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Original Article

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The Role of Calcitriol (Vitamin D) as Neuroprotection and Prognostic Biomarker in Patients With Ischemic and Hemorrhagic Stroke

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Abstract

Background: Stroke is a leading cause of long-term neurological disability, significantly impacting global morbidity and mortality. Vitamin D supplementation shows neuroprotective potential, yet research on its effects and role as a prognostic biomarker in stroke patients remains limited.

Methods: This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched Google Scholar, PubMed, and Scopus for studies assessing vitamin D's neuroprotective effects, measured by standardized mean difference (SMD) with a 95% confidence interval (CI). We also evaluated vitamin D levels as a biomarker for stroke prognosis using odds ratio (OR) with a 95% CI. Out of 3,171 identified articles, 23 relevant studies involving 4,911 patients with ischemic and hemorrhagic strokes were included.

Results: The analysis indicated that vitamin D supplementation significantly improved neurological function (SMD, 0.63; 95% CI, 0.31–0.95; P = 0.0001) for both high-dose intramuscular injections and low-dose oral supplementation given daily or weekly. Additionally, low vitamin D levels were associated with stroke severity (OR, 3.44; 95% CI, 1.84–6.44; P < 0.0001), suggesting that vitamin D levels have potential as a prognostic biomarker.

Conclusion: These findings underscore the importance of vitamin D as an additional therapeutic strategy in stroke management. Despite the heterogeneity in the analysis, the results support the need for further research to determine the optimal dosage and to understand the effects of comorbidities. Additionally, the development of evidence-based clinical practice guidelines is necessary for the implementation of vitamin D administration in stroke rehabilitation.

Keywords: Vitamin D; Calcitriol; Neuroprotection; Stroke

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Introduction

As one of the most urgent medical conditions, stroke is a leading cause of neurological disability and a major contributor to global morbidity and mortality, requiring substantial attention in both research and preventive strategies. According to the World Health Organization (WHO), stroke was the third leading cause of death and disability worldwide in 2021, with 11.9 million new cases and 93.8 million people living with stroke globally [1]. Epidemiological data further demonstrate the substantial burden of cerebrovascular disease. The cumulative incidence of stroke has been reported as 218 per 100,000 population in males (95% confidence interval (CI), 214–221) and 127 per 100,000 in females (95% CI, 125–128), highlighting significant sex-related differences in stroke incidence [2]. Stroke remains a major cause of death and long-term disability worldwide, underscoring the urgent need for effective preventive and therapeutic interventions [3].

One intervention of particular interest is vitamin D supplementation, which has been increasingly recognized for its potential neuroprotective effects [3]. Vitamin D is involved in modulating cognitive function, neurotrophic signaling pathways, and mechanisms that reduce oxidative stress and inflammation processes that play a critical role in neuronal injury following stroke [4]. Notably, the prevalence of vitamin D deficiency has been reported to reach up to 71% among stroke patients and has been associated with greater stroke severity and poorer functional outcomes [5, 6]. Therefore, this study aims to evaluate the neuroprotective effects of vitamin D supplementation and its potential role as a prognostic biomarker in patients with ischemic and hemorrhagic stroke.

Materials and Methods

Study design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic

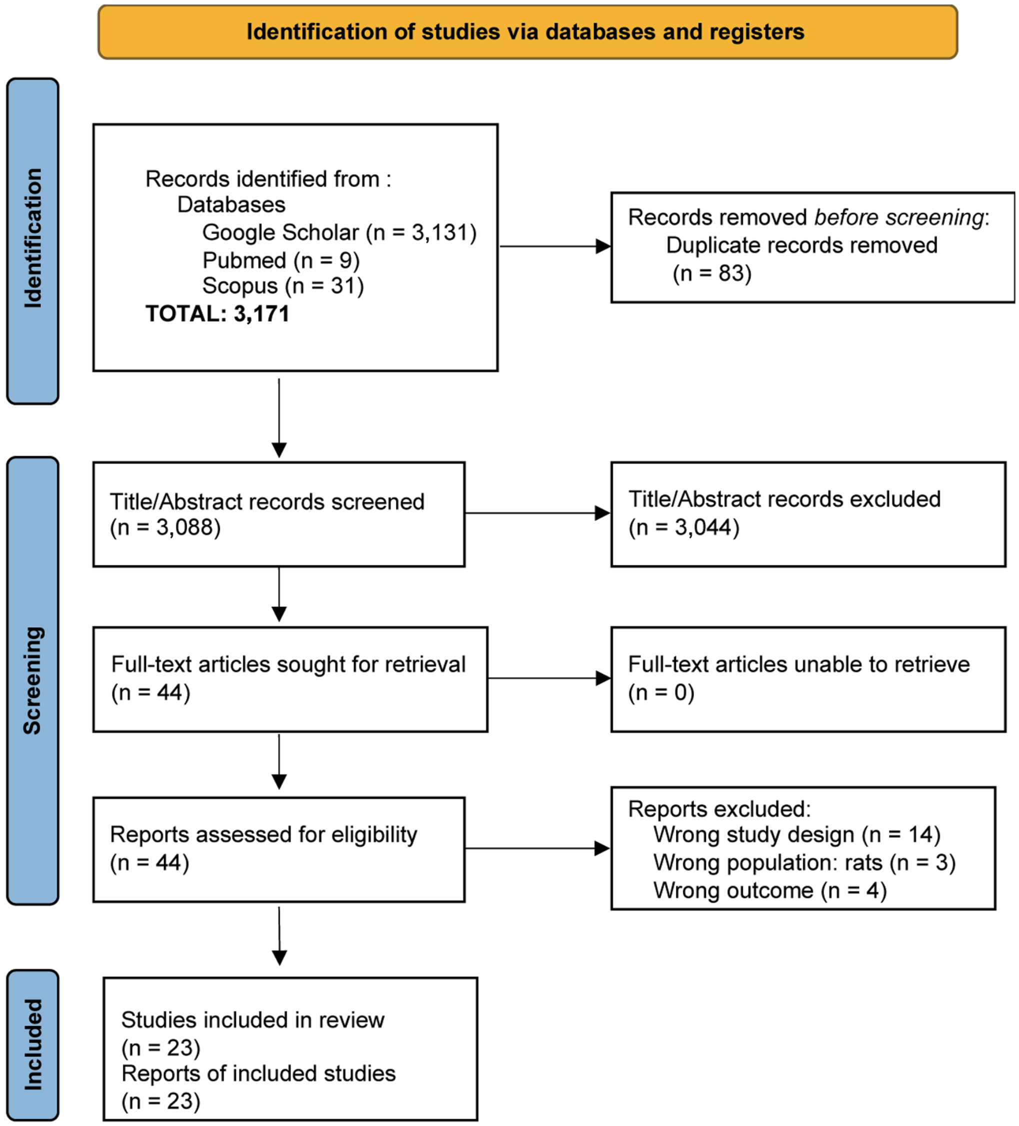

Figure 1. Flow diagram of the study selection process for articles included in the systematic review and meta-analysis.

Reviews and Meta-Analyses (PRISMA) guidelines. To ensure methodological transparency and integrity, the study has been registered with PROSPERO under registration number CRD42024600826, indicating that the protocol for this systematic review has been documented and verified.

Research ethics

As this study is a systematic review and does not involve the collection of primary data from human subjects, ethical approval from a review board was not necessary.

Data sources and literature search

Two independent reviewers conducted the article search using Google Scholar, PubMed, and Scopus databases. The search included all articles published from the inception of each database up to September 23, 2024. The search terms used were ("vitamin D" OR "calcitriol") AND ("neuroprotective effect" OR "neuroprotection" OR "neuroprotective efficacy") AND ("stroke" OR "ischemic stroke" OR "hemorrhagic stroke"). This search was limited to studies evaluating the neuroprotective effects and potential prognostic value of vitamin D in patients with ischemic and hemorrhagic stroke (Fig. 1).

Study selection criteria and quality assessment

The inclusion criteria for this study were established based on the following conditions: 1) adult patients suffering from ischemic or hemorrhagic stroke, with a National Institutes of Health Stroke Scale (NIHSS) score greater than 5, confirmed by findings of infarction or hemorrhage in the brain identified by a neurologist through computed tomography; 2) one episode of focal neurological deficit with acute onset, lasting more than 24 h; 3) patients admitted within the last 24 h after being diagnosed with ischemic or hemorrhagic stroke and having vitamin D deficiency (serum 25-OH vitamin D ≤ 30 ng/mL). Patients were excluded from the study if they had a history of acute or chronic renal failure (creatinine clearance < 30 mL/min/1.73 m^2), liver failure, secondary stroke due to neuroinfection, cancer, trauma, previous stroke, premorbid disability, or neurological disorders such as dementia, Alzheimer's disease, multiple sclerosis, or Parkinson's disease. Two authors independently reviewed the titles and abstracts. In cases of disagreement between reviewers, consultation was conducted to reach a final decision. The risk of bias was assessed using the Cochrane risk of bias 2 (ROB-2) tool for studies with a randomized controlled trial design to evaluate the methodological quality of the eligible articles. Additionally, the risk of bias in non-randomized studies of interventions (ROBINS-I) tool was used to assess the risk of bias in the effectiveness or safety (benefit or harm) of interventions in non-randomized studies. Any discrepancies in data extraction or quality assessment were resolved through discussion.

Data extraction

Two independent authors performed the data extraction process. Data collection was conducted by organizing the following variables: first author, year of publication, study location, sample size, study design, diagnosis, stroke assessment, serum vitamin D levels, intervention regimen, control regimen, and tools for assessing neurological clinical improvement.

Outcomes

The primary outcome of this meta-analysis was neurological function improvement following vitamin D supplementation. Neurological function was assessed using validated clinical scales, including NIHSS, Barthel Index (BI), Scandinavian Stroke Scale (SSS), Brunnstrom Recovery Stage (BRS), Functional Ambulation Classification (FAC), modified Rankin Scale (mRS), Functional Independence Measure (FIM), Mini-Mental State Examination (MMSE), Montgomery-Åsberg Depression Rating Scale (MADRS), and Neuron-Specific Enolase (NSE).

Secondary outcomes included the association between serum vitamin D levels and stroke severity, which was evaluated to explore the potential role of vitamin D as a prognostic biomarker.

Statistical analysis

We conducted a meta-analysis to evaluate the study outcomes. The effect of vitamin D supplementation on neurological function as a neuroprotective agent was measured using the standardized mean difference (SMD) with a 95% CI. For dichotomous data, specifically the assessment of vitamin D levels as a biomarker for stroke prognosis, we used the odds ratio (OR) with a 95% CI. Heterogeneity among studies was assessed using the I^2 statistic, with 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Statistical significance was set at a P-value of ≤ 0.05. In cases of moderate to high heterogeneity, a random-effects model was applied to the meta-analysis; otherwise, a fixed-effect model was used for low heterogeneity. All statistical analyses were performed using Review Manager 5.1.0, developed by Cochrane, UK.

Results

Article search and selection

A total of 3,171 potential research articles were identified. After removing duplicates, screening, conducting full-text reviews, and applying the inclusion and exclusion criteria, 23 relevant articles were selected for the systematic review and meta-analysis (Fig. 1).

Risk of bias assessment

Based on the ROB-2 assessment, which evaluates the quality of research on primary outcomes, two of the seven articles included in this study raised concerns regarding bias. These articles were authored by Karasu et al (2021) [7] and Narasimhan et al (2017) [8]. According to the ROBINS-I assessment, which evaluates the quality of research on secondary outcomes, 10 out of the 16 articles included in this study exhibited a moderate risk of bias. These articles were authored by Afshari et al (2015) [9], Aggarwal et al (2022) [10], Alfieri et al (2017) [11], Borowicz et al (2023) [12], Rad et al (2021) [13], Samarakoon et al (2024) [14], Turetsky et al (2015) [15], Wajda et al (2019) [16], Kim et al (2020) [17], and Park et al (2015) [18]. Figure 2 presents the evaluation of bias risk.

Study characteristics

Tables 1 and 2 provide a comprehensive overview of the studies included in this analysis. A total of 23 studies involving 4,911 stroke patients (both ischemic and hemorrhagic strokes) were published between 2014 and 2024. The sample sizes varied across studies, ranging from 40 to 818 stroke patients.

Meta-analysis results

Effect of vitamin D supplementation on neurological function improvement

Seven studies were included in the analysis to evaluate the effect of vitamin D supplementation on neurological function

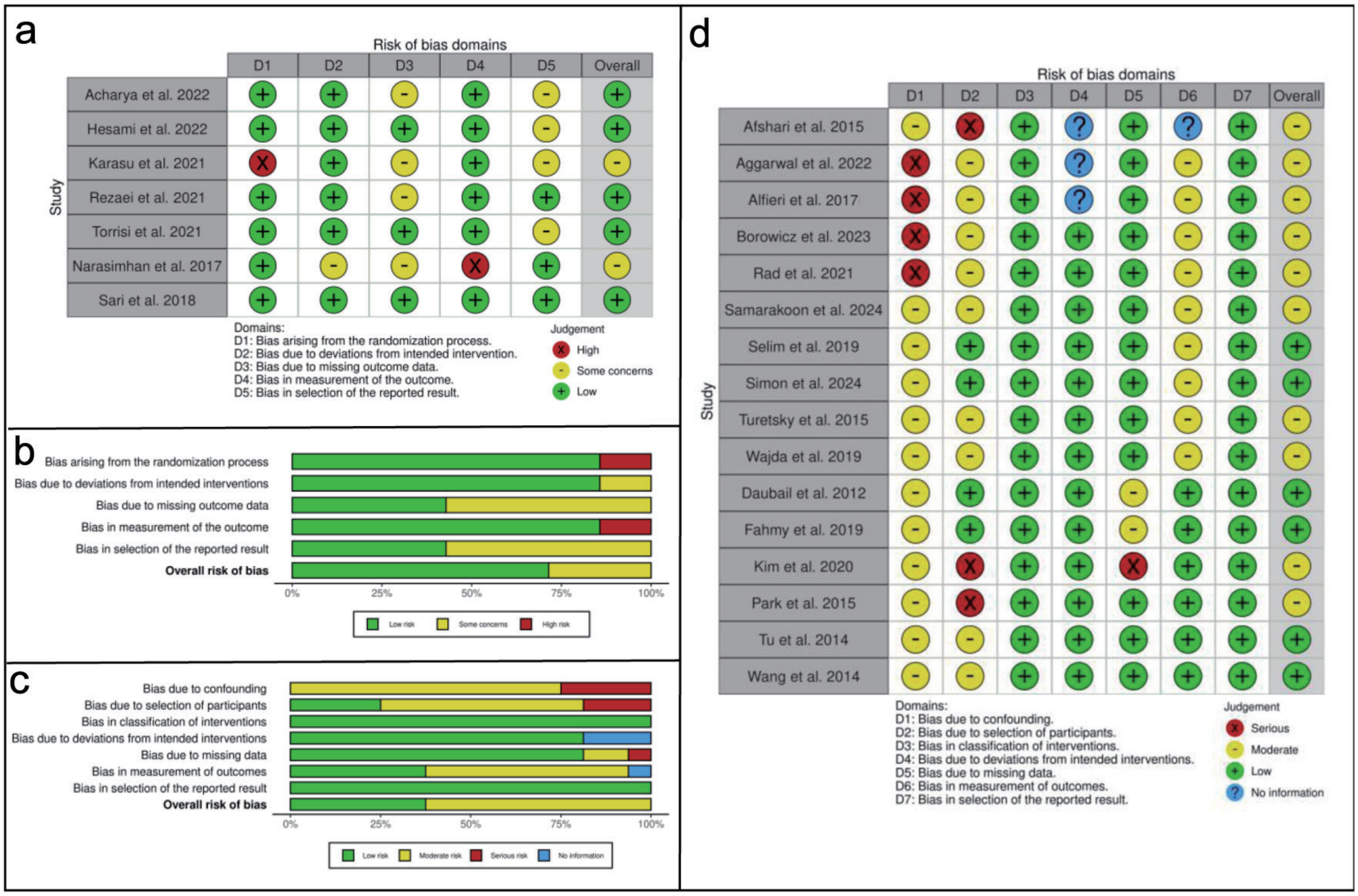

Figure 2. Risk of bias analysis. (a) Traffic-light plot of the risk of bias assessment using ROB-2, illustrating the bias risk results for the effect of vitamin D supplementation on neurological function improvement across each domain. (b) Overall risk of bias conclusion using ROB-2, summarizing the risk of bias regarding the effect of vitamin D supplementation on neurological function improvement. (c) Overall risk of bias conclusion using ROBINS-I, indicating the risk of bias for vitamin D levels as a prognostic biomarker in stroke severity. (d) Traffic-light plot of the risk of bias assessment using ROBINS-I, depicting the risk of bias for the analysis of vitamin D levels in stroke severity as a prognostic biomarker across each domain. ROB-2: risk of bias 2; ROBINS-I: risk of bias in non-randomized studies of interventions.

(Fig. 3a). Based on the heterogeneity test ($I^2 = 60\%$), the SMD for the effect of vitamin D supplementation on neurological function was analyzed using a random-effects model. Statistical analysis revealed that vitamin D supplementation significantly improved neurological function compared to the control group (SMD, 0.63; 95% CI, 0.31–0.95; P = 0.0001). Both low-dose oral daily and weekly administration (SMD, 0.91; 95% CI, 0.25–1.59; P = 0.007) and a single high-dose intramuscular injection (SMD, 0.52; 95% CI, 0.18–0.55; P = 0.002) were effective in enhancing neurological function.

Vitamin D levels in stroke severity as a prognostic biomarker

Eight studies were included in the analysis of vitamin D levels in relation to stroke severity as a prognostic biomarker (Fig. 3b). Based on the heterogeneity test ($I^2 = 77\%$), the OR for the prognostic biomarker value was pooled using a random-effects model. Statistical analysis indicated that low vitamin D levels in stroke patients were associated with increased severity of neurological dysfunction compared to the control group (OR, 3.44; 95% CI, 1.84–6.44; P < 0.0001).

Publication bias assessment

The analysis revealed a heterogeneity I^2 value of 60% for the primary outcomes and 77% for the secondary outcomes, indicating moderate heterogeneity among the included studies. This suggests that the study findings exhibit some variation or inconsistency, which may be attributed to differences in study design, population, interventions, or measurement tools used to assess improvements in neurological function. To evaluate the potential for publication bias in the primary and secondary outcome meta-analyses, we used the funnel plot function of meta-bias from Review Manager 5.1.0, Cochrane, UK. Upon examination of the funnel plot, it was challenging to determine whether the distribution of studies on both sides of the plot was

Table 1. Characteristics of Study Data on Primary Outcome (Effect of Vitamin D Supplementation on Neurological Function Improvement)

No.	Author	Location	Sample size	Study design	Diagnosis	Intervention regimen	Control regimen	Outcome measurement tools
1.	Acharya et al, 2022	India	325	Randomized controlled trial	Ischemic stroke and hemorrhagic stroke	Single intramuscular dose of 600,000 International Units (IU) of vitamin D	Vitamin D not administered	Scandinavian Stroke Scale (SSS) score
2.	Hesami et al, 2022	Iran	570	Randomized controlled trial	Ischemic stroke	Single intramuscular dose of 600,000 IU of vitamin D3	Vitamin D not administered	The Neuron-Specific Enolase (NSE) level, the National Institutes of Health Stroke Scale (NIHSS), and Barthel Index (BI)
3.	Karasu et al, 2021	Turkey	76	Retrospective	Ischemic stroke and hemorrhagic stroke	Weekly oral dose of 50,000 IU for 4–12 weeks, with a total dose ranging from 200,000 to 600,000 IU	Vitamin D not administered	Brunnstrom Recovery Stage and Functional Ambulation Classification (FAC) score
4.	Rezaei et al, 2021	Iran	60	Randomized controlled trial	Ischemic stroke	Single intramuscular dose of 300,000 IU of vitamin D	Vitamin D not administered	NIHSS, modified Rankin Scale (mRS), and the Mini-Mental State Examination (MMSE)
5.	Torrisi et al, 2021	Italy	40	Randomized controlled trial	Ischemic stroke and hemorrhagic stroke	Daily oral dose of 2,000 IU/day of vitamin D3 for 12 weeks	Vitamin D not administered	Montgomery-Aasberg Depression Rating Scale (MADRS) and Functional Independent Measures (FIM)
6.	Narasimhan et al, 2017	India	60	Randomized controlled trial	Ischemic stroke	Single intramuscular dose of 600,000 IU of vitamin D3	Vitamin D not administered	SSS score
7.	Sari et al, 2018	Turkey	64	Randomized controlled trial	Ischemic stroke	Single intramuscular dose of 300,000 IU of vitamin D	Vitamin D not administered	Brunnstrom Recovery Staging (BRS), Functional Ambulation Scale (FAS), Modified Barthel Index (MBI) scores, and Berg Balance Scale (BBS)

Table 2. Characteristics of Study Data on Secondary Outcome (Analysis of Vitamin D Levels in Stroke Severity as a Prognostic Biomarker)

No.	Author	Location	Sample size	Study design	Diagnosis	Assessment of stroke severity	Assessment of serum vitamin D levels
8.	Afshari et al, 2015	Iran	72	Case-control	Ischemic stroke	Brain computed tomography	Enzyme-linked immunosorbent assay (ELISA)
9.	Aggarwal et al, 2022	India	200	One-year prospective observational	Ischemic stroke	The National Institutes of Health Stroke scale (NIHSS) and modified Rankin scale (mRS)	Electrochemiluminescence (ECL) method
10.	Alfieri et al, 2017	Brazil	286	Case-control	Ischemic stroke	mRS	Chemiluminescent microparticle immunoassay (CMIA)
11.	Borowicz et al, 2023	Poland	80	Randomized controlled trial	Ischemic stroke	NIHSS, mRS, and Barthel index (BI)	CMIA
12.	Rad et al, 2021	Iran	140	Bi-center cross-sectional	Ischemic stroke and hemorrhagic Stroke	NIHSS and mRS	ECL
13.	Samarakoon et al, 2024	Sri Lanka	60	Prospective case-control	Ischemic stroke	NIHSS and mRS	ELISA
14.	Selim et al, 2019	Egypt	138	Case-control	Ischemic stroke and hemorrhagic stroke	NIHSS and mRS	ELISA
15.	Simon et al, 2024	India	86	Prospective observational	Ischemic stroke	NIHSS	Chemiluminescence immunoassay (CLIA)
16.	Turetsky et al, 2015	United States	96	Retrospectively analyze prospective	Ischemic stroke	NIHSS and mRS	CLIA
17.	Wajda et al, 2019	Poland	240	Retrospective cohort study	Ischemic stroke	NIHSS and mRS	ECL
18.	Daubail et al, 2012	France	386	Observational cohort study	Ischemic stroke and hemorrhagic stroke	NIHSS and mRS	High pressure liquid chromatography coupled with UV detection
19.	Fahmy et al, 2019	Egypt	96	Case-control	Ischemic stroke	NIHSS and mRS	ELISA
20.	Kim et al, 2020	South Korea	328	Single-center retrospective study	Ischemic stroke	NIHSS	Radioimmunoassay kit
21.	Park et al, 2015	South Korea	818	Observational cohort retrospective	Ischemic stroke	NIHSS and mRS	Liquid chromatography tandem mass spectrometry
22.	Tu et al, 2014	China	364	Prospective cohort	Ischemic stroke	NIHSS and mRS	Competitive chemiluminescent immunoassay on a calibrated Elecsys 2010
23.	Wang et al, 2014	New York	326	Prospective cohort	Ischemic stroke	NIHSS and mRS	The E601 modular (Roche Diagnostics, Mannheim, Germany) with a calibration range from 3 to 70 ng/mL

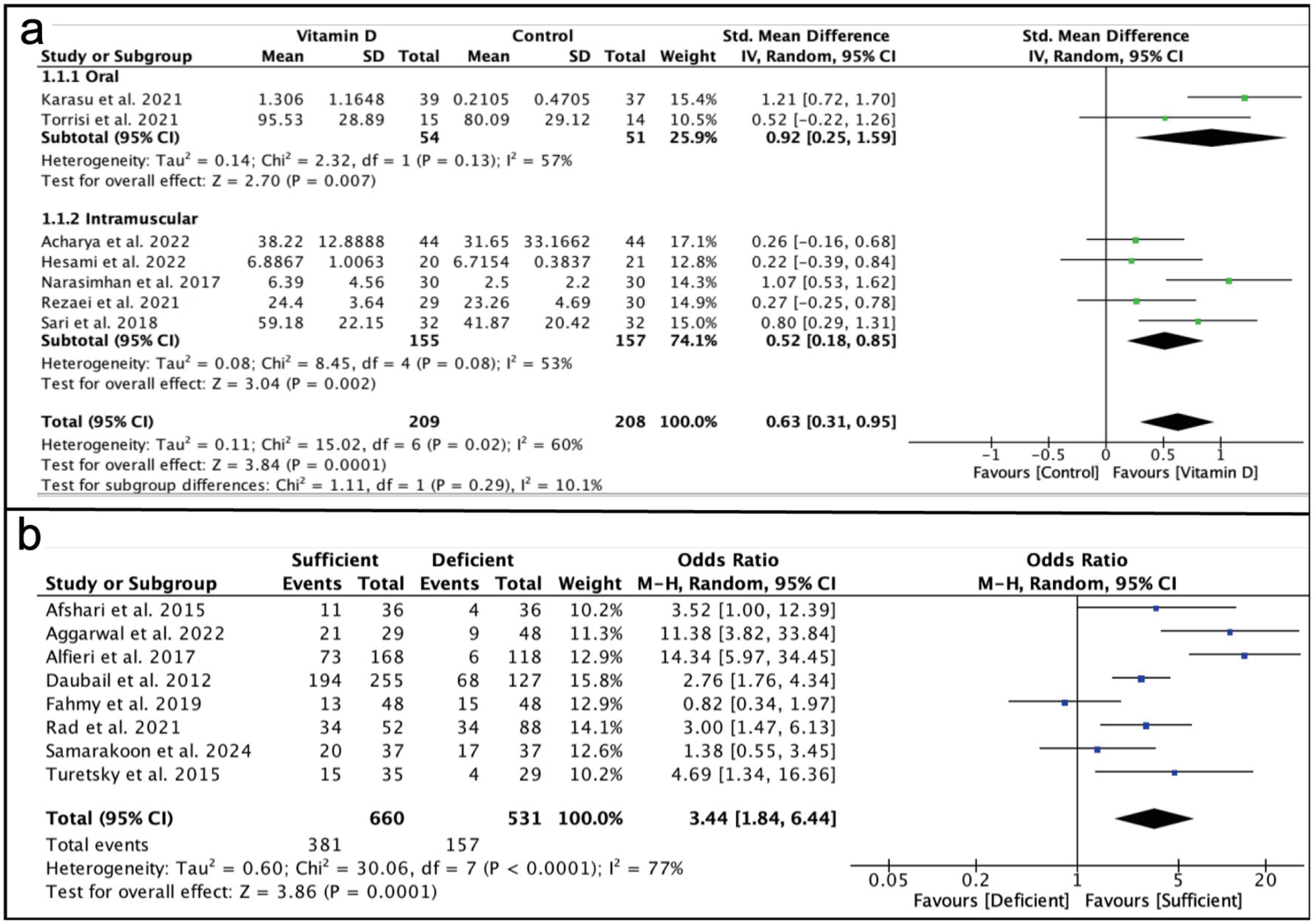

Figure 3. Analysis results. (a) Forest plot showing the effect of vitamin D supplementation on neurological function improvement compared to the control group. (b) Forest plot analyzing vitamin D levels in relation to stroke severity as a prognostic biomarker.

symmetric, as there were fewer than 10 studies included for each outcome. This suggests that the potential for publication bias could not be reliably assessed.

Discussion

The aim of this systematic review and meta-analysis was to evaluate the role of vitamin D in neuroprotective effects and its potential as a prognostic biomarker for stroke severity. Data analysis showed that vitamin D supplementation led to a significant improvement in neurological function compared to the control group (SMD, 0.63; 95% CI, 0.31–0.95; P = 0.0001). This improvement was observed with both high-dose single intramuscular injections (SMD, 0.52; 95% CI, 0.18–0.85; P = 0.002) and low-dose oral supplementation administered daily or weekly (SMD, 0.92; 95% CI, 0.25–1.59; P = 0.007) in patients with ischemic and hemorrhagic stroke.

Administering a single high-dose intramuscular injection of vitamin D to ischemic and hemorrhagic stroke patients may be a viable supplementation option, particularly for those with low adherence to daily or weekly oral treatments [19, 20]. Furthermore, a high-dose single injection can rapidly and safely increase serum 25-OH vitamin D levels [21–23]. The analysis also indicated that adequate vitamin D levels in stroke patients are associated with better prognosis regarding neurological function improvement compared to low vitamin D levels (OR, 3.44; 95% CI, 1.84–6.44; P < 0.0001). Our analysis suggests that daily and weekly vitamin D doses, totaling between 200,000 and 600,000 IU, can enhance neurological function in ischemic and hemorrhagic stroke patients, as assessed by SSS, mRS, NIHSS, and BI scores. Additionally, a single intramuscular injection of vitamin D at doses between 300,000 and 600,000 IU demonstrated significant improvements in neurological function.

It is important to note that the inflammatory process plays a crucial role in stroke pathogenesis [24]. The anti-inflammatory effects of vitamin D have been demonstrated in various diseases, such as multiple sclerosis (MS) and epilepsy [25]. The neuroprotective mechanisms induced by vitamin D are complex, involving the inhibition of the prostaglandin (PG) and cyclooxygenase-2 (COX-2) pathways, a reduction in matrix metalloproteinase-9 (MMP-9), and an increase in anti-inflammatory cytokines [26]. Deficiency in 25-hydroxyvitamin D (25(OH)D) can lead to prolonged immune-inflammatory responses, reducing neuroprotection and resulting in a poor prognosis for stroke patients [27]. Therefore, adequate vitamin D levels may serve as a protective factor against ischemic reperfusion injury in stroke cases, as well as offering protective effects against neurovascular injury [28]. Low serum vitamin D levels have been associated with an increased risk of stroke and poor stroke prognosis [29]. Poor vitamin D status in stroke patients is also closely linked to an elevated risk of future cerebrovascular incidents [30, 31].

Limitations

Several limitations of this study should be acknowledged. First, the included studies varied in design, encompassing both randomized controlled trials and non-randomized studies, which may have affected the consistency of the findings and increased the risk of bias. Additionally, moderate heterogeneity was observed, with I^2 values reaching 63% for primary outcomes and 71% for secondary outcomes. This heterogeneity is likely attributable to differences in study populations, vitamin D dosages, and outcome assessment methods. Variability in serum vitamin D measurement techniques across studies may have further influenced the results and their interpretation.

Another important limitation relates to sex-specific differences in stroke. Most of the included studies did not provide sufficient sex-disaggregated data to allow subgroup or stratified analyses. Consequently, the potential influence of sex on the neuroprotective effects of vitamin D supplementation and its role as a prognostic biomarker could not be fully explored.

Furthermore, comorbid conditions such as diabetes mellitus and hypertension, which may influence both stroke outcomes and vitamin D metabolism, were not consistently reported across studies and therefore could not be analyzed in detail. In addition, emerging aspects such as the effects of vitamin D on cerebral white matter integrity, cognitive impairment, and clusters of silent vascular risk factors associated with aging could not be systematically evaluated due to limited and non-standardized reporting of neuroimaging, cognitive, and subclinical vascular data across the included studies.

Future research

In addition to the outcomes assessed in this study, emerging evidence suggests that vitamin D may play a role in cerebral white matter integrity and cognitive function, both of which are important determinants of long-term outcomes after stroke. Alterations in white matter structure and cognitive impairment have been associated with aging-related cerebrovascular pathology and may be influenced by clusters of silent vascular risk factors. Although these aspects are clinically relevant, they could not be systematically evaluated in the present meta-analysis due to the lack of standardized reporting and insufficient data across the included studies.

These limitations highlight important directions for future research. Well-designed, large-scale randomized controlled trials are needed to clarify the optimal dosage, timing, and route of vitamin D supplementation in both ischemic and hemorrhagic stroke populations. Furthermore, future studies should incorporate sex-specific analyses, neuroimaging markers of white matter changes, detailed cognitive assessments, and comprehensive evaluation of subclinical vascular risk factors to further elucidate the neuroprotective mechanisms of vitamin D and refine its role as a prognostic biomarker in stroke outcomes.

Conclusions

This systematic review and meta-analysis demonstrates that vitamin D supplementation is associated with improved neurological function in patients with ischemic and hemorrhagic stroke, using both oral and intravenous regimens. In addition, low serum vitamin D levels are associated with greater stroke severity, supporting the potential role of vitamin D as a prognostic biomarker.

Despite heterogeneity among the included studies and the limited availability of sex-specific and comorbidity-related data, these findings underscore the clinical relevance of vitamin D in stroke management. Further well-designed prospective studies are required to determine optimal supplementation strategies and to establish evidence-based recommendations for the use of vitamin D in stroke care.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Informed Consent

Not applicable, as this study is a systematic review and meta-analysis of previously published data.

Author Contributions

I Nyoman Windiana conceived and designed the study, developed the research protocol, conducted literature search and study selection, performed data extraction and statistical analysis, and drafted the manuscript. Luh Putu Lina Kamelia contributed to literature search, study selection, data extraction, and critical revision of the manuscript for important intellectual content. I Nyoman Gede Narendra Yanakusuma participated in data extraction, quality assessment of included studies, and statistical analysis. Luh Made Karuni Kartika Sari contributed to data interpretation, manuscript editing, and critical review of the final version. All authors read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

BI: Barthel Index; BRS: Brunnstrom Recovery Stage; CI: confidence interval; COX-2: cyclooxygenase-2; FAC: Functional Ambulation Classification; FIM: Functional Independence Measure; I^2: I-squared statistic; MADRS: Montgomery-Åsberg Depression Rating Scale; MMSE: Mini-Mental State Examination; mRS: modified Rankin Scale; MMP-9: matrix metalloproteinase-9; MS: multiple sclerosis; NIHSS: National Institutes of Health Stroke Scale; NSE: Neuron-Specific Enolase; OR: odds ratio; PG: prostaglandin; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; ROB-2: risk of bias 2; ROBINS-I: risk of bias in non-randomized studies of interventions; SMD: standardized mean difference; SSS: Scandinavian Stroke Scale; WHO: World Health Organization; 25(OH)D: 25-hydroxyvitamin D

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