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REVIEW

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Intravoxel Incoherent Motion Diffusion-Weighted Imaging in Acute Stroke: A Comprehensive Review and Meta-Analysis

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Abstract

Background and objective: Intravoxel incoherent motion (IVIM) has the potential to provide both diffusion and perfusion information without an exogenous contrast agent, its application for the brain is promising, however, feasibility studies on this are relatively scarce. The present study aims to assess the evaluate the feasibility of using intravoxel incoherent motion (IVIM) to measure diffusion parameter variations in stroke.

Methods: To this end, we searched international databases (Web of Science, PubMed, Embase, and Scopus) and extracted related studies using the appropriate keywords. Collected data were analyzed with the aid of the random-effects model and STATA (version 15).

Results: A total of eight studies met the eligibility criteria, and the total sample size was 293 subjects. The mean age was 65.68 ± 13.68 years. The results showed a significant decrease between the ischemic core compared with the contralateral normal region for f value in stroke patients (SMD= −1.38, 95% CI −2.07 to −0.68, P < 0.001). Also, there was a significant decrease between the ischemic core compared with the contralateral normal region for D value in stroke patients (SMD = −3.14, 95% CI −3.38 to −2.89, P < 0.001). The D* parameter of the IVIM significantly decreases in the ischemic core compared with the contralateral normal region in stroke patients (SMD = −0.33, 95% CI −0.50 to 0.16, p = 0.09). Also, the results showed that the fD* parameter and ADC of the IVIM significantly decrease in the ischemic core compared with the contralateral normal region of stroke patients (SMD = −0.86, 95% CI −2.15 to 0.43, p < 0.01), and (SMD = −2.04, 95% CI −3.76 to −0.31, p < 0.01), respectively.

Conclusion: Our findings highlight the promising role of IVIM-DWI in offering quantitative insights into the pathophysiological alterations associated with acute stroke. By revealing significant reductions in diffusion parameters, particularly in perfusion fraction (f) and diffusion coefficient (D) values within ischemic regions compared to healthy tissue.

Keywords: Intravoxel incoherent motion, Diffusion-weighted imaging, Acute stroke

1. Introduction

Stroke is a leading cause of morbidity and mortality worldwide, imposing a substantial burden on healthcare systems and society [1]. Early and accurate diagnosis is crucial for effective management and intervention to mitigate the long-term consequences of stroke. Neuroimaging plays a pivotal role in the diagnosis and characterization of stroke, aiding in the differentiation of ischemic from hemorrhagic stroke, determining the extent of tissue damage, and guiding treatment decisions [2, 3]. Among various neuroimaging modalities, diffusion-weighted imaging (DWI) has emerged as a cornerstone in stroke imaging, offering exquisite sensitivity to the microstructural changes that occur in the brain following ischemic insult [4].

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Conventionally, DWI relies on the measurement of the apparent diffusion coefficient (ADC) to assess the diffusion of water molecules within brain tissue. However, ADC reflects a composite signal from multiple underlying tissue microenvironments, limiting its specificity in distinguishing between different tissue types or pathological conditions [5]. In recent years, there has been growing interest in the application of intravoxel incoherent motion (IVIM) DWI for the evaluation of stroke patients [6].

IVIM-DWI extends the conventional DWI framework by incorporating the effects of perfusion-related motion of water molecules within the imaging voxel. Unlike traditional DWI, which assumes a mono-exponential decay of the diffusion signal with increasing diffusion weighting, IVIM-DWI models the diffusion signal as a bi-exponential function, allowing for the separation of perfusion-related effects from true molecular diffusion [7]. By disentangling these components, IVIM-DWI holds promise for providing additional insights into the pathophysiology of stroke, particularly in the acute and subacute phases where alterations in tissue perfusion may precede irreversible damage [8].

Despite the growing interest in IVIM-DWI for stroke imaging, there remains a need for comprehensive synthesis and analysis of existing literature to evaluate its diagnostic utility and clinical relevance. A systematic review and meta-analysis offer a rigorous approach to assimilating data from multiple studies, providing a more robust assessment of the strengths and limitations of IVIM-DWI in the context of stroke management.

In this systematic review and meta-analysis, we aim to examine the current evidence regarding the application of IVIM-DWI in stroke patients. Specifically, we seek to elucidate the potential role of IVIM-DWI as a complementary tool to conventional DWI and other neuroimaging modalities in the comprehensive evaluation of acute stroke patients.

2. Materials and methods

We conducted this systematic review of the available evidence and presented our findings by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [9].

2.1. Search strategy

A comprehensive search was performed to extract the published studies on intravoxel incoherent motion diffusion-weighted imaging in stroke patients. The keywords used included "Intravoxel incoherent motion", "IVIM", "Diffusion-weighted imaging", "DWI", "stroke", "ischemic stroke", "neuroimaging", and "Diagnostic performance". International databases, including ISI, PubMed, Embase, and Scopus, were searched using various combinations of these keywords and Boolean operators ("OR" and "AND"). In order to locate studies that were not in the databases above, Google Scholar was also searched. Additionally, potentially relevant papers were found by looking through the extracted studies' references. The EndNote was then imported with all the records. Records that were duplicated were then removed. We also checked the reference list of related articles and searched Google Scholar as grey literature to prevent missing any eligible studies.

2.2. Inclusion and exclusion criteria

We included studies in our systematic review and meta-analysis according to the following criteria: 1) original articles written in English, and 2) studies involving human participants diagnosed with stroke using clinical criteria and confirmed with neuroimaging, including ischemic or hemorrhagic stroke, 3) studies utilizing IVIM-DWI as a diagnostic or prognostic tool in stroke patients, and 4) studies with available full-text articles or sufficient data for extraction.

We excluded 1) animal studies, review articles, editorials, conference abstracts, letters, and commentaries, 2) studies not focusing on stroke patients or not using IVIM-DWI as an imaging modality, 3) studies without clear reporting of relevant outcome measures, 4) studies published in languages other than English. The flow diagram (Fig. 1) shows the studies selected in this study.

2.3. Risk of bias in individual studies (Quality assessment)

The risk of bias in individual studies was evaluated using the Newcastle-Ottawa scale (NOS) [10], with 9 points for case-control studies and cohort studies, indicating excellent quality and low risk of bias: The studies 1–3, 4–6, and 7–9 were rated as being of low, moderate, and high quality, respectively (Table 1).

2.4. Data extraction

Two different authors extracted data from selected studies. Data such as the related data, including the name of the first author, place, year of publication, sample size, mean age, and design of the study. Also,

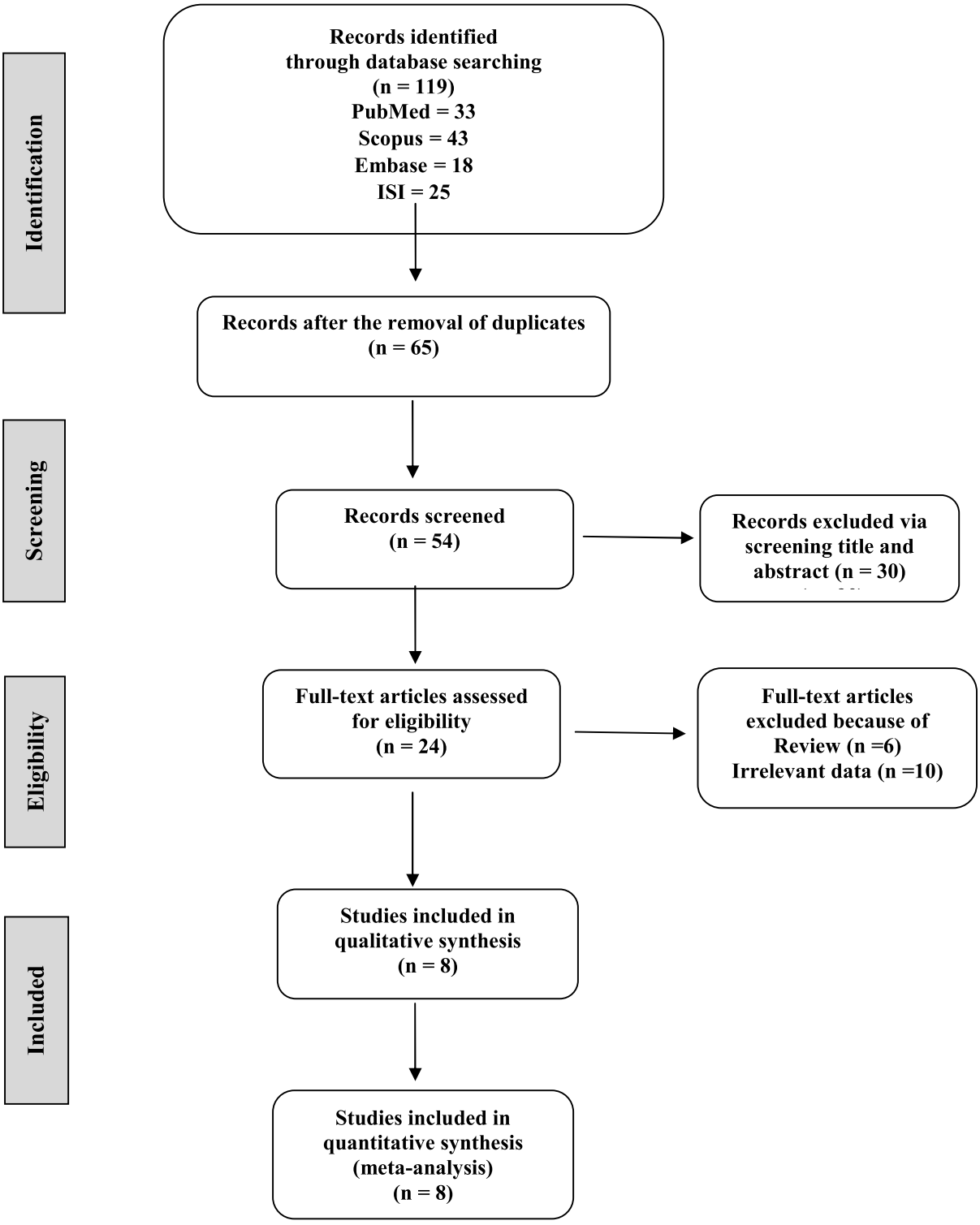

Fig. 1. PRISMA flow diagram illustrating the selection of articles.

we mentioned the mean ± SD of D, f, D*, fD*, and ADC parameters derived from IVIM in the ischemic core and contralateral normal region of patients. Data were reviewed for potential mistakes by other authors and then confirmed by all authors.

2.5. Risk of bias across studies

The Egger test and Begg's Funnel plots assessed the publication bias. P values under 0.05 were taken into consideration for heterogeneity.

Table 1. Characteristics of the studies reviewed in the present study.

Author Ref.	Year	Country	Total Sample Size	Male	Age (Mean ± SD)	Study design	Field strengths	Quality assessment Total score
Zhu G [11]	2019	China	20	11	67.1 ± 13.8	Prospective	3.0 T	8
Yao Y [12]	2016	China	38	-	55 ± 10.4	Prospective	3.0 T	5
Chen F [8]	2021	China	39	19	69 ± 13	Retrospective	3.0 T	6
Federau C [13]	2019	USA	34	17	68.6 ± 14.3	Prospective	3.0 T	8
Hu LB [14]	2015	China	15	9	68.7 ± 8	Prospective	3.0 T	7
Suo S [15]	2016	China	101	54	-	Retrospective	3.0 T	8
Federau C [16]	2014	USA	17	12	56.2 ± 24.3	Retrospective	3.0 T	6
Yamashita K [17]	2022	Japan	29	17	75.2 ± 12	Retrospective	3.0 T	7

2.6. Statistical analysis

Variables such as the sample size, mean, and standard deviation of expected data were pooled. Each study's weight was assigned based on its inverse variance. To evaluate test heterogeneity among included studies, the Q test and I^2 index were performed at a -level error of less than 10% significance. The random-effectsmodel was used to analyze heterogeneous data. Additionally, Stata 15 was used to analyze all the data.

3. Results

3.1. Study selection

After removing duplicate and irrelevant studies, finally, eight articles aligned with the inclusion criteria were included in the study. Four articles were prospective, and four articles were retrospective. The steps of selecting the studies are shown in Fig. 1. A total of 293 subjects were examined. The Mean ± SD age of the subjects was 65.68 ± 13.68 years (Table 1).

3.2. Pooled results

The results showed a reduction between the ischemic core compared with the contralateral normal region for f value in stroke patients based on the random effect model (SMD = −1.38, 95% CI −2.07 to −0.68, P < 0.001). Significant heterogeneity was detected among studies ($I^2 = 92.09\%$, $p < 0.001$) (Fig. 2). Also, based on a fixed-effects model, there was a significant decrease between the ischemic core compared with the contralateral normal region for D value in stroke patients (SMD = −3.14, 95% CI −3.38 to −2.89, P < 0.001). Significant heterogeneity was detected among studies ($I^2 = 36.64\%$, $p < 0.001$) (Fig. 3).

The aggregated results showed that the D* parameter of the IVIM significantly decreased in the ischemic core compared with the contralateral normal region in stroke patients (SMD = −0.33, 95% CI −0.50 to 0.16, p = 0.09) (based on a random effect model). Significant heterogeneity was detected among studies ($I^2 = 48.21\%$, $p < 0.001$). (Fig. 4). Also, the results showed that the fD* parameter and ADC of the IVIM significantly decreased in the ischemic core compared with the contralateral normal region of stroke patients (SMD = −0.86, 95% CI −2.15 to 0.43, $p < 0.01$, based on a random effect model), and (SMD = −2.04, 95% CI −3.76 to −0.31, $p < 0.01$ based on a random effect model), respectively (Fig. 5). Significant heterogeneity was detected among studies ($I^2 = 97.29\%$, $p < 0.19$, and $I^2 = 97.43\%$, $p < 0.02$) (Figs. 6 and 7).

3.3. Risk of bias between studies

Begg's method was applied to both outcomes, and no publication bias was found (P = 0.345). Fig. 7 illustrates the evaluation of publication bias across studies employing these tests.

4. Discussion

IVIM-DWI is a technique used in stroke imaging to assess perfusion-related information non-invasively. IVIM MRI can be performed in a short scanning time and provides qualitative information about perfusion in acute ischemic stroke (AIS) patients [18, 19]. It allows for the evaluation of intracranial arterial recanalization and determination of presumed penumbral regions, aiding in treatment strategy decisions [17].

IVIM analysis involves measuring diffusion and pseudo-diffusion parameters, such as diffusion coefficient, perfusion fraction, and pseudodiffusion coefficient [20, 21]. The technique has shown good interobserver agreement in assessing perfusion fraction and pseudodiffusion coefficient maps. IVIM MRI can be integrated with diffusion tensor imaging (DTI) to determine orientation-dependent perfusion parameters, providing additional insights into cerebral perfusion. Additionally, IVIM DWI can be performed in less than one minute, making it a time-efficient imaging technique [21]. A previous study found that IVIM with a combination of b-values of 0, 50, 200, and

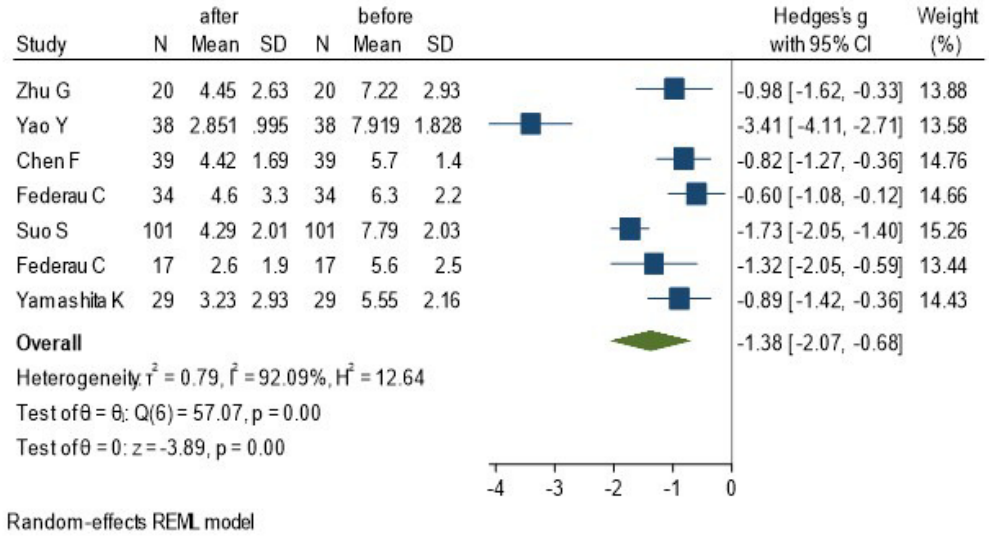

Fig. 2. Forest plot of the mean value of perfusion fraction (f) in the ischemic core compared with the contralateral normal region.

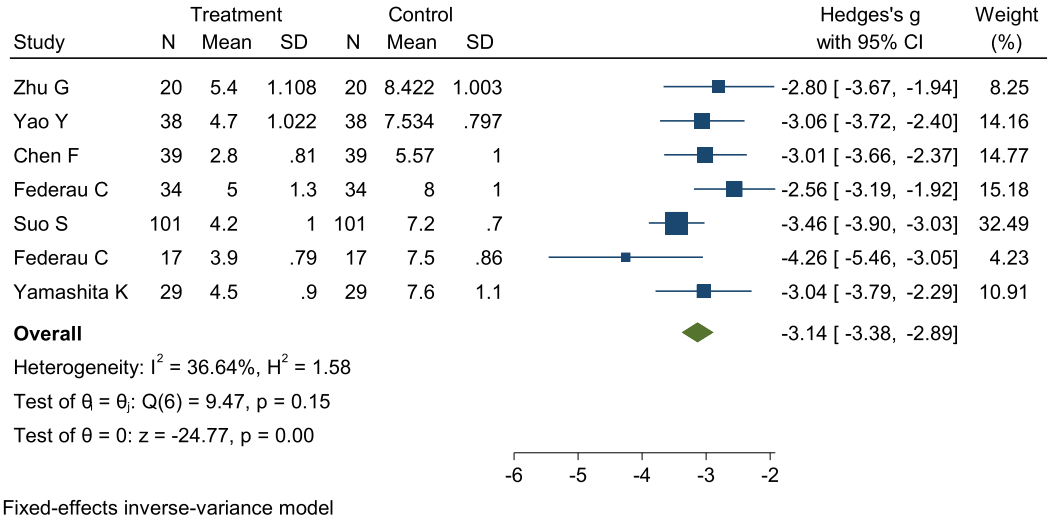

Fig. 3. Forest plot of the mean value of tissue diffusivity (D) in the ischemic core compared with the contralateral normal region.

1000 seconds/mm2 was consistent with the reference standard for generating perfusion information in AIS patients. This combination of b-values allows for the collection of diffusion and perfusion information in a single short MRI sequence, which is advantageous for imaging AIS patients [22]. Therefore, IVIM-DWI is a feasible and time-efficient imaging technique that provides perfusion-related information in patients with acute stroke [22].

The present study aims to assess the feasibility of IVIM-DWI in acute stroke and present compelling findings regarding the alterations in diffusion parameters within ischemic regions compared to healthy tissue. The results indicate significant decreases in diffusion parameters, particularly in the f and D values, in the ischemic core relative to the contralateral normal region in stroke patients. Moreover, the study reveals a decrease in the D* parameter in the ischemic core, although the effect size was not statistically significant. These findings underscore the potential utility of IVIM-DWI in characterizing ischemic stroke lesions and understanding the underlying pathophysiology.

The observed reductions in f and D values within the ischemic core suggest changes in tissue microstructure and perfusion dynamics associated with acute stroke. The decrease in the f value indicates a reduction in the perfusion fraction, reflecting compromised microvascular flow within the ischemic territory [23]. Meanwhile, the decline in the D value

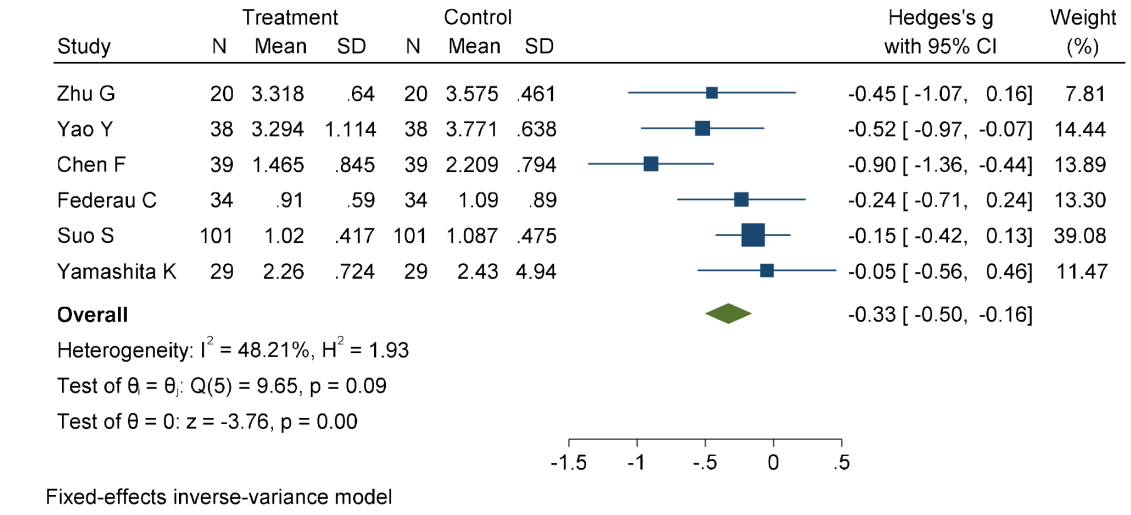

Fig. 4. Forest plot of the mean value of pseudo-diffusivity (D), in the ischemic core compared with the contralateral normal region.*

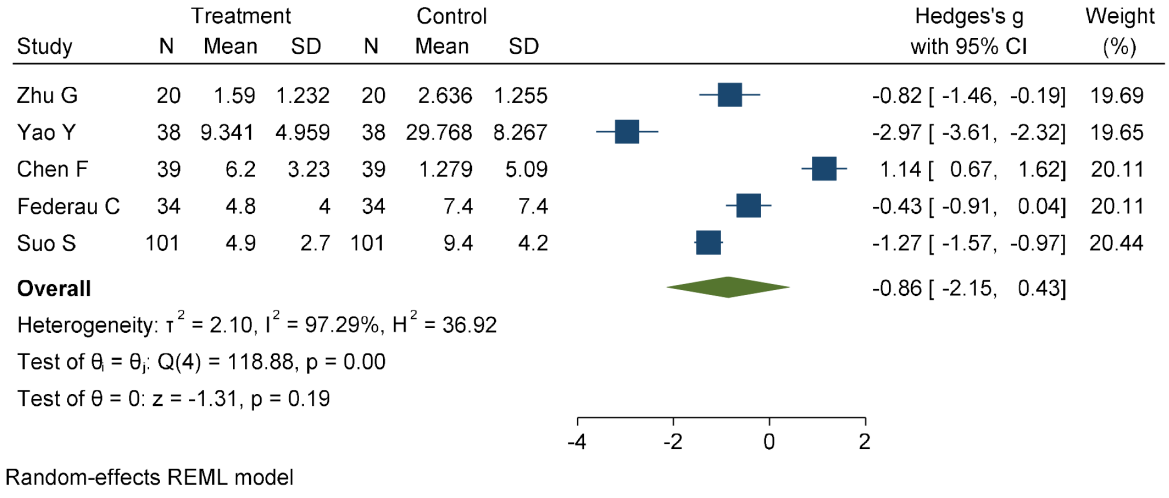

Fig. 5. Forest plot of the mean value of fD, in the ischemic core compared with the contralateral normal region.*

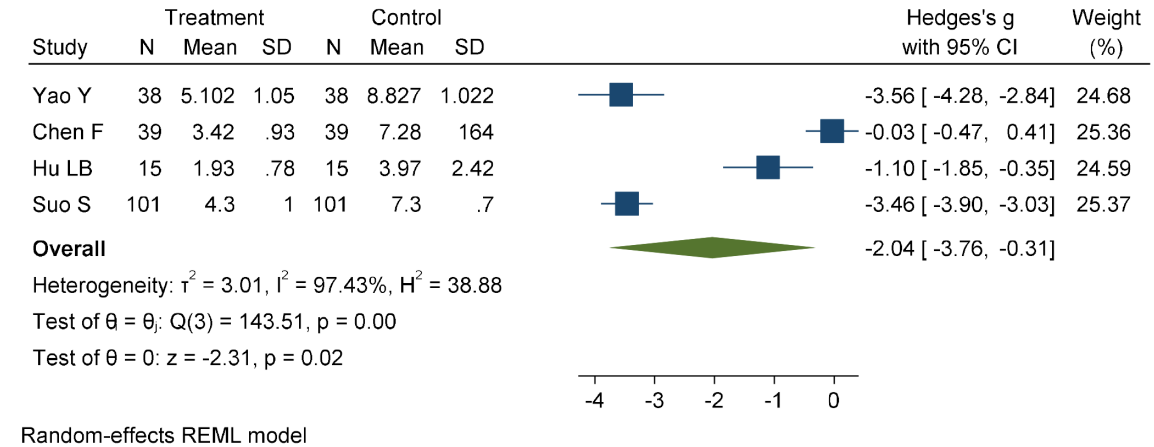

Fig. 6. Forest plot of the mean value of apparent diffusion coefficient (ADC), in the ischemic core compared with the contralateral normal region.

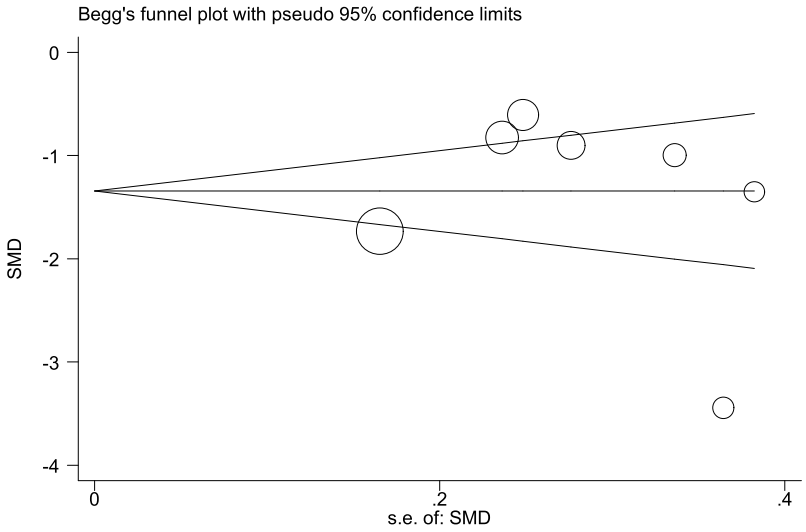

Fig. 7. Publication bias test using Begg's funnel plot test.

suggests restricted diffusion, likely attributable to cellular swelling, cytotoxic edema, and loss of tissue integrity. These alterations are consistent with the pathophysiological processes observed in acute ischemic stroke, where impaired blood flow leads to cellular injury and edema formation. The study conducted by Yoshie et al. showed that the perfusion parameter value thresholds that best delineate the ischemic core are more significantly abnormal and have higher accuracy with longer onset-to-imaging times. Perfusion abnormalities in ischemic core regions become progressively more abnormal with longer intervals from onset to imaging [24]. Also, Fiehler et al. (2001) reported that the severity of the perfusion deficit was substantially correlated with the distribution of ADC values, which decreased from the periphery toward the ischemic core [25].

Furthermore, the meta-analysis highlights the potential of IVIM-DWI parameters as quantitative biomarkers for assessing stroke severity and predicting clinical outcomes. The results of the Zhu et al. study revealed that IVIM and perfusion-weighted imaging parametric maps indicate moderate variations in brain perfusion measurement, while IVIM fD* and perfusion-weighted imaging CBF exhibit great agreement. IVIM is promising for cerebral perfusion evaluation in acute ischemic stroke patients [26].

The significant heterogeneity observed among studies underscores the need for standardized imaging protocols and analysis techniques to ensure the reproducibility and generalizability of findings across different research settings. Addressing this heterogeneity will be crucial for establishing IVIM-DWI as a reliable tool for clinical decision-making in stroke management.

Despite the valuable insights provided by this meta-analysis, several limitations should be acknowledged. Firstly, the presence of significant heterogeneity among studies raises concerns about the consistency of findings and the robustness of pooled effect estimates. Variability in patient populations, imaging protocols, and analysis methods across studies could contribute to this heterogeneity, potentially confounding the interpretation of results.

Secondly, while efforts were made to assess publication bias using Begg's method, the possibility of selective reporting and publication of studies with positive findings cannot be entirely ruled out. Finally, the interpretation of IVIM-DWI parameters in the context of acute stroke is subject to certain limitations inherent to the imaging technique itself. IVIM-DWI relies on assumptions regarding tissue microstructure and perfusion dynamics, which may not always hold in the complex pathophysiological milieu of acute stroke. Factors such as partial volume effects, motion artifacts, and variability in imaging timing could affect the accuracy and precision of IVIM-derived parameters, limiting their clinical utility in certain scenarios.

5. Conclusion

These findings underscore the potential of IVIM-DWI in providing quantitative insights into the pathophysiological changes occurring in acute stroke, thereby facilitating early diagnosis, and informing treatment strategies. Moving forward, further research efforts aimed at standardizing protocols, addressing methodological limitations, and validating findings across diverse patient populations will be

crucial in harnessing the full clinical utility of IVIM-DWI in the management of acute stroke.

Abbreviation

CI: confidence interval
IVIM: intravoxel incoherent motion

Ethical approvals

Not applicable.

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Conflicts of interest

The authors declare no conflict of interest.

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