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ASSOCIATIONS BETWEEN STROKE LOCALIZATION AND DELIRIUM: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objectives: Delirium is common among patients with acute stroke and associated with worse outcomes. However, it is unclear which stroke locations or types are most associated with delirium.

Materials and Methods: We systematically reviewed studies of patients with acute stroke that reported stroke locations and types by delirium status. We included papers in any language, through a combined search from January 2010 to June 2021. Case studies with less than 20 patients, case-control studies, and randomized controlled trials were excluded. MEDLINE, EMBASE, PsycINFO, CINAHL, and Alois databases were searched. Pooled relative risks were calculated using bivariate random effects models or network metaanalysis. Methodological quality was assessed across 8 factors.

Results: 31 patient samples representing 8,329 patients were included. Delirium was more common in patients with supratentorial lesions than infratentorial (RR [Relative Risk] 2.01, CI [Confidence Interval] 1.49-2.72); anterior circulation lesions than posterior (RR 1.41, CI 1.13-1.78); and cortical lesions than subcortical (RR 1.54, CI 1.25-1.89). Stroke side was not associated with delirium (right vs. left: RR 0.99, CI 0.77-1.28). Delirium was more common in patients with hemorrhagic strokes than ischemic (RR 1.74, CI 1.42-2.11) and patients with preexisting qualitative atrophy (RR 1.66, CI 1.21-2.27).

Conclusion: Several brain localizations and types of strokes were associated with delirium. Conclusions were in part limited by the heterogeneity of studies and broad or qualitative lesion

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Declaration of Competing Interest

none

descriptions. These results may assist in anticipating the risk of delirium in acute stroke and highlight brain networks and pathologies that may be involved in the pathophysiology of delirium.

Keywords

Stroke; Delirium; Localization; Meta-Analysis; Systematic Review

INTRODUCTION

Each year in the United States, 795,000 people have new or recurrent strokes.[1] Approximately 25% of patients with acute stroke will also experience delirium, an acute and fluctuating disturbance in attention and awareness.[2] Patients who suffer from delirium in the acute post-stroke setting have an increased risk of mortality,[3] increased likelihood of discharge to post-acute care facilities, and increased disability compared to those without delirium.[4] Therefore understanding who develops delirium after acute stroke impacts not only acute inpatient management, but also longer-term prognosis.

Although several predisposing and precipitating risk factors, such as age, cognitive reserve, and medications, have been associated with the development of delirium in patients with acute stroke,[5] the role of the acute stroke lesion itself remains unclear. Prior literature has varied, with some papers reporting that right-sided brain lesions increase the risk of delirium,[3,6] and others reporting that left-sided brain lesions increase the risk of delirium.[7,8] Prior studies have also variably reported that delirium is associated with either anterior[8] or posterior[7] circulation lesions. It therefore remains unclear whether delirium arises solely from nonspecific, generalized brain dysfunction or instead can also be precipitated by lesions in specific regions. The results of single studies may be insufficient to address this question, given the variability of strokes and the heterogeneity of delirium, hindering our understanding of factors involved in the pathophysiology of delirium in acute stroke.

We therefore undertook a broad systematic review and meta-analysis to determine whether specific types of acute stroke are associated with an increased risk of delirium, with a particular emphasis on the role that lesion locations may play in the risk of delirium.

METHODS

Eligibility Criteria and Search Strategy

A recent systematic review and meta-analysis by Shaw et al studied the prevalence of delirium in acute stroke, reviewing the literature from January 2010 to June 2018.[2] Given our goal to determine rates of delirium within subsets of patients with acute stroke, we both assessed the articles found by this systematic review and also chronologically expanded the search using the same criteria to include additional papers published more recently, between June 1, 2018-June 11, 2021. For our additional search, we used the same cross-disciplinary electronic databases as in the prior systematic review: MEDLINE, EMBASE, PsycINFO/PsycArticles, CINAHL, and Alois, all searched on June 11, 2021. Details are included in the supplement for the search strategy (Supplementary Appendix 1) and inclusion/exclusion criteria (Supplementary Appendix 2). We did not include studies where

localization and imaging data were not reported, since post-hoc inclusion would include data that did not undergo peer review. The study was registered at https://www.crd.york.ac.uk/prospero/ (CRD42021238301); a protocol was not otherwise prepared. The following stroke classifications were added after protocol submission: cortical versus subcortical strokes and TOAST classification of ischemic stroke subtypes. Due to the nature of the work, institutional review board approval was not required.

Data Collection Process

Each article was screened independently by at least two of five investigators trained in systematic reviews (JR, MC, MM, SS, EK), using Covidence. Screening was first performed on titles and abstracts, and at a second stage on full text papers. Any discrepancies were discussed collectively, using prespecified inclusion and exclusion criteria, and agreement was always reached. The systematic review and meta-analyses were completed in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Supplementary PRISMA Checklist).[9]

For each trial, we identified the number of patients with and without delirium, and then for each group extracted stroke characteristics including location (Supplementary Appendix 3). Most papers reported stroke locations using vascular territories (e.g., anterior circulation) rather than focal brain locations (e.g., frontal lobe), and most localizations were presented as single categories: e.g., right vs. left hemisphere, followed separately by other categories such as supratentorial vs. infratentorial location. When more specific data was given, we extracted categorical features to harmonize data across studies. As an example, a case of patient with an ischemic stroke in the right middle cerebral artery (MCA) territory was categorized according to delirium status into “ischemic” in the ischemic versus hemorrhagic category, “right” for the left versus right hemisphere category, and “anterior” in the vascular territory category. In the case of hemorrhage, the location or vascular territory feeding the hemorrhage as reported by the papers was used for categorization. Data extraction was performed in duplicate by two investigators (JR & EK) to ensure accuracy, and discrepancies were resolved by consensus discussion.

Meta-analysis Methods

The metabin function for R[10] was utilized to calculate differences in the binary outcome of delirium across studies using random effects models, to analyze whether delirium risk was associated with particular locations or stroke types. The network meta-analysis nme function[11] in R was used when more than two categories were present. Relative risk and 95% confidence intervals (CI) were calculated. Heterogeneity was assessed by I^2, τ^2, and Cochrane Q. Given the limited number of studies for many comparisons, no further analysis of heterogeneity was performed. Significance levels were set at $p = 0.05$. Corrections for multiple comparisons were not performed given the exploratory nature of this analysis. We displayed results graphically using forest plots for binary categories and using heat maps for multiple group analyses. Funnel plots were visualized to assess for possible reporting bias for binary comparisons.

Bias Assessment and Sensitivity Analyses

For sensitivity analyses, each paper was graded for risk of bias across eight different quality measures, including clearly defined inclusion criteria, clear definition of study subjects and setting, measurement of the exposure (stroke) in a valid and reliable way, use of objective and standard criteria for measurement of the affected stroke territories, identification of confounding factors and how those were dealt with, measurement of the outcome (delirium) in a valid and reliable way, and appropriate use of statistical analysis (Supplementary Appendix 4) using a modified bias appraisal tool[12,13]. Each paper was graded separately by two authors (JR and EK), and when there was disagreement, a discussion was held to achieve consensus. Papers at lower risk of bias were identified as those with a summed score of six or higher across all sensitivity measures. We then repeated metaanalyses using only these higher-quality studies.

Data Availability

Data not published within this article will be made available by request from qualified investigators.

RESULTS

The literature search yielded a total of 39 papers for inclusion, of which 8 papers included data from previously published patient samples. We therefore combined the papers to yield 31 unique patient samples (which we will refer to as “cohorts”, moving forward) (Figure 1), representing a total of 8,329 patients. Common reasons for papers to be excluded at the full text stage were because they did not have radiographically determined localization information or did not break down patients into those with and without delirium.

The final list of included studies and their relevant characteristics are included in Table 1. Most papers measured delirium using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or Confusion Assessment Method (CAM) based assessment, though occasionally other measures were also used. Quality and risk of bias assessments for each paper are presented in Supplementary Appendix 5.

Given the number of different stroke features analyzed, a summary of the results below is presented in Table 2. Funnel plots for each binary analysis are presented in Supplementary Appendix 6, and corresponding sensitivity analyses are presented in Supplementary Appendix 7.

Major Stroke Locations

Supratentorial versus Infratentorial Lesions—Given the major neuroanatomical differences between supratentorial and infratentorial locations, we first analyzed whether supratentorial or infratentorial strokes were associated with the risk of delirium (n=10 cohorts). Patients with supratentorial strokes had a higher risk of delirium than patients with infratentorial strokes (RR 2.01, CI 1.49-2.72, p<0.001) (Figure 2A). Sensitivity analysis with only high-quality studies yielded similar results (n=7, RR 2.24, CI 1.63-3.08, p<0.001, Supplementary Appendix 7).

Anterior versus Posterior Vascular Territory—We next analyzed whether the risk of delirium was associated with strokes in anterior (i.e., internal carotid artery, ACA, or MCA) versus posterior (i.e., vertebrobasilar or PCA) circulation territories (n=18 cohorts). Patients with anterior vascular territory strokes had a higher risk of delirium than patients with posterior vascular territory strokes (RR 1.41, CI 1.13-1.78, p=0.005) (Figure 2B). Sensitivity analysis with only high-quality studies yielded similar results (n=11, RR 1.72, CI 1.29-2.30, p=0.002, Supplementary Appendix 7).

Only four studies evaluated the risk of delirium within more specific intracranial arterial territories.[8,14-16] Rates of delirium were not significantly different between anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), and vertebrobasilar (VB) territory strokes (Supplementary Appendix 8).

Cortical versus Subcortical Stroke—We next analyzed the association of cortical or subcortical strokes with delirium (n=8 cohorts). Patients with cortical strokes had a higher risk of delirium than patients with subcortical strokes (RR 1.54, CI 1.25-1.89, p=0.002) (Figure 2C). Sensitivity analysis with only high-quality studies yielded similar results (n=4, RR 1.76, CI 1.19-2.60, p=0.019, Supplementary Appendix 7).

Right versus Left Hemisphere Strokes—We also evaluated whether right or left hemispheric strokes were associated with an increased risk of delirium (n=18 cohorts). There was no statistically significant difference in rates of delirium for right vs. left hemispheric strokes (RR 0.99, CI 0.77-1.28, p=0.930), although there was a high degree of heterogeneity among studies (Figure 2D). Sensitivity analysis with only high-quality studies yielded similar results (n=11, RR 1.04, CI 0.80-1.36, p=0.740, Supplementary Appendix 7).

Clinical Characteristics of Strokes

Lesion Volume—Data for lesion volumes by delirium status was reported in seven cohorts, though using different summary measurements in different patient populations. Three studies reported lesion volumes using medians and interquartile ranges in different populations (one post-procedural,[17] one with hemorrhagic strokes,[18] and one with ischemic strokes[5]). Lesions were significantly larger in patients with delirium in only one study[5] (1/3). Two studies reported lesion volumes using means: lesions were significantly larger in patients with delirium in both (2/2).[19,20] Two studies reported the proportions of patients who had lesions greater than or less than a cutoff volume. In one study using 40 ml as the cutoff, rates of delirium were not clearly significantly different between patients with larger and smaller lesions (p=0.069).[15] In the second study using 2.5 ml as the cutoff, delirium was more likely in the patients with larger lesions (p<0.05).[16] In summary, delirium was significantly associated with larger lesions in 4/7 studies, but study heterogeneity precluded more formal meta-analysis.

Oxfordshire Community Stroke Project (OCSP) Clinical Subgroups—We analyzed whether the risk of delirium varied according to clinically identified stroke subgroups (n=11 cohorts). Patients with total anterior circulation (TACI) infarcts were more likely to have delirium compared to those with partial anterior circulation infarcts (PACI)

(RR 2.63, CI 1.76-4.00), posterior circulation infarcts (POCI) (RR 3.15, CI 2.02-5.06), or lacunar infarcts (LACI) (RR 3.95, CI 2.57-6.15). No other comparisons were statistically significant (Figure 3A). Sensitivity analysis with only high-quality studies yielded similar results (Supplementary Appendix 7).

Ischemic Stroke Clinical Subtypes—Data were organized by Trial of Org 10172 in Acute Stroke Treatment (TOAST) clinical subtypes, including cardioembolic, large vessel, or small vessel strokes (n=8 cohorts). Compared to small vessel strokes, there was a statistically significantly increased risk for delirium for both large vessel strokes (RR 2.57, CI 1.58-4.02, Figure 3B) and cardioembolic strokes (RR 2.69, CI 1.75-4.51, Figure 3B). Sensitivity analysis with only high-quality studies yielded similar results (Supplementary Appendix 7).

Ischemic versus Hemorrhagic Strokes—We analyzed whether rates of delirium were associated with ischemic or hemorrhagic strokes, including subarachnoid hemorrhage (n=14 cohorts). There was a higher risk of delirium in patients with hemorrhagic strokes than patients with ischemic strokes (RR 1.74, CI 1.42-2.11, Figure 3C). No other comparisons were statistically significant (Figure 3C). Sensitivity analysis with only high-quality studies yielded similar results (Supplementary Appendix 7).

Chronic Pathology

Several studies evaluated whether pre-stroke, chronic pathology was associated with the risk of delirium, specifically atrophy and white matter changes or leukoaraiosis.

Atrophy—When comparing patients with or without evidence of atrophy (n=2 cohorts), there was a higher risk of delirium for patients with atrophy versus those without (RR 1.66, CI 1.21-2.27, p=0.03) (Figure 4A). Neither study met the standards for high-quality for further sensitivity analysis. Five additional studies examined atrophy in patients with and without delirium using ordinal scales, and all found significantly higher atrophy scores in patients with delirium (5/5).[5,6,21-23]

Leukoaraiosis—When comparing patients with and without leukoaraiosis (n=4 cohorts), there was no clear effect of leukoaraiosis on the risk of developing delirium (RR of 1.33, CI 0.58-3.01, p = 0.353) (Figure 4B). Sensitivity analysis with only high-quality studies yielded similar results (n=2, RR 1.45, CI 0.00-5677.15, p=0.672, Supplementary Appendix 7).

Four additional studies examined white matter changes in patients with and without delirium using ordinal scales. One study found significantly greater white matter changes in patients with delirium in deep white matter, but not periventricular white matter.[24] Another study found significantly greater white matter changes in patients with delirium in anterior white matter, but not posterior.[23] The final two studies did not find significant differences in white matter changes between patients with and without delirium.[5,22]

DISCUSSION

Our study affirmed that strokes in supratentorial, anterior, and cortical locations were more likely to be associated with delirium, as was more extensive clinical involvement of the anterior circulation. Conversely, there was no association between delirium and right- or left-sided lesions. While delirium is often considered to be a disorder of generalized brain dysfunction, a recent meta-analysis has identified discrete localizations of other cognitive impairments in stroke,[25] supporting the hypothesis that for delirium, an acute change in cognition, more specific localization may also be possible. The supratentorial compartment and anterior circulation comprise a broad network of cortical and subcortical structures, but papers did not consistently report more specific localizations within this territory. Further analysis, however, demonstrated that cortical strokes have a higher risk of delirium than subcortical strokes. Cortical networks in the anterior circulation, such as frontoparietal networks, are involved in higher-level cognitive skills including, but not limited to, attention, executive function, and language; deficits in these cognitive areas are core features in delirium. It remains unclear, however, whether anterior circulation strokes directly cause delirium, or rather increase the risk of delirium either by reflecting underlying comorbidities or by predisposing patients to further precipitating factors, such as infection or medication sensitivity. We were unable to evaluate these hypotheses due to the limited and heterogeneous reporting of covariates between studies in the context of localization.

Our meta-analysis demonstrated that there is no clear indication that right hemispheric strokes are more associated with delirium than left hemispheric strokes, despite prior reports.[3,6] It is possible that specific locations within the right hemisphere are associated with specific delirium symptoms, for example right MCA infarcts causing inattention in the context of neglect. However, due to the limited availability of combined hemisphere and vascular territory data, we were unable to compare the risk of delirium by more specific territories. Additionally, it remains unclear whether the precipitation of individual delirium symptoms such as inattention necessarily leads to development of the complete delirium syndrome[26], reflecting a pathobiological encephalopathy[27] superimposed on a vulnerable substrate. While delirium screening in stroke may have additional challenges that may be less common in more general medical contexts, delirium screens as used in the cited stroke studies have been validated according to reference standards[28-30] and at times have been adjusted to take into account focal deficits such as aphasia.[28]

Different symptom domains of delirium may ultimately have different localizations themselves and mapping of specific symptoms to specific focal lesions may yield an incomplete picture of delirium. For example, even aphasia can localize to multiple territories and neural networks, and dysfunction in regions connected to the lesion site rather than the lesion itself may also cause the neurologic deficit. Lesion-associated networks have been critical in understanding lesion-induced symptoms that may not map to a single brain location.[31] Such an approach may be even more valuable for delirium, in which broader network consequences of lesions associated with delirium may trigger the more complete syndrome.

In addition to delirium's associations with the described locations, delirium was also more likely to occur in patients with hemorrhagic strokes than ischemic strokes. The pathophysiology for this unclear, but may relate to additional hypoxic or ischemic dysfunction in tissue surrounding the hemorrhagic injury;[32] secondary phenomena, including inflammation, peripheral immune dysregulation, or a propensity for systemic infection;[33] or higher rates of intensive care.

More broadly, the pathophysiology of delirium is thought to be a multifactorial interplay between the severity of acute precipitating factors and the susceptibility caused by chronic predisposition and brain vulnerability. Even in the context of acute stroke, it appears that both acute factors, such as more widespread anterior circulation involvement, and chronic factors, such as brain atrophy, are both associated with higher risks of delirium. We were unable to study the quantitative influence of both acute and chronic factors jointly, however, given heterogeneity in reporting stroke volumes and chronic pathology and limitations in how various features were reported independently. Prospective studies are needed to address the interactions between acute and chronic factors, including how any prior history of cognitive impairments may relate to the associations between stroke locations and delirium.

Our systematic review used a rigorous search strategy with strict inclusion and exclusion criteria, offering a representative summary of the published literature evaluating delirium and stroke localization. Our sensitivity analyses strengthened the results by confirming their significance, despite study heterogeneity in how stroke and/or delirium diagnoses were made. As with any meta-analysis and systematic review, however, our results are limited by the studies currently available. Variability in reporting limited some analyses, in particular analysis of the joint and/or independent effects of the identified delirium associations. Furthermore, though there was no statistically significant difference between left and right sided lesions, insufficient data made it difficult to evaluate whether more specific foci within either hemisphere are involved in delirium. Lastly, interactions between specific brain regions and important covariates known to affect delirium in the non-stroke context, such as age, previous cognitive status, and comorbidities, remains a topic for future study. These limitations highlight important considerations for future work and reporting. More rigorous localization using a more sophisticated approach, such as voxel-by-voxel association analyses may allow for greater inferences to be drawn about neural networks and patterns of dysfunction and could be the next step in better understanding the localization of delirium.[34]

SUMMARY/CONCLUSIONS

This meta-analysis lays the groundwork for anticipating the risk of delirium during acute stroke, based on the stroke location and type, as well as chronic atrophy. While all patients with stroke merit some delirium prevention, better and earlier anticipation of patients with stroke at higher risk of delirium could help target more intensive multicomponent delirium prevention interventions as they continue to be developed[35-37]. This work also suggests that stroke may be an informative context in which to study the brain networks involved in both the acute precipitating and chronic predisposing factors of the pathophysiology of delirium. Future research using more quantitative imaging and more detailed covariates may

clarify whether delirium risk can be localized more precisely within specific anterior cortical locations or networks. A better understanding of specific localization of networks[34] involved in delirium may ultimately lead to more further insights into the pathophysiology of clinical delirium in broader clinical contexts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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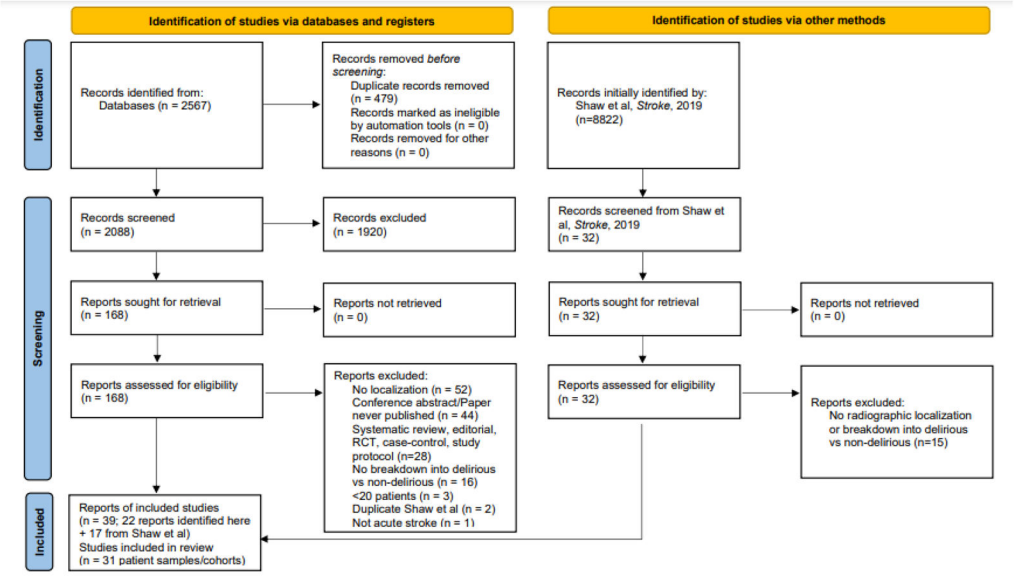

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1.
Flow diagram of the systematic review

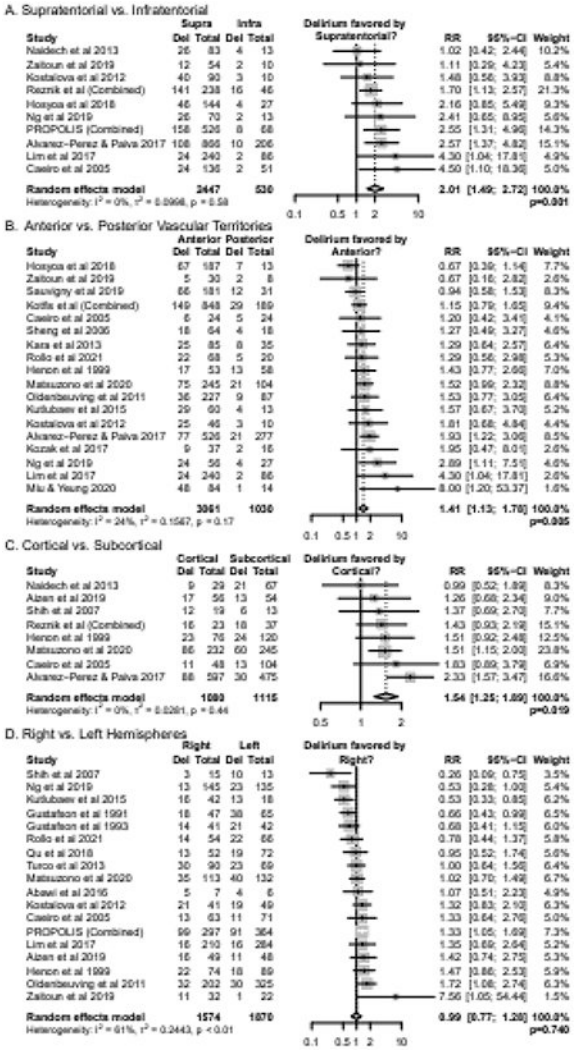

Figure 2. Relative Risks of Delirium by Stroke Locations.

Results of random-effects meta-analysis are displayed as Relative Risks (RR) alongside 95% confidence intervals (CI).

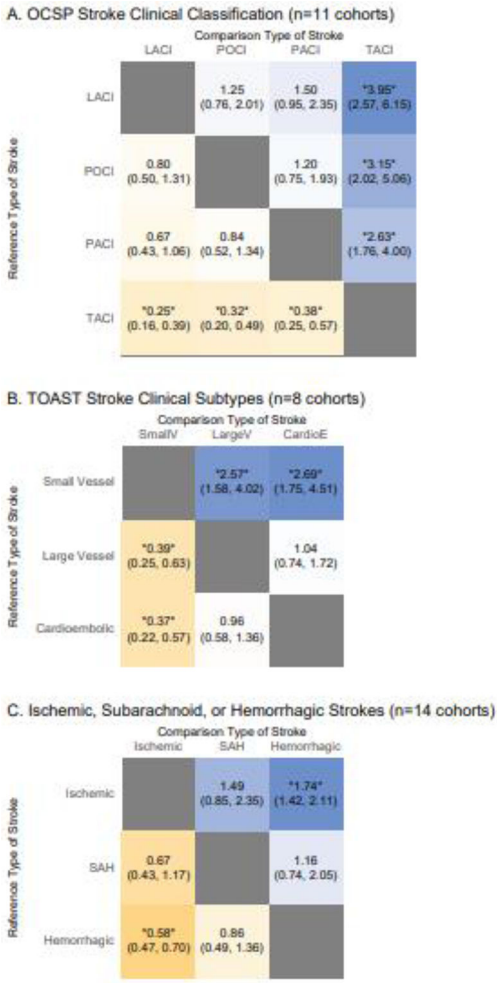

Figure 3. Relative Risks of Delirium by Types of Strokes.

Results of random-effects meta-analysis are displayed as Relative Risks alongside 95% confidence intervals in each cell, demonstrating a comparison between two groups as indicated. *= $p<0.05$.

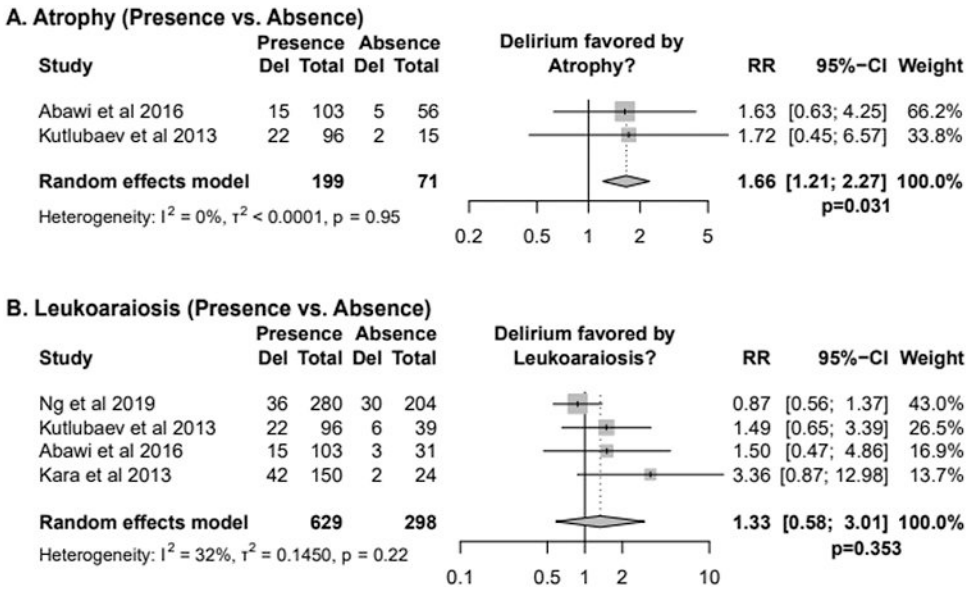

Figure 4. Relative Risks of Delirium by Chronic Pathology.

Results of random-effects meta-analysis are displayed as Relative Risks (RR) alongside 95% confidence intervals (CI).

Table 1.

Characteristics of patient cohorts included in the meta-analysis

Study	Country	n	Clinical Setting	Type of Stroke	Delirium Assessment	Excluded Stroke Impairments	Excluded Psychiatric Illness	Mean age, y	Women, n (%)	Delirium cases, n	Delirium cases, %
Abawi et al 2016[17]	Netherlands	103	Inpatient	Ischemic	DSM	No	No	80±8	53 (51%)	15	15
Aizen et al 2019[38]	Israel	110	Geriatric Rehabilitation Hospital	All stroke	CAM	No	No	80.2±8	57 (51.8%)	30	27.3
Alvarez-Perez & Paiva 2017[39]	Portugal	1072	Stroke Service	All stroke	Case note review DSM	No	No	68 (median), range: 77–83	507 (47.3%)	118	10.2
Caeiro et al 2005[40]	Portugal	218	Acute Stroke Unit	All stroke (including SAH)	DSM	Not reported	Not reported	57±13	88 (40.4%)	29	13
Gustafson et al 1991[41]	Sweden	145	Stroke Unit	All stroke, TIA	DSM	Yes, decreased GCS, aphasia	Not reported	73, range: 40–101	55 (37.9%)	69	48
Gustafson et al 1993[42]	Sweden	83	Stroke Unit	Supratentorial cerebral infarction	DSM	Yes, decreased GCS	Yes	74.7±8.1	31 (37.3%)	35	42
Haight & Marsh 2020[19]	USA	102	Intensive Care Unit	Ischemic stroke or ICH	CAM-ICU	Coma without recovery, presented outside of 72 hours, withdrawal of care on admission	Not reported	65, range: 26-97	49 (48%)	51	50
Henon et al 1999[21]	France	202	Stroke Unit	All stroke	DSM	No	Yes	75 (median), range: 45–101	105 (52.0%)	49	24.3
Hosoya et al 2018[14]	Japan	269	Stroke Unit	Any	ICDSC	No	No	75 ± 1.3 Delirium, 69.3 ± 1.0 Control	123 (45.7%)	97	36
Kara et al 2013[43]	Turkey	150	Neurology department	Unspecified	DSM	Yes, aphasia	Not reported	68.0±1.9	45 (30.0%)	42	28
Kostalova et al 2012[15]	Czech Republic	100	Stroke Unit	All stroke	Clinical	Not reported	Yes	73.5±11.5	47 (47.0%)	43	43
Kotfis et al (combined)[16,44]	Poland	760	Stroke Unit	Ischemic	CAM-ICU	No	No	75.95 ± 13.49 Delirium, 0.82 ± 12.15 Control	Not available for subgroup	121	15.9

Study	Country	n	Clinical Setting	Type of Stroke	Delirium Assessment	Excluded Stroke Impairments	Excluded Psychiatric Illness	Mean age, y	Women, n (%)	Delirium cases, n	Delirium cases, %
Kozak et al 2017[45]	Turkey	60	Stroke Unit	Acute ischemic stroke	DSM, DRS	Yes, aphasia	Yes	66.2±12.5	31 (51.7%)	11	18.3
Kutlubaev et al 2013[46]	Russia	96	Stroke Unit	Unspecified	DSM	Not reported	Yes	68.0±10.5	46 (47.9%)	22	23
Kutlubaev et al 2015[23]	Russia	73	Stroke Unit	Ischemic stroke or IPH, but not TIA, SAH, SDH	DSM	Not reported	Yes	74 (69.5-78)	52 (71.2%)	33	45.2
Lim et al 2017[47]	Korea	576	Stroke Unit	All stroke	CAM	Not reported	Not reported	65.2 (median), range: 23.0–93.0	208 (36.1%)	38	6.7
Matsuzono et al 2020[48]	Japan	461	N/A	Ischemic	Unspecified	Not reported	Not reported	Medians: 80 delirium, 69 No delirium	45.5 % delirimu 37.7 % no delirium	119	25.8
Miu and Yeung 2020[49]	Japan	314	Stroke Unit	All stroke	CAM	Not reported	Yes	72.9±10.3	151 (48.1%)	86	27.4
Naidech et al 2013[18]	USA	114	Stroke Unit	ICH	CAM	Not reported	Not reported	63.0±13.8	52 (45.6%)	31	27
Ng et al 2019[8]	Australia	280	Stroke Unit, General Medicine	Ischemic stroke	CAM	No	No	63.6±13.7	94 (33.6%)	36	12.9
Oldenbeuving et al 2011[6]	The Netherlands	527	Stroke Unit	All stroke	CAM	Not reported	Not reported	72.0 (median), range: 29.0–96.0	239 (45.4%)	62	11.8
PROPOLIS Combined[4,22,50-53]	Poland	750	Stroke Unit	All stroke	CAM	Not reported	Not reported	71.8±13.1	398 (53.1%)	203	27.1
Qu et al 2018[5]	China	261	Neurology Service	Ischemic	CAM	No	No	61.3 (IQR 14.8)	77 (29.2%)	38	14.5
Reimann et al 2021[54]	Austria	276	Neurology Intensive Care Unit	Non-traumatic SAH	ICDSC	Not reported	Not reported	56, range; 47-67	171 (62.0%)	65	23.6
Reznik et al (combined)[20,28,55]	USA	311	Neurology Intensive Care Unit	ICH	CAM-ICU	No	No	70.1±15.8	139 (50%)	157	55.3
Rollo et al 2021[24]	Italy	120	Stroke unit	Ischemic or ICH	CAM-ICU	No	No	71.8±12.6	48 (40%)	36	39
Sauvigny et al 2019[56]	Germany	212	Intensive Care Unit	SAH	RASS	No	No	53.8 ± 13.4 (Control),	134 (63.2%)	78	34.6

Study	Country	n	Clinical Setting	Type of Stroke	Delirium Assessment	Excluded Stroke Impairments	Excluded Psychiatric Illness	Mean age, y	Women, n (%)	Delirium cases, n	Delirium cases, %
								56.6 ± 13.4 (Delirium)			
Sheng et al 2006[57]	Australia	156	Stroke Unit	All stroke	Clinical	Not reported	Yes	79.2±6.7	73 (46.8%)	39	25
Shih et al 2007[7]	Taiwan	29	Neurology Service	Ischemic stroke in PCA territory	No official measurement	No official territory	Not reported	66.3 ± 13.05 (Delirium), 64.8 ± 9.85 (Control)	4 (13.8%)	14	48.3
Turco et al 2013[58]	Italy	176	Rehabilitation unit	Unspecified	CAM	No	No	81.7±6.4	118 (67.0%)	58	33
Zaitoun et al 2019[3]	Egypt	74	ICU and Stroke Unit	All stroke	DSM-IV	Not reported	Not reported	60.7±11.5	34 (45.9%)	15	20.3

Table 2.

Summary of Meta-Analysis

	Patients (n) with Delirium/Group (%)	RR [95% CI]	p-value
Supra- vs. Infra-tentorial Strokes (n=10)			
Supratentorial	605/2447 (24.7%)	**2.01 [1.49, 2.71]**	**0.001**
Infratentorial	53/530 (10.0%)	**1**	
Anterior vs. Posterior Territory Strokes (n=18)			
Anterior	722/3061 (23.6%)	**1.41 [1.13, 1.78]**	**0.005**
Posterior	152/1030 (14.8%)	1	
Cortical vs. Subcortical Strokes (n=8)			
Cortical	262/1080 (24.3%)	**1.54 [1.25, 1.89]**	**0.019**
Subcortical	185/1115 (16.6%)	**1**	
Right vs. Left Sided Strokes (n=18)			
Right	391/1574 (24.8%)	0.99 [0.77, 1.28]	0.740
Left	410/1870 (21.9%)	1	
OCSP Vascular Classification (n=11)			
Total anterior circulation infarct (TACI)	162/556 (29.1)	**3.95 [2.57, 6.15]**	**<0.05**
Partial anterior circulation infarct (PACI)	99/629 (15.7)	1.50 [0.95, 2.35]	ns
Posterior circulation infarct (POCI)	49/448 (10.9)	1.25 [0.76, 2.01]	ns
Lacunar Infarct (LACI)	65/977 (6.7)	1	Ref
TOAST Classifications (n=5)			
Cardioembolic	86/246 (35.0%)	**2.69 [1.75, 4.51]**	**<0.05<0.05**Ref
Large Vessel	123/355 (34.6%)	**2.57 [1.58, 4.02]**	
Small Vessel	58/422 (13.7%)	**1**	
Hemorrhagic vs. Ischemic Strokes (n=9)			
Hemorrhagic	198/578 (34.2%)	**1.74 [1.42, 2.11]**	**<0.05**
Subarachnoid	21/66 (31.8%)	1.52 [0.83, 2.31]	ns
Ischemic	641/3326 (19.3%)	1	Ref
Qualitative Atrophy (n=2)			
Present	37/199 (18.6%)	**1.66 [1.12, 2.27]**	**0.031**
Absent	7/71 (9.9%)	1	
Leukoaraiosis (n=4)			
Present	115/629 (18.3%)	1.33 [0.58; 3.01]	0.353
Absent	41/298 (13.8%)	1	

The relative risk (RR) of delirium according to different types or localizations of strokes were calculated using random-effects models (ns = not significant, i.e. p>0.05). Ref = reference, to clarify the reference group against which all other groups were compared for the purposes of this table in network meta-analyses across 3 or more groups. In all other cases, an RR value of 1 indicates the reference group.