analysis by Hamilton et al. concluded that POD had no significant effect on mortality after controlling for confounders specific to the perioperative setting [77]. These two conflicting findings indicate that there are potential differences in the pathophysiology of delirium due to different causes. In our study, the association between PSD, mortality, and function persisted even after adjusting for several key confounders, supporting the independent nature of delirium as an exposure to outcomes in stroke patients. However, our predefined confounders were not sufficient to control for confounding factors in the association between delirium and other outcomes, indicating that more high-quality studies with adequate adjustment for confounders are warranted. Second, our results underline the need for prospective cohort studies with standardized methods to assess the impact of delirium on endpoints (cognition and quality of life) in acute stroke patients. Third, we found that the stroke type could account for the heterogeneity of several endpoints. As such, future studies should be designed to allow for discriminative analysis according to stroke type. Finally, high-quality clinical trials are required to evaluate the efficacy of single and bundled interventions in reducing the prevalence and burden of delirium in patients with acute stroke.

This study has some limitations. First, most of the included studies were unadjusted or inadequately adjusted for the selected covariates. To overcome this, we performed a meta-analysis of inadequately adjusted and unadjusted effect estimates to validate the results of the PSD-outcomes relationship. Second, there is insufficient evidence regarding the most suitable screening tool for assessing delirium in acute stroke patients [75]. Patients who are comatose or have other cognitive dysfunctions may be excluded from neurocognitive assessment, or misclassified as having delirium. Third, all the included studies were observational; therefore, the causation between PSD and poor outcomes could not be determined.

Conclusions

The results of this meta-analysis suggest that PSD is independently associated with an increased risk of mortality and poor function. Furthermore, the unadjusted results indicated that PSD was associated with longer hospitalization, more institutionalization, cognitive impairment, and worse quality of life. PSD prevention is a high clinical and research priority, meaning that collaborative scientific efforts should be directed towards addressing these challenges.

Abbreviations

PSD	Post-stroke delirium
ORs	Odds ratios
CIs	Confidence intervals
SMDs	Standardized mean differences
HRs	Hazard ratios
SD	Standard deviation
LoS	Length of stay
MOOSE	Meta-analysis of Observational Studies in Epidemiology
DSN	Diagnostic and Statistical Manual of Mental Disorders
CAM	Confusion assessment method
CAM-ICU	Confusion assessment method for the intensive care unit
ICDSC	Intensive care delirium screening checklist
mRS	Modifiable Rankin scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03689-1.

Additional file 1: MOOSE Checklist of the study

Additional file 2: PRISMA Checklist of the study

Additional file 3: Table S1-S5. Table S1: Characteristics of included studies. Table S2: Methodological quality for outcomes of poststroke delirium. Table S3: The meta-analysis of outcomes for post-stroke delirium with excluding outliers. Table S4: Uni- and multivariable Meta-regression for heterogeneity-originated covariates of outcomes. Table S5: Sensitivity analysis. Figure S1: Funnel plot assessing publication bias on mortality of post-stroke delirium Figure S2: Funnel plot assessing publication bias on hospital stay of post-stroke delirium Figure S3: Funnel plot assessing publication bias on institutionalization of post-stroke delirium Figure S4: Funnel plot assessing publication bias on cognitive outcomes of post-stroke delirium Figure S5: Funnel plot assessing publication bias on dementia of post-stroke delirium Figure S6: Funnel plot assessing publication bias on functional outcomes of post-stroke delirium Figure S7: Funnel plot assessing publication bias on life quality of post-stroke delirium

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Authors' contributions
G.B.Z., G.Z.S., H.W.H. contributed to the conception and design of the study; G.B.Z., W.J.Y., J.M.L., H.Y.L., L.W., S.L.Z. contributed to acquiring the data; G.B.Z., W.J.Y., J.M.L., H.Y.L. contributed to analyzing and interpreting the data; H.W.H., G.Z.S., G.B.Z. contributed to writing the original draft and supervision. G.Z.S. and H.W.H. contributed to writing, reviewing and editing. All the authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors provided consent for publication.

Competing interests
The authors declare no competing interests.

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