Review

Stroke Survivors Have Almost Three Times Higher Risk of Depression; A Systematic Review and Meta-Analysis

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Posted Date: 7 October 2025

doi: 10.20944/preprints202510.0553.v1

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 doi:10.20944/preprints202510.0553.v1

Review

Stroke Survivors Have Almost Three Times Higher Risk of Depression; A Systematic Review and Meta-Analysis

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Abstract

Background: Post-stroke depression (PSD) is one of the most frequent and important complications following stroke that adversely conditions functional recovery and patient's quality of life. Meanwhile the prevalence proportion of PSD has been widely documented, ranging from 20 till 60%, the relationship between stroke and the manifestation of PSD, quantified with the odds ratio (OR), has been less explored. The primary aim of this meta-analysis is to determine prevalence odds ratio of suffering depression in stroke survivors. Prevalence proportion of PSD was also analyzed as a secondary aim. **Methods**: A pre-registered meta-analysis designed based on Prisma guidelines with searches from inception to 2024 September 23 was carried out on PubMed and Web of Science databases. Studies reporting the prevalence OR associated with PSD manifestation were eligible for inclusion to achieve the primary aim. Twenty-four comparative studies, including a total population of 947617 people, met the inclusion criteria. PSD prevalence proportion was extracted from 193 articles, including 484846 stroke patients. Quality assessments were performed using the Newcastle-Ottawa scale (NOS). Data were meta-analyzed using random effects model. **Results**: Compared with control population, stroke survivals had higher odds of developing PSD (OR: 2.81; 95% CI: 2.36-3.35). Prevalence of PSD was 32.15% ± 15.81. **Conclusions**: Stroke survivals have almost 3 times higher probability of suffering depression after stroke than the general population and almost one third of stroke patients will suffer PSD.

Keywords: depression; stroke; prevalence; meta-analysis; odds ratio

Introduction

Stroke is characterized by an interruption of blood flow to critical regions of the brain, leading to irreversible damage and long-term effects on the nervous system. The underlying etiology of stroke can be thrombotic, hemorrhagic, or embolic, with most cases (around 85%) being ischemic in nature. Stroke is the second leading cause of death and the third leading cause of acquired disability in adults worldwide [1–4].

One of the major contributors to stroke-related disability associated is the development of neuropsychiatric disorders. Post-stroke emotional and mood disorders include depression, anxiety, emotional incontinence, anger propensity, and fatigue [5]. These emotional disturbances negatively impact clinical outcomes for patients [6].

Depression worsens functional recovery after stroke, reduces quality of life, leads to less efficient use of rehabilitation services, and increases mortality [7]. Longitudinal studies have shown that post-stroke depression (PSD) increases its prevalence during the first few weeks following the stroke and

 doi:10.20944/preprints202510.0553.v1

seriously impairs cognitive recovery. Interestingly, more than half (53%) of patients who suffer from early-onset PSD (within the first 3 months after the stroke) end up with persistent depression [8–10].

The estimated prevalence of PSD is around 30-35%, with reported rates ranging from 20 to 60% [11,12]. Several observational studies and systematic reviews have reported prevalence proportions of PSD in varying degrees and formats. However, despite the abundance of primary studies, it is surprising that no systematic review focusing specifically on comparative studies with a control arm is currently available [13].

The odds ratio, derived from longitudinal, case-control, and cross-sectional studies, offers a more robust measure of association than a simple percentage percentages. It accounts for the relative likelihood of an outcome following a specific exposure, thereby providing deeper insight into potential individualized risk. For this reason, we aimed to conduct a meta-analysis of all peer reviewed, two-armed primary studies to calculate a pooled odds ratio for PSD [14].

Methods

Study Design and Search Strategy

A pre-registered systematic review and meta-analysis (INPLASY registration number: INPLASY202440106) was conducted on studies reporting the prevalence of depression as a consequence of brain stroke published from inception up to September 23, 2024. The search was performed across two major medical databases, PubMed and Web of Science, in accordance with the Prisma 2020 guidelines [15].

A comprehensive and unrestricted search protocol was developed based on the following PICO framework: Patients: adult patients with brain stroke; Intervention: N/A; Comparison: Prevalence of depression in stroke patients vs. control group; Outcome: Prevalence.

The PubMed query was: ((((stroke [Text Word]) OR (post-stroke [Text Word])) OR (stroke [MeSH Terms])) AND ((depression [Text Word]) OR (depression [MeSH Terms]))) AND ((((prevalence [Text Word]) OR (prevalence [MeSH Terms])) OR (incidence [Text Word])) OR (incidence [MeSH Terms])). An identifcal search strategy, with appropriate adaptations for database-specific syntax, was applied to the Web of Science database.

Inclusion and Exclusion Criteria

The inclusion screening process consisted of two main stages: (1) title and abstract screening; and (2) full-text screening. During the title and abstract screening, studies that clearly did not report on PSD were excluded. In the full-text screening stage, studies were categorized into three groups: 1. Excluded: Studies that did not report the prevalence of PSD; 2. Partially included: Studies that repored the prevalence of PSD only as a percentage. For these, only the sample size and percentage of stroke survivors with depression were recorded; 3. Fully included: Comparative studies with a control group that reported our outcome of interest (prevalence odds ratio (OR) with 95% confidence intervals (CI)) and prevalence proportion of PSD. These studies underwent complete data extraction and quality assessment.

Data Extraction and Quality Assessment

In this systematic review, the prevalence OR was set as the main outcome of interest hence, all studies reporting OR or sufficient data to calculate the OR with a 95% CI, were chosen for quality assessment and complete data extraction, consisting of first author's name, publication year, sample size, country where the study was conducted, follow-up duration and the scale implemented for depression assessment.

As recommended, for quality or risk of bias assessment of cohort and case-control studies, Newcastle-Ottawa score (NOS) was applied [16]. Also to evaluate cross-sectional studies, an adapted version of NOS was used which is attached as appendix A. A color code was designed for better

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visualization of risk of bias being red for score 0 to 3 (high risk of bias), yellow for 4 to 6 (average risk of bias) and green for 7 to 9 (low risk of bias).

Among assessed studies, there were studies titled as case-control studies, but the design matched better with cohort studies, since all of them had a prospective nature. On such occasions the cohort questionnaire of NOS scale was applied for more adequate evaluation.

For having a comprehensive sum of mean ± standard deviation (SD) of PSD prevalence proportion in actual literature, associated data was extracted from all included studies.

EndNote 21 and Microsoft excel 2024 softwares were used for above mentioned data extraction and quality assessment process.

Statistical Analysis

In this meta-analysis, the OR with 95% CI [95% CI] was the primary outcome of interest. The effect size was expressed as the log odds ratio with its standard error. Due to the heterogeneous nature of the included studies, a random-effects model was used to calculate the pooled effect, which is presented in a forest plot.

A Begg's funnel plot was used for the qualitative evaluation of publication bias. For quantitative evaluation, Begg and Mazumdar's rank correlation test and Egger's regression tests were applied. Given the discrepancy between the quantitative and qualitative assessments, the results of Duval and Tweedie's trim and fill method were also reported [17,18].

Heterogeneity was assessed using the I^2 and Q statistics, along with their corresponding *P-values*. To evaluate the sensitivity of the meta-analysis results to individual studies, a one-study-removed sensitivity analysis was performed and presented as forest plot. In this analysis, each primary study was sequentially excluded, and the overall effect size was recalculated to assess the robustness of the findings.

All meta-analytical tests were conducted using Comprehensive Meta-Analysis software, version 4 (Borenstein, M., Hedges, L., Rothstein, H. Biostat, Englewood, NJ 2022). A *P-value* < 0.05 was considered statistically significant in all analyses.

IBM SPSS Statistics (version 27) was applied to calculate the mean ± SD of PSD prevalence proportion and to generate the associated distribution chart.

Results

Search Results

The initial search retrieved a total of 5887 published papers. After removing 1735 duplicates and 3 retracted articles, 4149 studies were screened based on their titles and abstracts. Of these, 3881 papers were excluded, and 268 studies were selected for full-text screening, as illustrated in Figure 1.

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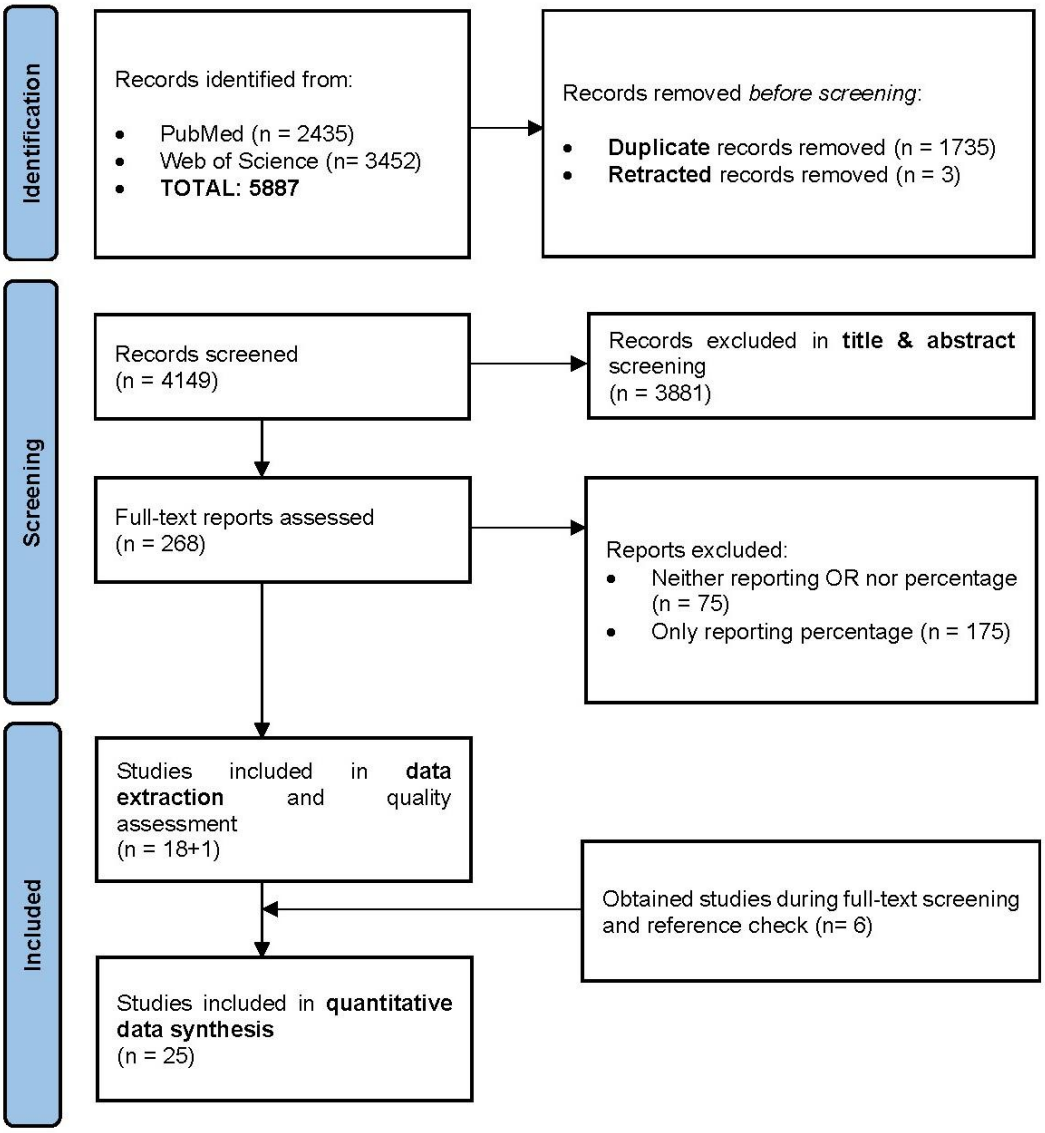

Figure 1. PRISMA flow diagram for search strategy.

During the full-text screening, 75 articles were excluded. A total of 175 primary studies reporting the prevalence proportion (%) of PSD were separately recorded for prevalence estimation. Additionally, 18 comparative studies with control arms, reporting both prevalence OR and the prevalence proportion of depression following stroke, were finally enrolled for complete data extraction and quality assessment.

These study groups are summarized in Figure 2.

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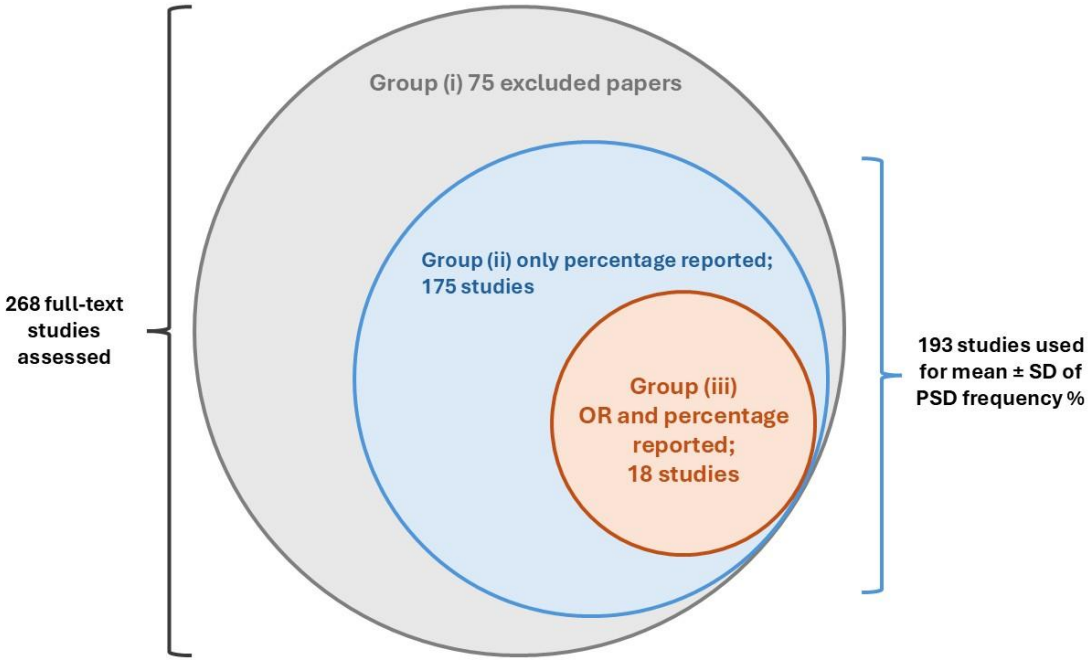

Figure 2. Study inclusion groups.

During the full-text screening phase, six aging cohort studies were also identified and directly included in the data synthesis [19–24]. These cohorts had previously been analyzed in a similar meta-analysis with a different study design [25].

Studies and Patients' Characteristics

This meta-analysis encompasses a total number of 947617 participants, comprising 349093 individuals with brain stroke and 598524 controls. The reported OR [95% CI] ranged from 1.25 [1.07-1.45] to 42.68 [2.50-727.47]. Two studies reported ORs of 1.37 [0.90-2.09] [22] and 1.48 [0.99-2.23] [26], neither of which reached statistical significance.

Among the 24 included studies, the earliest was published in 1994 and the most recent in 2024, spanning three decades of medical literature. The primary studies varied widely in the depression assessment tools used, and the follow-up periods ranged from no follow-up to as long as 10 years.

Notably, Brodaty *et al*. reported their findings at two different follow-up intervals, 3 months and 15 months, which led to the inclusion of 25 data points derived from 24 studies.

The study designs included longitudinal, case-control, cross-sectional, and retrospective cohort studies. Detailed information is presented in Data Extraction Table 1. Of all included studies, only two did not report a statistically significant increase in the prevalence of depression among stroke survivors compared to control groups; the corresponding OR values in these cases are highlighted in red in the data extraction table [22,26].

Table 1. Complete data extraction table.

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First author's name	Publication year	Sample size	Depression prevalence (among stroke patients)	Follow-up duration	Depression assessment scale	Study type	country	Odds ratio [95% CI]
Andersen, G. et al.	1994	Stroke: 211 Control: 122	25.1%	1 year	HDRS	Prospective case-control	Denmark	4.21 [1.99-8.89]
Beekman, A. T. et al.	1998	Strok: 173 Control: 1026	27.2%	10 years	CES-D	Longitudinal	Netherlands	3.88 [2.60-5.78]
Brodaty, H. et al. 3m	2007	Stroke: 158 Control: 100	12.0%	3 months	DSM-IV	Longitudinal	Australia	4.15 [1.19-14.41]
Brodaty, H. et al. 15m	2007	Stroke: 140 Control: 100	20.7%	15 months	DSM-IV	Longitudinal	Australia	7.23 [2.13-24.54]
Lindén, T. et al.	2007	Stroke: 149 Control: 745	33.6%	20 months	DSM III-R	Case-control	Sweden	3.40 [2.30-5.00]
Fatoye, F. O. et al.	2009	Stroke: 118 Control: 118	39.6%	11 months	BDI	Case-control	Nigeria	4.22 [2.21-8.02]
Hornsten, C. et al.	2012	Stroke: 129 Control: 472	50.4%	N/A	GDS-15, MADRS, OBS	Cross-sectional	Sweden	1.94 [1.31-2.88]
Fuller-Thomson, E. et al.	2012	Stroke: 858 Control: 65855	7.4%	N/A	CIDI-SF	Cross-sectional	Canada	2.21 [1.61-3.04]
Paul, N. et al.	2013	Stroke: 241 Control: 262	46.8%	8-10 months (average 10.79)	bGDS	Case-control within a prospective cohort	India	19.95 [10.09-39.47]
Steptoe, A. et al.	2013	Stroke: 127 Control: 4852	37.8%	7.8 years	CESD-8	Cohort	England	1.83 [1.27-2.64]
Börsch-Supan, A. et al.	2013	Stroke: 1082 Control: 25485	39.6%	3.8 years	EURO-D	Cohort	Europe	1.75 [1.55-1.99]
Mbelesso, P. et al.	2014	Stroke: 35 Control: 70	88.6%	N/A	MADRS	Cross-sectional case-control	Central Africa republic	19.37 [6.05-62.00]
Sonnega, A. et al.	2014	Stroke: 820 Control: 12991	31.6%	6.9 years	CESD-8	Cohort	USA	1.25 [1.07-1.45]
Zhao, Y. et al.	2014	Stroke: 89 Control: 4932	48.3%	6.9 years	CESD-10	Cohort	China	1.37 [0.90-2.09]
Bulloch, A. G. M. et al.	2015	Not Specified	22.7%	N/A	CIDI-SFMD	Cross-sectional	Canada	4.70 [2.40-9.40]
Jørgensen, T. S. et al.	2016	Stroke: 135417 Control: 145499	25.4%	2 years	ICD-10	Cohort	Denmark	4.02 [3.93-4.11]
Maajiwee, N. A. et al.	2016	Stroke: 325 Control: 147	19.5%	10 years	HADS	Cohort	Netherlands	4.70 [2.00-11.00]
Wong, R. et al.	2017	Stroke: 135 Control: 6855	35.5%	6 years	CESD-9	Cohort	Mexico	1.45 [1.01-2.07]
Oni, O. D. et al.	2018	Stroke: 70 Control: 70	22.9%	N/A	ICD-10	Cross-sectional case-control	Nigeria	42.68 [2.50-727.47]
Shin, C. et al.	2019	Stroke: 157 Control: 4625	57.3%	7.9 years	CESD-10A & B	Cohort	Korea	2.04 [1.48-2.82]
Khedr, E. M. et al.	2020	Stroke: 103 Control: 50	36.9%	N/A	DSM IV TR	Cross-sectional	Egypt	4.28 [1.67-10.99]
Li, X. Y. et al.	2020	Stroke: 374 Control: 18784	6.9%	N/A	WMH-CIDI	Cross-sectional	Canada	1.48 [0.99-2.23]
Lee, E. J. et al.	2022	Stroke: 343 Control: 10779	21.8%	N/A	PHQ9	Cross-sectional	Korea	2.72 [2.08-3.54]
Choi, H. L. et al.	2023	Stroke: 207678 Control: 294506	33.6%	2 years	ICD-10	Retrospective cohort	Korea	2.49 [2.46-2.53]

Quality Assessment

The results of quality assessment are presented in Table 2. The overall quality of published evidence is acceptable, and, importantly, no study with high risk of bias was included.

Table 2. Quality assessment (risk of bias) table.

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Study name	Selection	Comparability	Outcome	Score (risk of bias)
Beekman, A. T. et al. (1998)	★★☆☆	★★	★★★	7 (low)
Brodaty, H, et al. (2007)	★★★☆	★★	★★★	8 (low)
Hornsten, C. et al. (2012)	★☆★(★★)	★	(★★)★	8 (low)
Paul. N. et al. (2013)	★★★★	★★	★★★	9 (low)
Mbelesso, P. et al. (2014)	★☆☆(★★)	☆	(★★)☆	5 (average)
Jørgensen T. S. et al. (2016)	★★★★	★★	★★★	9 (low)
Maaijwee, N. A. et al. (2016)	★★★☆	★★	★★★	8 (low)
Oni, O. D. et al. (2018)	★★★(★★)	☆	(★★)★	8 (low)
Lee, E. J. et al. (2022)	★★★(★★)	☆	(★★)★	8 (low)
Choi, H. L. et al. (2023)	★★★★	★★	★★☆	8 (low)
Dymm, B. et al. (2024)	★★★☆	☆☆	★★★	6 (average)
Andersen, G. et al. (1994)	★★★☆	★☆	★★★	7 (low)
Lindén, T. et al. (2007)	★★★☆	★★	★★★	8 (low)
Fatoye, F. O. et al. (2009)	★★☆☆	★★	★★☆	6 (average)
Fuller-Thomson, E. et al. (2012)	★★★(★☆)	★	(★★)★	8 (low)
Bulloch, A. G. M. et al. (2015)	★★★(☆☆)	★	(★★)★	7 (low)
Khedr, E. M. et al. (2020)	★☆☆(★★)	☆	(★★)★	6 (average)
Li, X. Y. et al. (2020)	★★☆(★☆)	★	(★★)★	7 (low)
Sonnega, A. et al. (2014)	★★★☆	☆☆	★★★	6 (average)
Steptoe, A. et al. (2013)	★★★☆	☆☆	★★★	6 (average)
Börsch_supan, A. et al. (2013)	★★★☆	☆☆	★★★	6 (average)
Zhao, Y. et al. (2014)	★★★☆	☆☆	★★★	6 (average)
Shin, C. et al. (2019)	★★★☆	☆☆	★★★	6 (average)
Wong, R. et al. (2017)	★★★☆	☆☆	★★★	6 (average)

It is also worth noting that the six aging cohorts directly included in the quality assessment and data synthesis phase were categorized as having an average risk of bias, with score of 6 out of 9. This rating is primarily due to their differing research focus, which was not on depression, and because the cohort arms were not adjusted accordingly. Therefore, the obtained score should not be seen as diminishing the strong methodology of these cohorts, but rather as reflecting the lower relevance of their data to our specific review question.

Meta-Analysis Results and Frequency Analysis

The present study reveals the concerning finding that stroke survivors have nearly a threefold higher risk of depression compared to general population (OR = 2.81 [2.36-3.35]), as shown in the forest plot (Figure 3).

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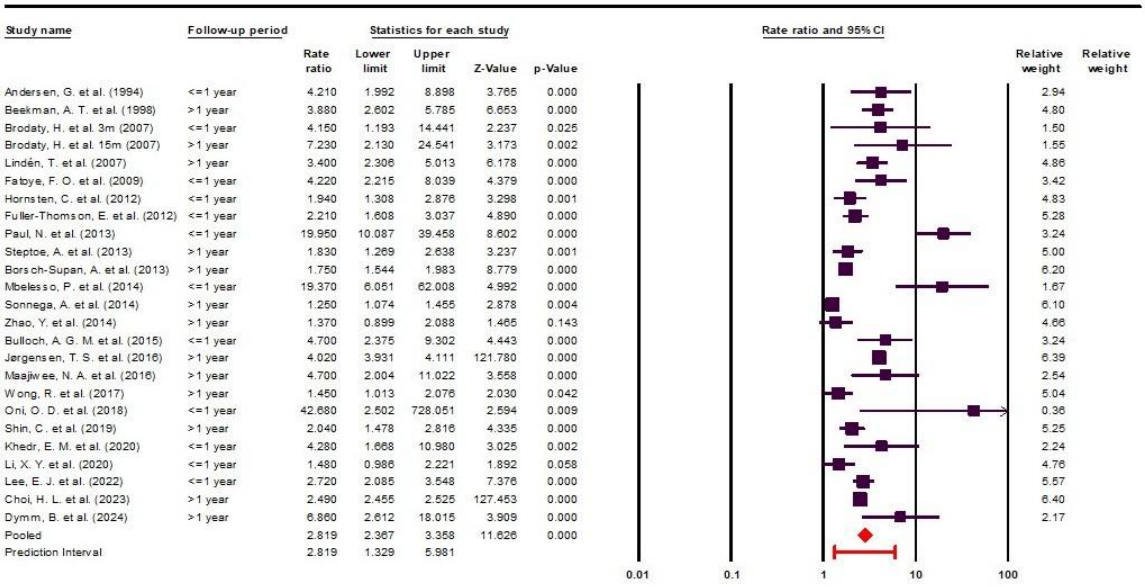

Figure 3. Forest plot indicating that patients with brain stroke history are more vulnerable to suffer depression compared to control group OR 2.81 [95% CI 2.36-3.35]. Heterogeneity indices: I^2= 98.44, Cochrane Q statistic= 1542.56 [P-value<0.05].

As expected, there is substantial heterogeneity among the included studies (I^2 = 98.44, Cochrane Q= 1542.56, P < 0.05), which persisted across various subgroup analyses. This suggests that the high variability arises from heterogenous nature of the primary studies.

Regarding publication bias, Begg's funnel plot appears asymmetric, and three studies may have contributed to potential bias (Figure 4, showing both observed and imputed studies). The results of quantitative analyses were somewhat inconsistent: Egger's regression test indicated no evidence of bias (P= 0.98), while the Begg and Mazumdar rank correlation suggested possible bias (P < 0.05, Kendall's tau= 0.41). Therefore, the Duval and Tweedie trim-and-fill test method was applied. Even after imputing the three hypothetical studies indicated in the funnel plot, the pooled OR [95% CI] changed only from 2.81 [2.36-3.35] to 2.55 [2.15-3.03], which does not undermine the robustness our findings.

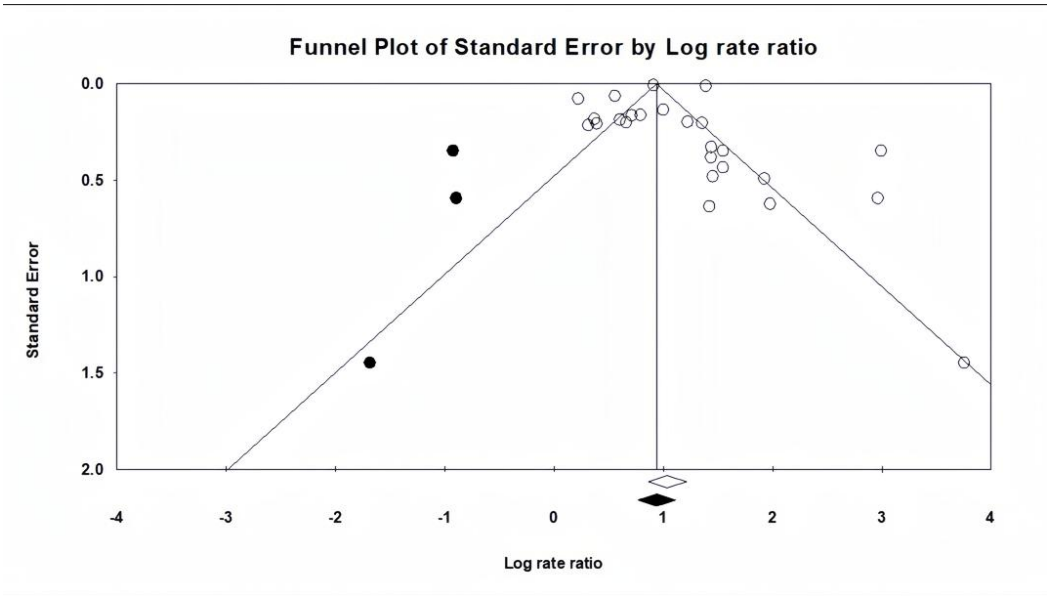

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Figure 4. Begg's funnel plot of imputed and observed studies. Egger's regression test P-value= 0.98 and Begg and Mazumdar rank correlation P-value<0.05; Kendall's tau= 0.41.

To assess the potential influence of individual studies on the overall result, a leave-one-out sensitivity analysis was conducted. As presented in the forest plot (Figure 5), no single study exerted an undue influence on the pooled effect size.

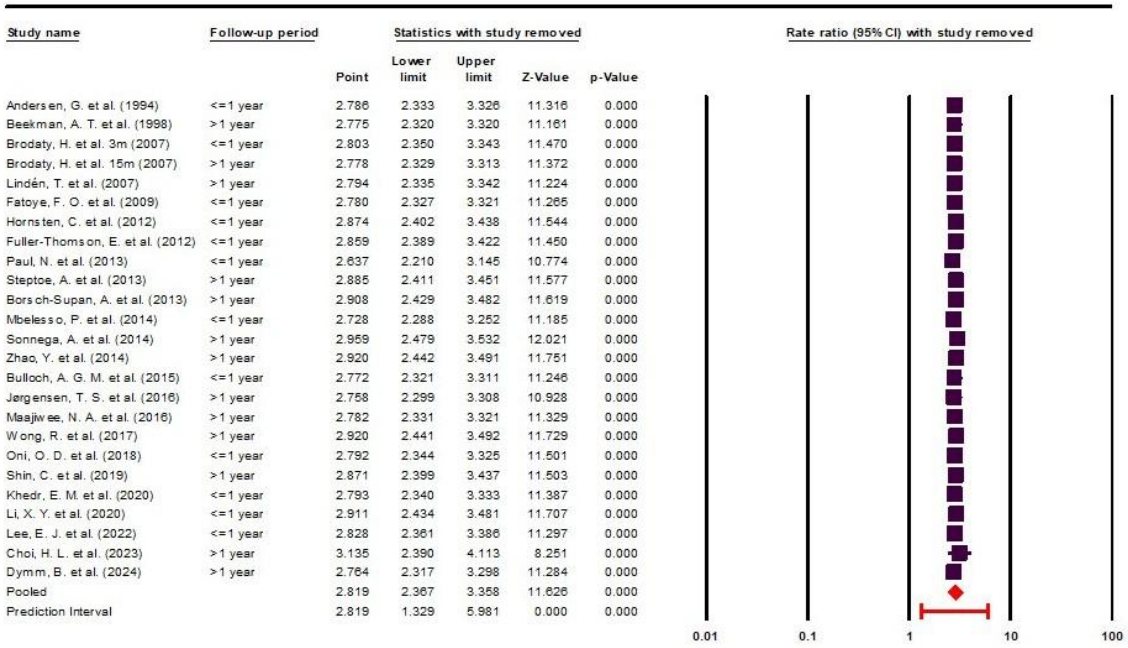

Figure 5. One study removed method results for sensitivity analysis.

In addition to the meta-analysis, the mean ± SD prevalence of PSD was calculated as 32.15% ± 15.81%, based on 193 studies encompassing 484846 stroke survivors. The distribution of this data is summarized in Figure 6.

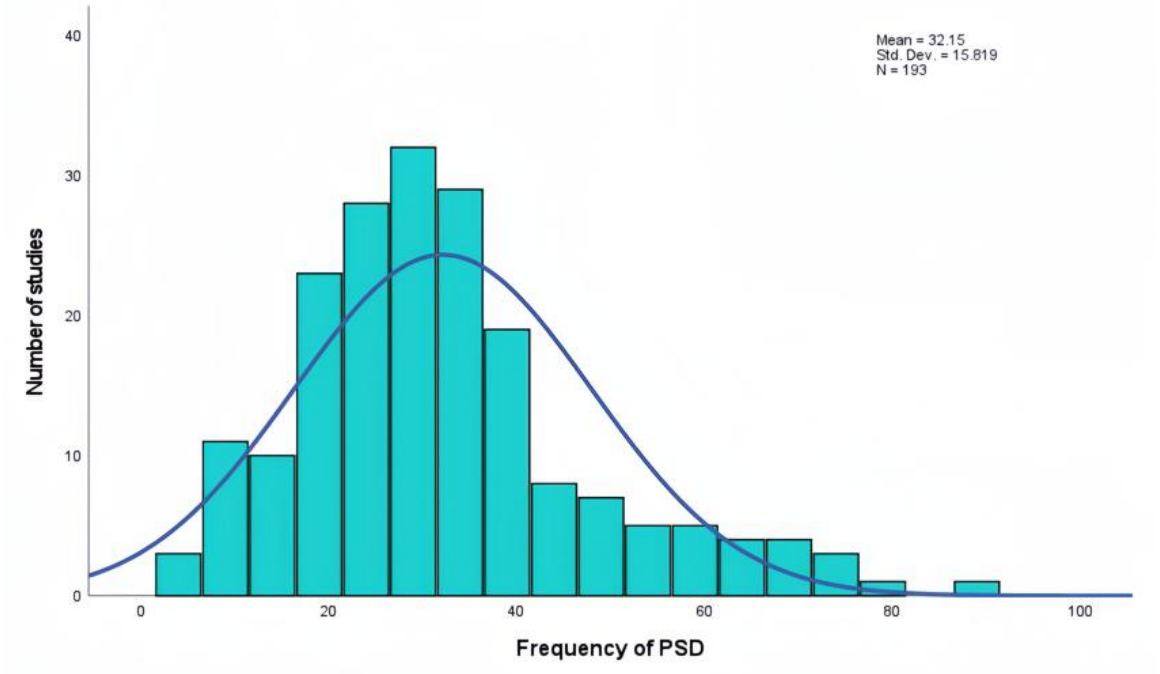

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Figure 6. Mean prevalence of depression followed by stroke reported by 193 different papers on a total sample size of 484846 patients is 32.15% ± 15.81.

Subgroup Analysis

To better understand the course of depression in stroke survivors, studies were stratified by follow-up duration into two groups: ≤ 1 year and > 1 year. This subgroup analysis did not reduce heterogeneity within either group: I^2 = 83.58, Cochrane Q= 67.02, P< 0.05 for the ≤ 1-year group; and I^2 = 99.18, Cochrane Q= 1475.52, P< 0.05 for the > 1-year group.

As shown in Figure 7, the risk of depression during the first year after stroke is almost twice as high compared to the period beyond the first year, although with a wider predictive interval. Specifically, the OR [95% CI] was 4.08 [2.70-6.15] with a predictive interval of [0.97-17.13] in the ≤ 1-year group, versus 2.39 [1.91-2.99] with a predictive interval of [1.06-5.38] in the > 1-year group.

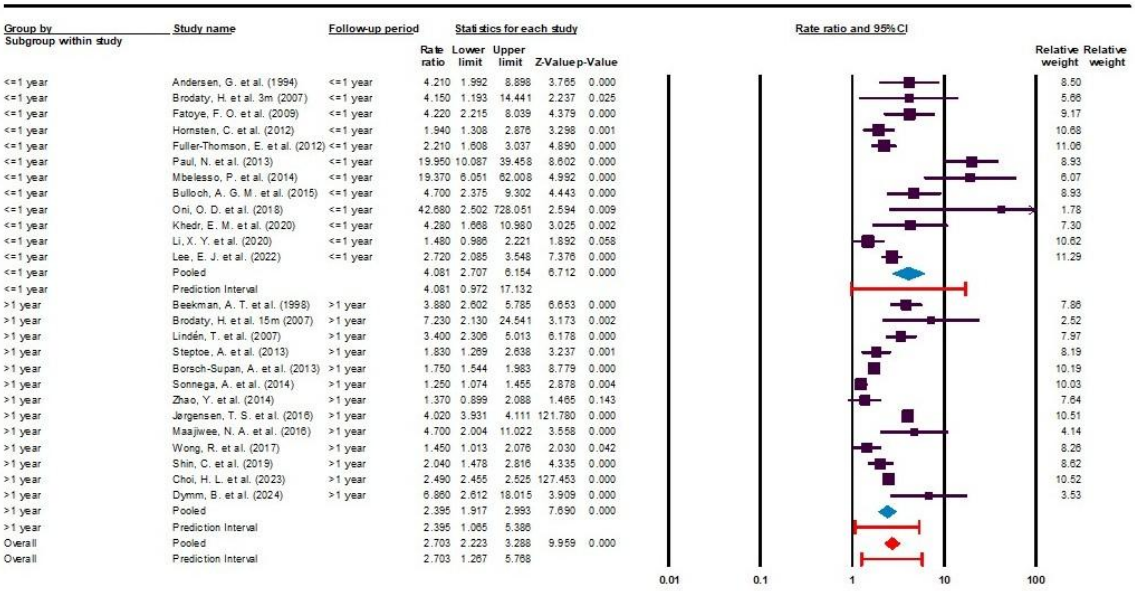

Figure 7. Subgroup analysis indicates existence of higher odds to be diagnosed with depression during the first year OR [95 CI] 4.08 [2.70-6.15] versus 2.39 [1.91-2.99].

Discussion

~~Novelty~~

This study is the first systematic review and meta-analysis of comparative studies using odds ratios as the effect size, covering publications up to September 23, 2024. It advances the literature by enabling a more precise evaluation of the individual risk of depression among stroke survivors.

Several meta-analyses of varying quality have been published on the proportional prevalence of PSD. However, these studies typically report depression prevalence in their study populations as percentages, without accounting for the already high prevalence of depression in the general, apparently healthy population, prevalence that may not be attributable to stroke.

Considering the progressively rising global prevalence of depression, attributing depression solely to the stroke event requires the inclusion of a control group and a focus on odds ratio evaluation, an approach that distinguishes the present study [27].

Result Analysis

Odds Ratio and Frequency

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In recent years, the odds ratio has been increasingly used in the medical literature because it is simple to interpret, easy to calculate, and highly relevant for clinical decision-making. From a clinical perspective, it is valuable for the healthcare providers to understand, for example, the odds of treatment success or the likelihood of developing a specific complication.

Moreover, the ease of understanding the odds ratio also makes it a useful tool in communicating with patients, particularly when addressing neuropsychiatric sequelae of acute, debilitating conditions such as stroke [28].

Through this study, we identified a highly concerning finding: post-stroke patients are nearly three times more likely to develop depression compared to the general population (OR = 2.81 [2.36-3.35]). This result is crucial for raising awareness among healthcare providers about the psychological vulnerability of stroke patients, as well as for improving patient compliance with necessary psychiatric treatments or interventions.

Beyond reporting a pooled odds ratio as the novel aspect of our study, we also utilized the search results to provide a more comprehensive estimate of proportional prevalence of depression among stroke survivors. This analysis was based on 193 PubMed and Web of Sciences reports, including a total of 484,846 patients.

In a recent meta-analysis published by Patra A. et al. in 2021, the authors reported a pooled prevalence of 55% [95% CI 43-65] of depression in the Indian population. This figure is higher than the overall prevalence of 32.15% observed in our study but is consistent with another study conducted in India in 2013 (46.8%). These findings reinforce the hypothesis that genetic or racial variability may influence the prevalence of PSD [33,34].

Similarly, a meta-analysis conducted in Iran by Dalvand S. et al. in 2018 reported an overall prevalence of 46.94% [95% CI 30.14-63.75] for PSD, with regional variability ranging from 18% to 72.5% [35]. These results are in line with the findings of our study.

Heterogeneity

In this meta-analysis, we encountered high heterogeneity, which was primarily due to the inherent nature of the included studies. Notably, heterogeneity did not decrease across various subgroup analyses. This outcome is unsurprising, given that the included studies were not matched and reported data from diverse populations across different races, countries and age groups, using non-uniform depression assessment scales. Nevertheless, this does not imply that conducting a meta-analysis is unfeasible.

A critical review on PSD concluded that small sample sizes are one of the main limitations in the published literature. Regardless of the underlying cause, one effective solution is to design systematic reviews and meta-analyses that pool such small studies to generate more robust and meaningful results [29].

It is nearly impossible to achieve this without accepting a degree of heterogeneity, especially in health science reseach. As recommended in such cases, applying a random-effects model is the appropriate approach in meta-analyses with substantial heterogeneity [30]. Another useful parameter for interpreting results under these conditions is the predictive interval, which reflects the expected variability of the true effect size in future studies while accounting for observed heterogeneity [31].

As shown in Figure 8, the true effect size with a 95% of predictive interval ranges from 1.32 and 5.98, meaning that future studies will report an odds ratio of at least 1.86 with 95% certainty.

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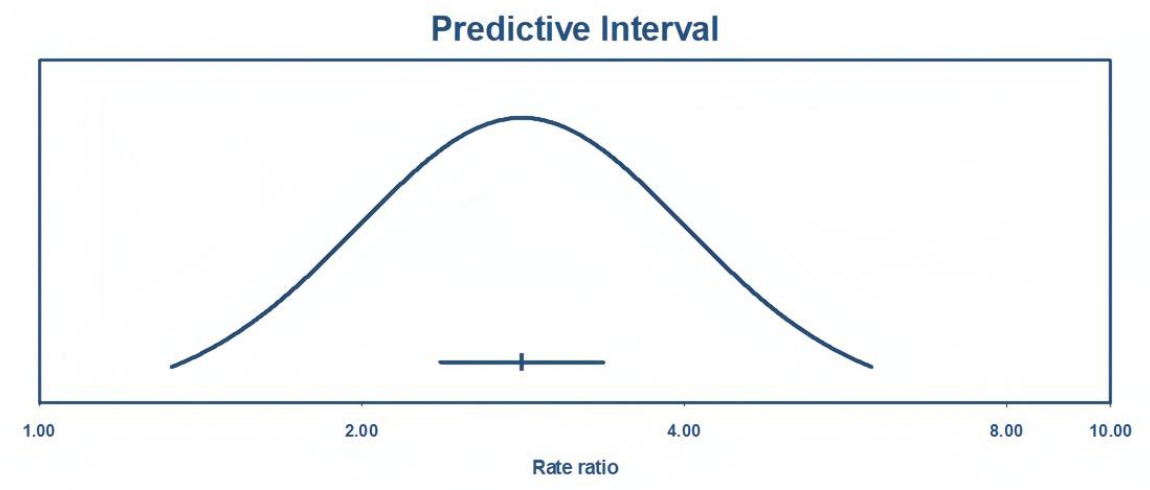

Figure 8. The pooled effect size is 2.81 [95% CI 2.36-3.35] and the true effect size in 95% of all comparable populations falls in the predictive interval of 1.32 to 5.98.

Publication Bias

Regarding publication bias, it is important to note that asymmetries in funnel plots do not always indicate the presence of publication bias. This is especially true in the present study, where the results do not show conflicting directions but rather varying effect sizes in the same direction. In fact, the funnel plot reflects "small-study effects", which may be strongly influenced by heterogeneity rather than publication bias [32].

Considering all the above-mentioned data and the results of the trim-and-fill test results, it can be concluded that the findings of the present meta-analysis are not significantly affected by publication bias.

Frequency (%)

Subgroup Analysis

The natural history of depression in stroke survivors has always been a major concern for clinicians and researchers, and numerous studies with varying designs have been published on this topic. For example, Liu L. *et al*. recently published a comprehensive systematic review showing that most depression cases have an early onset (within first 3 months). Moreover, more than half of these early-onset cases are at risk of persistent depression, highlighting the importance of early diagnosis and treatment in the stroke survivor population [8].

In addition to this, Ayerbe L. *et al*. investigated the natural history of depression in the South London Stroke Register with up to 15 years of follow up. Their results suggest that most depressive episodes begin within the first year, with one-third of cases diagnosed within the first 3 months, and no new cases reported after year 10. These findings emphasize the dynamic course of PSD: while most stroke survivors experience short-duration episodes, the risk of recurrence remains high in the long term [36].

Overall, nearly all comprehensive studies and reviews are consistent in describing the natural history of PSD. They consider depression an early onset consequence of stroke, with peak incidence occurring between 6 months and 2 years. It is also evident that depression may persist for several years, with the incidence of new cases declining over time [37].

In our systematic review, we performed a subgroup analysis based on follow-up duration. Although this analysis did not reduce heterogeneity within groups, the results remain valuable. They demonstrate that the overall pooled effect and its predictive interval more closely resemble studies with follow-up periods longer than one year. Interestingly, the predictive interval of both the overall effect and the > 1-year follow-up group is entirely encompassed by that of the ≤ 1-year group.

 doi:10.20944/preprints202510.0553.v1

These findings suggest that evaluating depression after the first year may yield more realistic, stable, and persistent results compared to assessments during the first year post-stroke, possibly due to greater confounding factors in the early phase after stroke. It is important to note that in the >1-year follow-up group, patients were not under continuous treatment or monitoring for depression. In fact, the follow-up period was defined as the time point at which the authors assessed stroke patients for depressive symptoms for the first time.

Other studies

Meta-analysis

In a meta-analysis conducted by Ayerbe L. *et al*. in 2013, the authors included 50 studies with percentage as the effect size and reported a pooled prevalence of 29% [95% CI: 25-32] for depression in patients with a history of stroke, which is very similar to our findings. In the same study, the authors concluded that the principal predictors of PSD are disability, cognitive impairment, pre-stroke depression, anxiety and stroke severity. They also reported that PSD independently contributes to lower quality of life, increased mortality and greater disability [38].

One of the most frequently studied and discussed predictors of PSD is pre-stroke depression. In this regard, Taylor-Rowan M. *et al*., in a meta-analysis with rigorous pre-registered methodology, reported that the pooled prevalence of pre-stroke depression is aproximately 12%. Compared to the 39-52% prevalence of PSD [38], this suggests that the majority of PSD cases cannot be explained merely as unmasking or recurrence of pre-stroke depression. According to the authors, most cases of PSD are direct consequences of stroke itself. They further reported that the odds of developing PSD are three-times higher in patients pre-stroke depression compared to those without (OR= 3.0 [95% CI: 2.3-4.0]) [39].

Similarly, Hackett M.L. *et al*., in their 2014 meta-analysis of 61 primary studies, reported a pooled prevalence of PSD of 31% [95% CI: 28-35], which was not significantly different from their earlier report in 2005 (33% [95% CI: 29-36]) [40,41]. This prevalence is almost identical to the results of our study.

Finally, it is important to highlight the association between PSD and mortality. In a study conducted by Bartoli F. *et al*., it was demonstrated that stroke survivors with depression are at a significantly higher risk of mortality compared to those without depression (RR = 1.50 [95% CI: 1.28-1.75]) [9].

Original papers

Most of the included studies were conducted on patients with different types of stroke, and the primary papers excluded other possible vascular pathologies that might mimic stroke symptoms, except for the cohort study by Maaijwee, N. A. *et al*., which included both transient ischemic attack (TIA) and stroke patients. Fortunately, the authors reported the results for two groups separately. In the present meta-analysis, only the data related to stroke patients were used. Interesting, according to the authors, although both TIA and stroke groups experienced higher rates of depressive symptoms, the odds ratio was higher in ischemic patients compared to TIA patients (4.7 [2.0-22.0] vs. 2.8 [1.2-6.6], respectively) [42].

In a study conducted in China, Zeng, Y. Y. *et al*. [2021] compared the prevalence of PSD in hemorrhagic stroke survivors and acute ischemic stroke survivors. They concluded that depression is significantly more common among hemorrhagic stroke survivors than among ischemic stroke survivors (42.3% vs. 22.9). After adjusting for confounding variables, the authors reported that the odds of developing depression were more than twice as high in hemorrhagic stroke patients (OR 2.65 [1.34-5.24]) [43].

Several predictors of PSD have been suggested in the literature, including older age, female sex, stroke severity and outcomes, a history of depression or other psychiatric disorders, stressful life events prior to stroke, and lesion location and size [44]. In a narrative review based exclusively on

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PubMed database, the authors were unable to identify a consistent association between lesion location and PSD due to methodological limitations in the primary studies. Nevertheless, the overall findings indicate that lesions in the frontal lobes and lesions involving the basal ganglia are more likely to be associated with depression in stroke survivors [45].

Limitations and Strengths

This meta-analysis has some limitations. The included studies were highly heterogeneous in terms of design, populations, follow-up duration, and depression assessment tools, and this variability persisted despite subgroup analyses. Furthermore, we only analyzed published studies, excluding unpublished literature, which may have introduced publication bias. In addition, some primary studies were not specifically designed to assess post-stroke depression, and differences in adjustment for confounding factors such as pre-stroke psychiatric history or stroke severity may have influenced the results.

Despite these limitations, the study also has important strengths. Our comprehensive and highly sensitive search strategy initially identified 5,887 primary studies, ensuring broad coverage of the literature. The novelty of focusing on comparative studies with odds ratios, together with transparent reporting of the search process, objectives, and inclusion criteria, enhances the reproducibility of our findings. These features allowed us to move beyond simple prevalence estimates and provide a more robust measure of the risk of depression following stroke.

Conclusion

This meta-analysis aimed to determine the prevalence and odds of depression in stroke survivors compared with a control population. The results highlight a concerning finding: stroke survivors are almost three times more likely to experience depression, with a prevalence of 32%, compared to controls (OR [95% CI]: 2.81 [2.36-3.35]).

Overall, this systematic review and meta-analysis provides a clearer understanding of depression as a serious and debilitating consequence of stroke. Early identification and treatment of depression in stroke survivors may reduce the risk of persistent symptoms, prevent related comorbidities, and lower depression-associated mortality.

Conflicts of Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Appendix A. Newcastle - Ottawa Quality Assessment Scale (Adapted for Cross Sectional Studies)

Selection: (Maximum 5 Stars)

1. Representativeness of the cases:

a) Truly representative of the HCC patients (consecutive or random sampling of cases). 1 score

b) Somewhat representative of the average in the HCC patients (non-random sampling). 1 score

c) Selected demographic group of users. 0 score

d) No description of the sampling strategy. 0 score

2. Sample size:

a) Justified and satisfactory (≥ 400 HCC included). 1 score

b) Not justified (<400 HCC patients included). 0 score

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3. Non-Response rate

a) The response rate is satisfactory (≥95%). 1 score

b) The response rate is unsatisfactory (<95%), or no description. 0 score

4. Ascertainment of the screening/surveillance tool:

a) Validated screening/surveillance tool. 2 scores

b) Non-validated screening/surveillance tool, but the tool is available or described. 1 score

c) No description of the measurement tool. 0 score

Comparability: (Maximum 1 Stars)

1. The potential confounders were investigated by subgroup analysis or multivariable analysis.

a) The study investigates potential confounders. 1 score

b) The study does not investigate potential confounders. 0 score

Outcome: (Maximum 3 Stars)

1. Assessment of the outcome:

a) Independent blind assessment. 2 scores

b) Record linkage. 2 scores

c) Self-report. 1 score

d) No description. 0 score

2. Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate. 1 score

b) The statistical test is not appropriate, not described or incomplete. 0 score

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