The Impact of Delirium On Prognosis In Stroke: A Systematic Review and Meta-Analyses of Observational Studies

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Abstract

Background The outcomes of post-stroke delirium are inconsistent. Therefore, we conduct a meta-analysis to provide a comprehensive description of the impact of delirium on the outcomes including length of hospital stay and inpatient mortality after stroke.

Methods We searched electronic databases including PubMed, Google scholar, Web of Science and Cochrane Library databases up to April, 2021. Fixed-effect or random-effect model was used to summary odds ratio (OR) and mean difference (MD) with 95% confidence interval (CI).

Results 13 individual studies with total of 3592 patients met the inclusion criteria. The summary results revealed that stroke patients with delirium increased risk of inpatient mortality (OR = 6.35, 95% CI: 4.35–9.25, $p < 0.0001$), and had longer length of hospital stay (MD = 5.93, 95% CI: 2.79–9.07, $p < 0.0001$) compared to non-delirious patients.

Conclusions Delirium is associated with unfavorable outcomes in patients with stroke, particularly in higher inpatient mortality and longer length of stay. We should pay more attention to this clinical problem and managed appropriately to prevent poor prognosis.

Introduction

Delirium (acute confusional state) is a disorders characterized by disturbances in cognition, attention and consciousness with fluctuating intensity, which often develops within a few days or hours [1] and it is common in senile in-patient [2]. The reported prevalence of delirium during admission ranging from 13 to 48% [3–7].

The stroke itself is considered to be a risk factor for the delirium [8]. At present, the pathophysiology of delirium is unclear. However, current theories showed that neuro-inflammation and oxidative stress play a key role in development of delirium [9, 10]. In addition, several studies identified several risk factors for delirium post-stroke: cardio-embolic stroke, neglect, pre-existing cognitive impairment, left-sided strokes and metabolic disorders [4–6]. Stroke patients with delirium is associated with longer duration of hospitalization, higher mortality, higher institutionalization and lower quality of life [11].

Large amount of studies were performed on the prognosis in stroke with delirium [6, 12–23]. However, the findings were controversial. The present article was aimed to build powerful evidence regarding the impact of delirium on the prognosis of stroke: inpatient mortality and length of hospital stay.

Material And Methods

We used the PRISMA guidelines for guiding our systematic review of observational studies [24].

Search strategy

We searched electronic databases including PubMed, Google scholar, Web of Science and Cochrane Library databases up to April, 2021. The main search terms and strategy were used: “stroke” or “cerebral infarction” or “hemorrhagic stroke” or “ischemic stroke” or “subarachnoid hemorrhage (SAH)” or “transient ischemic attack (TIA)” and “delirium” or “confusion” or “acute confusional syndrome (ACS)” or “hallucination” and outcomes or prognosis or mortality or hospital stays or length of stay. We also manually searched the eligible candidate articles. The type of study design was not restricted, but only articles written in English were considered for inclusion.

Inclusion and exclusion criteria

A preliminary screening was carried out to elite the duplicates. After we reviewed the titles and abstracts for relevance to delirium in patients with stroke. Then, we reviewed full-text to identify studies according to the following criteria: (a) Studies reported at least 1 outcome in stroke with and without delirium; (b) The group was composed patients with stroke without delirium; (c) The main outcomes of interest include inpatient mortality and length of hospital stay; (d) screened delirium within 10 days after admission; (e) included enough data to calculate the odds ratio (OR) and mean difference (MD) with 95% confidence interval (CI). Studies were excluded if they: discussions, abstracts, comments, case reports, letters, reviews, and editorials.

Data extraction and quality assessment

Two independent investigators (Jing Zhang and Kai Liu) evaluated all included studies and inconsistencies between above two investigators were solved by discussion with a third author (Jie Wang). For each study, we extracted following items: primary author's last name, publication year, race, region, sample size, mean age, diagnostic tools, screening time, and relevant outcomes data (in-hospital mortality and length of hospital stay). Quality assessments of studies were conducted by the Newcastle-Ottawa scale (NOS) [25]. Studies with scores of 5 or above were considered "moderate or high" quality [26].

Statistical analysis

We calculated OR with 95% CI of inpatient mortality and MD with 95% CI of length of hospital stay via the crude data provided in the included articles. The heterogeneity was assessed using I^2 statistic, and $I^2 > 50\%$ suggested possibly significant heterogeneity [27]. If significant heterogeneity was observed, the random effect model was adopted for synthetic analyses. Otherwise, a fixed model was used. Sensitivity analysis was conducted to estimate the stability of results. Subgroup analysis and meta-regression were performed to explore source of the heterogeneity between the different studies. The publication bias was examined with Begg's test, and $p < 0.05$ was indicated statistically significant [28, 29]. Subgroup analysis was performed based on ethnicity, and meta-regression based on the publication year, ethnicity, sample size. All statistical analyses were conducted using Stata 12.0 (Stata Corp, College Station, Texas, USA) software.

Results

Study characteristics

We initially searched 1362 potential articles after searching electronic databases. Of these 1362 studies, 13 studies were included based on the inclusion and exclusion criteria. Of 13 included studies, 10 studies reported on the inpatient mortality, and 10 studies on the length of hospital stay (Table 1). The selection process is summarized in Fig. 1. The characteristics of all studies are shown in Table 1. According to the NOS, all articles included in the meta-analysis were considered to be "moderate or high" quality.

Table 1
Baseline characteristics of studies included in meta-analysis.

First author, Year	Region	Mean/Median Age, SD/IQR (Year)		No. of participants	Race	Tools of assessing delirium	Screening time	Outcomes
		D+	D-					
Nydahl, 2017	German	Median (IQR), 80.5 (75.0–87.2)	Median (IQR), 72.0 (60.0–81.0)	54	Caucasian	DSM-IV	Within 2 days of admission	I, L
Oldenbeuving, 2011	Netherlands	Mean (SD), 78 (8.7)	Mean (SD), 71 (12.4)	527	Caucasian	CAM	During the first week of admission	I, L
Kozak, 2016	Turkey	Mean (SD), 64.63 (13.18)	Mean (SD), 72.91 (5.61)	60	Caucasian	DSM-V and DRS	On admission	L
Turco, 2013	Italy	Mean (SD), 81.9 (6.1)	Mean (SD), 81.6 (6.6)	176	Caucasian	CAM	On admission	I, L
Zaitoun, 2019	Egypt	Mean (SD), 68.6 (9.6)	Mean (SD), 58.8 (11.2)	74	African	CAM	Within 3 days after stroke	I
Miu, 2012	China	Mean (SD), 78.8 (8.9)	Mean (SD), 70.7 (9.9)	314	Asian	CAM	Day 1 to day 5 after admission	I, L
Gustafson, 1991	Sweden	Mean, 76	Mean, 69	145	Caucasian	DSM-III	On admission	I, L
Mcmanus, 2009	United Kingdom	-	-	82	Caucasian	CAM	Within 4 days of admission	I
Lim, 2017	Korea	Mean (SD), 70.6 (9.3)	Mean (SD), 64.9 (13.4)	576	Asian	CAM	On admission	I, L
Sheng, 2006	Australia	Mean (SD), 81.5 (5.5)	Mean (SD), 78.4 (6.9)	156	Brown race	DSM-IV	Within 3d of admission	I, L
Dostovic, 2018	Bosnia and Herzegovina	-	-	200	Caucasian	DRS and DSM-IV	Within 24 hours after hospitalization	I
Kotfis, 2019	Poland	Median (IQR), 79.00 (67.50–87.00)	Median (IQR), 70.00 (63.00–81.00)	1001	Caucasian	CAM-ICU	At admission	L
Silva, 2021	Brazil	Mean (SD), 67.993 (12.717)	Mean (SD), 59.9 (13.1)	227	American	CAM-ICU	At admission	L
I: Inpatient mortality; L: Length of hospital stay; D+: Stroke with delirium; D-: Stroke without delirium; IQR, Interquartile Range; SD: Standard Deviation; ICU: Intensive care unit; RASS: Richmond Agitation-Sedation Scale; CAM: Confusion								
Assessment Methods; DSM, Diagnostic and statistical manual of mental disorders; DRS, Delirium Rating Scale.								

Results of meta-analysis and study quality

Overall, 13 studies investigated the impact of delirium on the outcomes including inpatient mortality and length of hospital stay after stroke [6, 12–23]. There was significant heterogeneity ($I^2 = 92.10\%$) in length of hospital stay, and a random effect model was applied. No significant heterogeneity was found in inpatient mortality ($I^2 = 14.80\%$). The delirium was associated with a 6.35-fold increased risk of inpatient mortality under the fixed model after stroke (OR = 6.35, 95% CI: 4.35–9.25, $p < 0.0001$, Fig. 2). Our results indicated that delirium in patients with stroke was significantly correlated with longer length of hospital stay compared to stroke without delirium, with a pooled MD of 5.93 (MD = 5.93, 95% CI: 2.79–9.07; $p < 0.0001$, Fig. 3). Subgroup analysis was performed based on ethnicity. Regarding ethnicity, delirium was associated with an increased risk of inpatient mortality in Caucasian (OR = 6.63, 95%CI: 4.20–10.46, $p < 0.0001$, Fig. 2) and others (OR = 5.69, 95%CI: 2.92–11.90, $p < 0.0001$, Fig. 2). For length of hospital stay, we found that delirium had a longer hospital stay than non-delirium in Caucasian (MD = 3.57, 95%CI: 0.32–6.82, $p = 0.031$) and others (MD = 10.51, 95%CI: 3.40–17.63, $p = 0.004$). Meta-regression did not identify any source of heterogeneity for length of stay (race: Caucasian and Others, $Pr = 0.124$; sample size: < 300 and ≥ 300 , $Pr = 0.475$; publication year: 2015–2021 and 1991–2014, $Pr = 0.519$).

Sensitivity analysis and publication bias

We performed sensitivity analysis to measure the robustness of the pooled results, the results of sensitivity analysis suggested that there was no unstable data (Fig. 4 and Fig. 5). The funnel plot for inpatient mortality and length of stay were symmetric visually (Fig. 6 and Fig. 7). Furthermore, there was no evidence of publication bias (inpatient mortality: $P_p = 0.721$; length of hospital stay: $P_p = 0.371$).

Discussion

To better understand the prognosis of strokes with delirium, we performed a large systematic review and meta-analysis of 13 observational studies. Three outcome parameters related to delirium in stroke patients were estimated: inpatient mortality and length of hospital stay.

As for inpatient mortality, the results of published article were controversial. The pooled estimates of 10 studies demonstrated that post-stroke delirium had higher inpatient mortality compared to patients without delirium (OR = 6.35, 95% CI: 4.35–9.25, $p < 0.0001$). With regard to length of hospital stay, the pooled results of 10 studies suggested that stroke with delirium had a 5.93 days longer than stroke without delirium (MD = 5.93, 95% CI: 2.79–9.07; $p < 0.0001$). This is similar to previous studies on delirium in postoperative patients and intensive care unit [30–32]. In 2012, Shi et al [11] showed that post-stroke delirium had higher hospital mortality (OR = 4.71), and longer hospital stays (MD = 9.39 days). However, only a small number of eligible studies were included. Subgroup analysis suggested that there was no significant difference in inpatient mortality between Caucasian and Others (OR: 6.63 vs 5.59, respectively). In addition, significant difference was found in length of hospital stay between Caucasian and Others (MD: 3.57 days vs 10.51 days, respectively).

We found significant heterogeneity among studies exists in length of hospital stay. However, meta-regression did not identify any source of heterogeneity. We supposed that the reasons of significant heterogeneity may be explained by followings: diagnostic criteria for delirium, stroke severity, location of stroke lesions, sample size and delirium onset, development level of country. NOS showed that all selected studies were considered to be moderate or high. Potential publications were not detected in length of hospital stay and inpatient mortality. According to above, we have reasons to think, the pooled results were robust.

The following limitations of our study should be emphasized. First, the included studies showed that delirium was screened by different tools, thus, the results should be interpreted with caution. Second, the severity of delirium was not assessed. In fact, no available tools was used for the severity of delirium. Different degrees of delirium may have different outcomes. Thirdly, the language was restricted to English. Thus, the other available studies published in non-English may be ignored.

Our comprehensive systematic review and meta-analysis suggested that delirium was associated with poor prognosis including inpatient mortality and length of hospital stay. However, our results should be interpreted with caution because of the above

limitations. In consideration of these poor outcomes, early screening and effective intervention for delirium may protect against delirium and improve the prognosis. Future larger, well-designed multi-centred cohort studies is needed.

Declarations

Founding

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not available

References

1. Inouye SK, Westendorp RG, Saczynski JS (2014) Delirium in elderly people. *Lancet* 383:911–922. [https://doi.org/10.1016/S0140-6736\(13\)60688-1](https://doi.org/10.1016/S0140-6736(13)60688-1)
2. Inouye SK (2006) Delirium in older persons. *N Engl J Med* 354:1157–1165. <https://doi.org/10.1056/NEJMra052321>
3. Gustafson Y, Olsson T, Hagg E et al (1993) Acute confusional state (delirium) soon after stroke is associated with hypercortisolism. *Cerebrovasc Dis* 3: 33–38. <https://doi.org/10.1159/000108667>
4. Eleonora R, Antonio C, Giacomo DM et al (2021) Delirium in acute stroke: A prospective, cross-sectional, cohort study. *Eur J Neurol*. 2021 May;28(5):1590–1600. doi: 10.1111/ene.14749
5. Caeiro L, Ferro JM, Albuquerque R et al (2004) Delirium in the first days of acute stroke. *J Neurol* 251:171–178. <https://doi.org/10.1007/s00415-004-0294-6>
6. Sheng AZ, Shen Q, Cordato D et al (2006) Delirium within three days of stroke in a cohort of elderly patients. *J Am Geriatr Soc* 54:1192–1198. <https://doi.org/10.1111/j.1532-5415.2006.00806.x>
7. Hénon H, Lebert F, Durieu I et al (1999) Confusional state in stroke: relation to preexisting dementia, patient characteristics, and outcome. *Stroke* 30:773–779. <https://doi.org/10.1161/01.str.30.4.773>
8. Ferro JM, Caeiro L, Verdelho A (2002) Delirium in acute stroke. *Curr Opin Neurol* 15:51–55. <https://doi.org/10.1097/00019052-200202000-00009>
9. Zaal IJ, Slooter AJ (2012) Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management. *Drugs* 72:1457–1471. <https://doi.org/10.2165/11635520-000000000-00000>
10. Maldonado JR (2013) Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry* 21:1190–1222. <https://doi.org/10.1016/j.jagp.2013.09.005>
11. Shi Q, Presutti R, Selchen D et al (2012) Delirium in acute stroke: a systematic review and meta-analysis. *Stroke* 43:645–649. <https://doi.org/10.1161/STROKEAHA.111.643726>
12. Nydahl P, Bartoszek G, Binder A et al (2017) Prevalence for delirium in stroke patients: A prospective controlled study. *Brain Behav* 7:e00748. <https://doi.org/10.1002/brb3.748>
13. Oldenbeuving AW, de Kort PL, Jansen BP et al (2011) Delirium in the acute phase after stroke: incidence, risk factors, and outcome. *Neurology* 76:993–999. <https://doi.org/10.1212/WNL.0b013e318210411f>
14. Kozak HH, Uğuz F, Kılınç İ et al (2017) Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: Incidence and association between clinical features and inflammatory markers. *Neurol Neurochir Pol* 51:38–44. <https://doi.org/10.1016/j.pjnns.2016.10.004>

15. Turco R, Bellelli G, Morandi A et al (2013) The effect of poststroke delirium on short-term outcomes of elderly patients undergoing rehabilitation. *J Geriatr Psychiatry Neurol* 26:63–68. <https://doi.org/10.1177/0891988713481265>
16. Zaitoun AM, Elsayed DAF, Ramadan BM et al (2019) Assessment of the risk factors and functional outcome of delirium in acute Stroke. *The Egyptian Journal of Neurology Psychiatry Neurosurgery* 55:17. <https://doi.org/10.1186/s41983-019-0059-x>
17. Miu DK, Yeung JC (2013) Incidence of post-stroke delirium and 1-year outcome. *Geriatr Gerontol Int* 13:123–129. <https://doi.org/10.1111/j.1447-0594.2012.00871.x>
18. Gustafson Y, Olsson T, Bucht G et al (1991) Acute confusional states (delirium) in stroke patients. *Cerebrovasc Dis* 1:257–264. <https://doi.org/10.1159/000108852>
19. McManus J, Pathansali R, Hassan H et al (2009) The course of delirium in acute stroke. *Age Ageing* 38:385–389. <https://doi.org/10.1093/ageing/afp038>
20. Lim TS, Lee JS, Yoon JH et al (2017) Cigarette smoking is an independent risk factor for post-stroke delirium. *BMC Neurol* 17:56. <https://doi.org/10.1186/s12883-017-0840-3>
21. Dostovic Z, Smajlovic D, Ibrahimagic OC et al (2018) Mortality and Functional Disability of Poststroke Delirium. *Mater Sociomed* 30:95–97. <https://doi.org/10.5455/msm.2018.30.95-97>
22. Kotfis K, Bott-Olejnik M, Szylińska A et al (2019) Could Neutrophil-to-Lymphocyte Ratio (NLR) Serve as a Potential Marker for Delirium Prediction in Patients with Acute Ischemic Stroke? A Prospective Observational Study. *J Clin Med* 8. <https://doi.org/10.3390/jcm8071075>
23. Fialho SIT, Assis LP, Timotio AT et al (2021) Impact of Delirium and Its Motor Subtypes on Stroke Outcomes. *Stroke* 52:1322–1329. <https://doi.org/10.1161/STROKEAHA.120.026425>
24. Moher MDFM, Thombs D BD et al (2018) Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* 319:388–396. <https://doi.org/10.1001/jama.2017.19163>
25. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 25:603–605. <https://doi.org/10.1007/s10654-010-9491-z>
26. Asbridge M, Hayden JA, Cartwright JL (2012) Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ* 344:e536. <https://doi.org/10.1136/bmj.e536>
27. Higgins JP, Thompson SG, Deeks JJ et al (2003) Measuring inconsistency in meta-analyses. *BMJ* 327:557–560. <https://doi.org/10.1136/bmj.327.7414.55>
28. Egger M, Davey SG, Schneider M et al (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–634. <https://doi.org/10.1136/bmj.315.7109.629>
29. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50:1088–1101
30. Francis J, Martin D, Kapoor WN (1990) A prospective study of delirium in hospitalized elderly. *JAMA* 263:1097–1101
31. Ely EW, Gautam S, Margolin R et al (2001) The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 27:1892–1900. <https://doi.org/10.1007/s00134-001-1132-2>
32. Olofsson B, Lundström M, Borssén B et al (2005) Delirium is associated with poor rehabilitation outcome in elderly patients treated for femoral neck fractures. *Scand J Caring Sci* 19:119–127. <https://doi.org/10.1111/j.1471-6712.2005.00324.x>

Figures

Figure 1

Flow chart of literature screening for systematic review and meta-analysis.

Figure 2

Forest plot for inpatient mortality in patients with and without delirium.

Figure 3

Forest plot for length of hospital stay in patients with and without delirium.

Figure 4

Sensitivity analysis for inpatient mortality.

Figure 5

Sensitivity analysis for length of hospital study.

Figure 6

Funnel plot for inpatient mortality.

Figure 7

Funnel plot for length of hospital study.