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Impact of insulin resistance on post-stroke depression and outcomes in diabetes

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ABSTRACT

Aims: This study aimed to examine the association between insulin resistance (IR) and post-stroke depression (PSD) occurrence in diabetic patients, providing novel insights for PSD prevention and treatment strategies.

Materials and methods: Clinical data from 124 patients with acute cerebral infarction and diabetes mellitus were retrospectively analyzed. Based on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), participants were stratified into two groups: an IR group (HOMA-IR > 2.69, $n = 96$) and a control group (HOMA-IR ≤ 2.69, $n = 28$). The occurrence of PSD was compared between the two groups by unadjusted analysis and inverse probability of treatment weighting (IPTW), and the correlation between HOMA-IR scores and PSD was analyzed by multivariate logistic regression.

Results: At 3-month follow-up, the IR group exhibited significantly higher Hamilton Depression Scale (HAMD) scores (median 8 vs 6, $P = 0.029$) and a 3.28-fold increased PSD risk (OR = 3.28, 95% CI: 1.37–7.88, $P = 0.006$). After adjusting for baseline confounders using IPTW, the IR group maintained elevated PSD risk (adjusted OR = 2.64, $P = 0.035$). Multivariate analysis confirmed HOMA-IR as an independent PSD predictor (OR = 1.755, 95% CI: 1.360–2.263, $P < 0.001$), with ROC analysis demonstrating moderate predictive accuracy (AUC = 0.76, 51.4% sensitivity, 94.2% specificity at cutoff 5.2).

Conclusions: Elevated HOMA-IR levels in diabetic patients with acute cerebral infarction are significantly associated with increased PSD incidence.

INTRODUCTION

In recent years, stroke prevalence has shown a marked upward trend globally. Public health systems have been increasingly threatened by the rising rates of stroke-related mortality and disability. In developed countries, cerebrovascular events are the second leading cause of mortality according to the 2021 Global Burden of Disease (GBD) study, surpassed only by ischemic heart disease[1]. Stroke accounts for over 1 million annual deaths in China[2]. Post-stroke depression (PSD), a prevalent complication affecting 18–33% of stroke survivors, exhibits a peak incidence 3–6 months post-stroke[3]. Global epidemiological estimates suggest that approximately 400,000 individuals annually develop depression secondary to cerebrovascular events[4].

In addition to exacerbating pre-existing neurological deficits, PSD presents with core depressive symptoms including persistent dysphoria, insomnia, and maladaptive cognitive patterns such as excessive guilt[5]. These psychological and physiological factors collectively hinder functional rehabilitation and reduce health-related quality of life. Consequently, these combined effects result in prolonged hospitalization, higher healthcare costs, and increased mortality risks[6]. However, post-stroke cognitive impairment and aphasic disorders are often perceived by clinicians as inherent neurological sequelae of cerebrovascular events. This diagnostic oversight frequently delays initiation of early neuropsychological interventions, leading to suboptimal functional recovery.

The pathogenesis of PSD involves complex interactions between biological and psychosocial factors[7]. Emerging evidence has identified multiple risk factors for PSD, including genetic predisposition, premorbid psychiatric history, demographic characteristics such as advanced age and female gender, stroke-related parameters such as lesion location, and clinical severity assessed through National Institutes of Health Stroke Scale (NIHSS) scores during the acute phase[8–13].

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The underlying pathophysiology involves multiple mechanisms: hypothalamic–pituitary–adrenal (HPA) axis dysregulation, an inflammatory response, monoaminergic dysfunction involving serotonin (5-HT), dopamine (DA) and norepinephrine (NE) pathways, and altered neurotrophic factor expression[14–17]. Emerging evidence suggests that metabolic dysregulation (encompassing dyslipidemia, hyperuricemia, and insulin resistance (IR)) may represent novel pathophysiological determinants of PSD[18]. Insulin exerts dual regulatory effects on glucose homeostasis: (1) suppressing hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis pathways, and (2) enhancing glucose utilization through activation of glucose transporters in peripheral tissues. IR manifests as impaired suppression of hepatic glucose output coupled with diminished peripheral tissue glucose uptake capacity, reflecting defective insulin receptor signaling. Previous studies demonstrate a bidirectional association between IR and depression. Specifically, IR increases the risk of depression via impaired insulin signaling pathways, whereas depression exacerbates metabolic dysfunction through dysregulation of the HPA axis[19]. A critical research gap persists regarding PSD in individuals with diabetes mellitus, particularly in those with pre-existing glycemic dysregulation. Compelling evidence positions insulin resistance both as the hallmark metabolic defect in type 2 diabetes mellitus pathophysiology and as a secondary phenomenon in type 1 diabetes mellitus, driven by chronic hyperglycemia-induced receptor desensitization[20]. Longitudinal studies have demonstrated that the presence of diabetic neurovascular complications is associated with an elevated risk of depression[21]. Elevated blood glucose levels during the acute post-stroke period have been shown to increase the risk of PSD[22].

Consistent with recent meta-analytic evidence demonstrating a bidirectional relationship between IR and affective disorders[23], our findings extend this association to the post-stroke neuropsychiatric domain. This retrospective cohort study was designed to investigate the association between IR and 3-month post-stroke depression incidence in patients with acute cerebral infarction and comorbid diabetes mellitus. Through rigorous stratification based on validated Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) thresholds and multivariate adjustment for potential confounders, we aimed to establish the prognostic value of IR metrics in predicting neuropsychiatric complications during stroke rehabilitation, ultimately providing evidence-based targets for metabolic intervention strategies in this vulnerable population.

MATERIALS AND METHODS

Participants

This retrospective study analyzed clinical data from patients diagnosed with acute ischemic stroke and comorbid diabetes mellitus who received treatment at our institution between January 2020 and May 2023. Inclusion criteria comprised the following: (1) fulfillment of the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke diagnostic criteria for cerebral infarction[24], confirmed through CT/MRI imaging; (2) all enrolled patients met diagnostic criteria for type 2 diabetes mellitus per 2020 CDS guidelines[25]; (3) first-onset acute cerebral infarction with symptom duration <2 weeks. Exclusion criteria were as follows: (1) pre-existing psychiatric disorders (including depression) or use of psychotropic medications; (2) concurrent brain neoplasms; (3) severe systemic infections; (4) major organ dysfunction (cardiac, hepatic, or renal); (5) inability to complete study protocols. The final cohort included 124 patients (68 males and 56 females) with age ranging from 31 to 86 years.

Data collection

Demographic and clinical characteristics including age, sex, height, weight, medical history (hypertension, diabetes, etc.), social support (living alone, divorce, or widowed status), and lifestyle factors (smoking, alcohol consumption) were systematically collected upon hospital admission. Smoking was defined as daily consumption of ≥1 cigarette for over 1 year. Chronic alcohol use was defined as daily intake exceeding 100 mL/day of liquor (≥50% alcohol by volume) for more than 12 months. Stroke location was determined by neuroimaging evidence (MRI/CT). Body mass index was calculated as weight in kilograms divided by height in meters squared. The HOMA-IR was calculated using the formula: [fasting plasma glucose (mmol/L) × fasting serum insulin (μIU/mL)]/22.5[26]. IR was defined according to WHO criteria as glucose utilization rates below the lowest quartile measured by hyperinsulinemic-euglycemic clamp in non-diabetic populations[27]. The lack of standardized insulin assays and methodological heterogeneity across studies, particularly regarding demographic variations in gender and ethnicity, hinders the establishment of universal HOMA-IR thresholds. Population-based studies in Chinese cohorts have identified 2.69 as the 75th percentile HOMA-IR value[28]. Using this threshold, we divided participants into an insulin-resistant group (HOMA-IR > 2.69) and a control group (HOMA-IR ≤ 2.69).

Outcome assessment

Depression severity was evaluated using the 17-item Hamilton Depression Rating Scale (HAMD-17) in patients with acute cerebral infarction and comorbid diabetes mellitus. According to the 2016 *Chinese Expert Consensus on Clinical Practice of Post-Stroke Depression*[29], the HAMD-17 is recommended for diagnosis. A score <7 indicates normal status, while a score of 7–17 suggests probable depression. The severity of neurological impairment was assessed with the NIHSS, an 11-item instrument assessing domains including limb ataxia, motor function (upper/lower extremities), language capacity, and consciousness level. The scale generates a composite score between 0 and 42, where a higher value corresponds to greater neurological impairment severity. Standardized assessments were conducted by trained clinicians at two time points: baseline evaluation during hospital admission and follow-up assessment at 3 months post-stroke.

Laboratory measurements

Following an overnight fast, venous blood samples were obtained for biochemical analyses. Fasting parameters included blood glucose, serum insulin, insulin-like growth factor-1 (IGF-1), glycosylated hemoglobin (HbA1c), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C). Biochemical measurements were performed using standardized laboratory protocols: blood glucose levels were measured by the glucose oxidase method; insulin and IGF-1 concentrations were determined through chemiluminescent immunoassay; HbA1c quantification employed ion-exchange high-performance liquid chromatography; lipid profiles including TC and low-density LDL-C were analyzed using automated biochemistry analyzers.

Statistical analysis

Statistical analyses were conducted using SPSS 25.0 and R version 4.4.2. Normally distributed continuous variables are expressed as mean ± SD, while non-normally distributed variables are reported as median with interquartile range (IQR). Group comparisons employed Student's *t*-test/Mann–Whitney *U*-test for continuous variables and chi-squared tests for categorical variables. To identify risk factors for PSD, we performed a two-stage regression analysis. First, variables were screened through univariate logistic regression with a threshold ($P < 0.2$) to maximize sensitivity for potential predictors. Candidate variables meeting this criterion were then entered into a multivariable logistic regression model, where statistical significance was defined as $P < 0.05$. Additionally, receiver operating characteristic (ROC) analysis was performed to assess the predictive capability of the risk factors. The inverse probability of treatment weighting (IPTW) analysis was performed using R version 4.4.2 with the twang and ggplot2 packages.

RESULTS

The HAMD scores and depression incidence in two groups

Longitudinal comparisons of HAMD scores and depression incidence revealed significant intergroup differences. At baseline, the median HAMD score was significantly higher in the IR group (3, IQR 2–4) than in controls (2, IQR 1–3; Mann–Whitney *U*-test, $P = 0.030$). At the 3-month follow-up, both groups showed significant increases in HAMD scores from baseline (both $P < 0.01$), with the IR group persistently exhibiting higher median scores (8, IQR 6–14) compared to controls (6, IQR 5.25–8.75; $P = 0.029$), as detailed in Table 1.

Participant characteristics

A total of 164 patients with acute cerebral infarction and comorbid diabetes mellitus were initially enrolled. After applying exclusion criteria (severe heart failure [$n = 8$], renal insufficiency [$n = 8$], hepatic dysfunction [$n = 3$], and history of depression/psychotropic medication use [$n = 5$]), 140 participants remained eligible for analysis. Sixteen patients were lost to 3-month follow-up. The participant recruitment flowchart is shown in Figure 1.

Table 1 | Comparison of HAMD scores between the IR and control groups across time points

Time points	Groups	Number of cases	HAMD score	*P*
Baseline	IR	96	3 (2, 4)	0.030*
	Control	28	2 (1, 3)	
3-month follow up	IR	96	8 (6, 14)**	0.029*
	Control	28	6 (5.25, 8.75)**	

Data are presented as [M (P25, P75)]. *$P < 0.05$ for intergroup comparisons. **$P < 0.01$ for intragroup comparisons. HAMD, Hamilton Depression Rating Scale; IR, insulin resistance.

Inverse probability treatment weighting analysis

IPTW was applied to balance baseline covariates, including age, sex, smoking, alcohol use, BMI, baseline HAMD-17 score, and unmarried status (divorced, widowed, or living alone; Table 2). To address low statistical power from limited observations and sparse events, marital status variables (divorced/widowed/living alone) were collapsed into a dichotomous 'unmarried status' indicator. And the threshold for acceptable balance was relaxed from a standardized mean difference (SMD) of <0.2 to a more lenient value. The Love plot demonstrates covariate balance before and after IPTW (Figure 2). According to the result, the crude odds ratio (OR) for IR was 3.28 (95% CI: 1.37–7.88, $P = 0.006$) before IPTW adjustment, indicating a significant association with PSD. The IR–PSD association remained statistically significant in the IPTW-adjusted logistic regression model (OR = 2.64, 95% CI: 1.07–6.54, $P = 0.035$; Table 3). To further evaluate robustness, we performed an *E*-value analysis, which suggested that an unmeasured confounder would need to have a risk ratio of 2.62 to fully explain the observed effect.

HOMA-IR exhibits high specificity as a diagnostic exclusion tool for post-stroke depression

Univariate analyses were conducted to identify predictors of PSD in diabetic patients with acute cerebral infarction. Given the small sample size, we employed a *P*-value threshold of <0.2 in the univariate analysis to improve the sensitivity of variable selection and reduce the likelihood of missing potentially critical predictors. In univariate analysis using depression status as the dependent variable, significant associations ($P < 0.2$) were observed for smoking history, glycated hemoglobin (HbA1c), and HOMA-IR (Table 4). Multivariable logistic regression analysis revealed that elevated HOMA-IR levels independently predicted PSD, with an adjusted odds ratio of 1.755 (95% CI: 1.360–2.263, $P < 0.001$; Table 5). Bootstrap validation (1,000 resamples) corroborated the robustness of insulin resistance (IR) as a predictor (Bias = 0.037, 95% CI: 0.383–0.894, $P = 0.001$), whereas smoking status exhibited unstable estimates (Bias = 0.071, 95% CI: −0.379–2.021, $P = 0.185$), potentially attributable to class imbalance in smoking subgroups. The model demonstrated moderate explanatory power (Nagelkerke

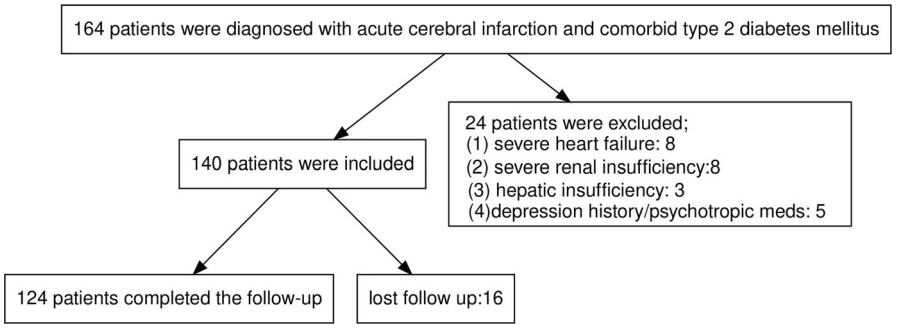

Figure 1 | Patient enrollment flowchart. A consort-style diagram detailing the screening process, application of exclusion criteria (n = 40 excluded: severe heart failure [n = 8], renal insufficiency [n = 8], hepatic dysfunction [n = 3], history of depression/psychotropic medication use [n = 5], and lost to follow-up [n = 16]), and final analytical cohort selection (n = 124 included for analysis).

Table 2 | Before and after adjustment with stabilized IPTW from propensity score model fitted values

Characteristic	Total (n = 124)		P value		SMD	
	IR (n = 96)	Control (n = 28)	Before IPTW	After IPTW	Before IPTW	After IPTW
Age	64.02 ± 10.90	61.93 ± 12.47	0.389	0.889	0.186	0.035
Sex						
Male (%)	52 (54.2%)	16 (57.1%)	0.781	0.705	−0.060	0.098
Female (%)	44 (45.8%)	12 (42.9%)				
Smoking	18 (18.8%)	9 (32.1%)	0.131	0.963	−0.323	0.010
Alcohol	23 (24.0%)	6 (21.4%)	0.781	0.468	0.060	0.145
BMI	26.33 ± 3.15	24.28 ± 3.21	0.003	0.929	0.627	−0.033
HAMD-17 scores	3 (2, 4)	2 (1, 3)	0.030	0.516	0.457	0.187
Unmarried	13 (13.5%)	4 (14.3%)	0.920	0.740	−0.022	−0.093

An absolute standard difference of <0.2 is considered well balanced. BMI, body mass index; HAMD-17 scores, Baseline HAMD-17 scores; IPTW, inverse probability of treatment weight; SMD, standardized mean difference; unmarried, divorced, widowed, or living alone.

R^2 = 0.342), adequate calibration (Hosmer–Lemeshow χ^2 = 2.146, P = 0.976), and an overall classification accuracy of 72.6%. Then, the ROC curve of IR was performed in Figure 3. It identified insulin resistance (IR ≥ 5.2) as a predictor of PSD, yielding an AUC of 0.76 (95% CI: 0.68–0.84). At this threshold, specificity reached 94.2%, demonstrating strong capacity to exclude non-PSD cases, while sensitivity was 51.4% (95% CI: 30.6–63.9%), indicating limited ability to detect true PSD cases.

IR exhibited no significant association with neurologic recovery

NIHSS scores at baseline and 3-month follow-up were analyzed to characterize neurologic recovery trajectories. No significant intergroup difference in NIHSS scores was observed at disease onset (3, IQR 2–4 vs 2, IQR 1–4; P = 0.215). Although both groups demonstrated significant NIHSS score improvement at 3-month follow-up compared to baseline, intergroup differences remained non-significant (0, IQR 0–2 vs 0, IQR 0–1; P = 0.138), with detailed results presented in Table 6.

DISCUSSION

This retrospective cohort study analyzed clinical data from patients with acute cerebral infarction complicated by diabetes mellitus, aiming to explore the association between IR and the development/prognosis of PSD. At the 3-month follow-up, both groups demonstrated elevated HAMD scores compared to baseline measurements (both P < 0.05), with the IR group persistently exhibiting higher median scores (8, IQR 6–14) compared to controls (6, IQR 5.25–8.75; P = 0.029). The patients in the IR group exhibited 3.28 times higher odds of developing PSD compared to the control group (OR = 3.28, 95% CI: 1.37–7.88, P = 0.006). After adjusting for baseline confounders using IPTW, the IR group retained a significantly elevated risk of PSD, with an adjusted OR of 2.64 (95% CI: 1.07–6.54, P = 0.035). The robustness of this association was further supported by E-value analysis, which yielded a lower bound E-value of 2.62, indicating that unmeasured confounding factors would need to explain at least 2.62-fold stronger associations with both exposure and outcome to nullify the observed results. These findings suggest that IR may contribute to PSD

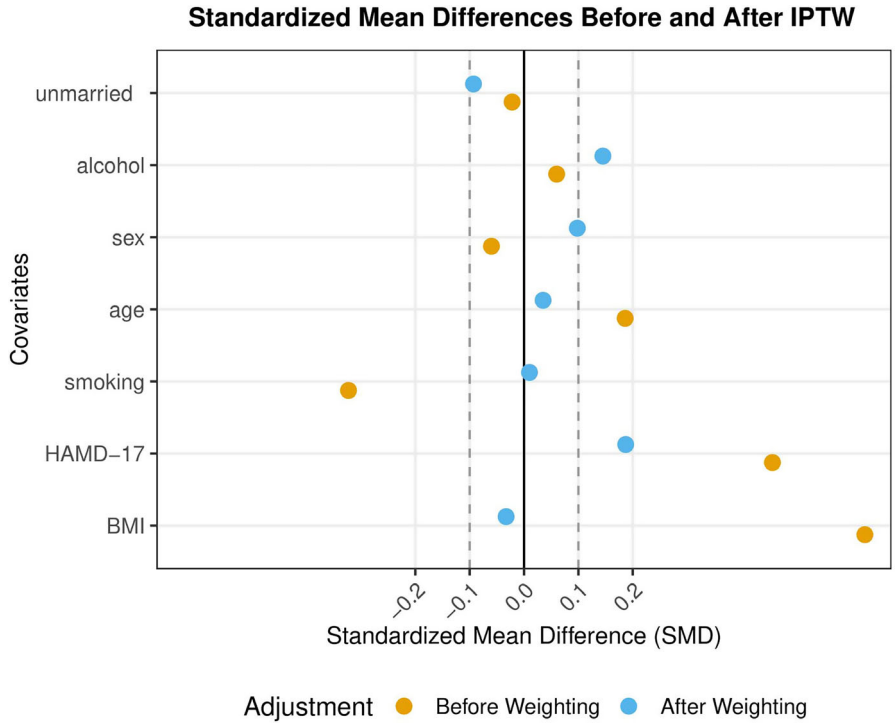

Figure 2 | Covariate balance assessment using Love plot. Standardized mean differences (SMD) of baseline characteristics before (golden circles) and after (blue circles) IPTW are shown. The dashed horizontal line indicates the conventional balance threshold (SMD < 0.1); however, we pragmatically relaxed this criterion to 0.2 to account for limited sample size (n = 124).

Table 3 | Comparison of PSD incidence between groups before and after IPTW adjustment

Group	Total (n = 124)		Unadjusted		IPTW-adjusted	
	PSD (n = 72)	Non-PSD (n = 52)	OR	P	OR	P
IR	62	34	3.28 (1.37–7.88)	0.006	2.64 (1.07–6.54)	0.035*
Control	10	18				

IPTW, inverse probability of treatment weight; PSD, post-stroke depression. *P < 0.05.

pathogenesis. PSD not only prolongs the cognitive recovery period and diminishes quality of life, but also accelerates stroke recurrence. The median time to first stroke recurrence was significantly shorter in PSD patients (8.15 years, 95% CI 7.11–9.19) compared to non-PSD patients (9.63 years, 95% CI 8.89–10.38)[30]. Given its insidious clinical presentation, PSD is often undetectable during initial stages. Diabetes mellitus has been identified as a significant risk factor for PSD development[31]. Patients with diabetes mellitus exhibit suboptimal glycemic control following acute cerebral infarction. Under stressful conditions, activation of the HPA axis promotes adrenal hormone secretion, thereby elevating blood glucose levels. Impaired glycemic regulation is associated with IR, a metabolic alteration that demonstrates significant correlation with depression pathogenesis[32]. Insulin is associated with metabolic disorders, signaling dysregulation, and neurodegenerative diseases. It participates in multiple neurobiological processes and plays a critical role in cognitive function[33]. IR, a key feature of metabolic syndrome, can induce various pathological alterations, including reduced kinase activity of insulin receptor complexes, impaired glucose transport, defective insulin signaling pathways, diminished glycogen synthase activity, and aberrant glucose phosphorylation[34–37]. Dysregulated insulin sensitivity triggers microglial and astrocytic activation, which initiates neuroinflammatory cascades through pro-inflammatory cytokine release. This pathological process culminates in neuroglial apoptosis and cognitive and affective dysfunction[38]. Hippocampal cholinergic neurotransmission demonstrates significant attenuation under IR conditions. These alterations precipitate progressive neurodegeneration, exacerbating domain-specific

Table 4 | Clinical characteristics of patients in the PSD and non-PSD groups

Variables	PSD group (n = 72)	Non-PSD group (n = 52)	$\chi^2/t/Z$	P-value
Sex				
Male (%)	36 (50%)	20 (38.5%)	1.623	0.203
Female (%)	36 (50%)	32 (61.5%)		
Age (years)	63 (55.25, 70)	66 (57.25, 71.75)	−0.684	0.494
Smoking (%)	12 (16.7%)	15 (28.8%)	2.630	0.105*
Alcohol	17 (23.6%)	12 (23.1%)	0.005	0.945
BMI (kg/m^2)	26.06 ± 3.19	25.60 ± 3.39	0.780	0.437
HbA1c (%)	8.15 (7.10, 9.50)	7.60 (6.95, 8.6)	−1.512	0.130*
TC (mmol/L)	4.36 (3.54, 5.45)	4.40 (3.33, 5.13)	−0.706	0.480
LDL-C (mmol/L)	2.88 (2.03, 3.40)	2.79 (2.15, 3.42)	−0.182	0.855
NIHSS scores	2.5 (2, 4)	3 (2, 4)	−0.216	0.829
3 months NIHSS scores	0 (0, 1)	0 (0, 2)	−0.648	0.517
IGF-1 (ng/mL)	124.50 ± 47.3	122.76 ± 43.49	0.208	0.835
HOMA-IR	5.25 (3.43, 7.43)	3.22 (2.36, 4.33)	−4.953	0.000*
Hypertension	46 (63.9%)	30 (57.7%)	0.489	0.485
Unmarried	9 (12.5%)	8 (15.4%)	0.212	0.645
HAMD-17 scores	3 (2, 4)	3 (1, 4)	−0.218	0.827
Infarction location				
Left (%)	29 (40.3%)	27 (51.9%)	11.886	0.338
Right (%)	38 (52.8%)	23 (44.2%)		
Bilateral (%)	5 (6.9%)	2 (3.8%)		

Data are shown as mean ± SD, median (interquartile range) or n (%). *P < 0.2. BMI, body mass index; HAMD-17 scores, baseline HAMD-17 scores; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; LDL-C, low-density lipoprotein cholesterol; NHISS, National Institutes of Health Stroke Scale; TC, total cholesterol.

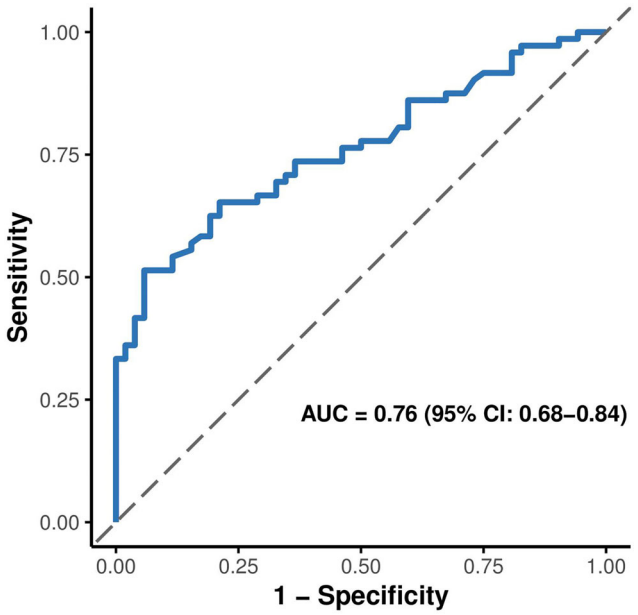

Figure 3 | Predictive performance of HOMA-IR for PSD. Receiver operating characteristic (ROC) curve demonstrating HOMA-IR's discriminative ability for post-stroke depression (area under curve [AUC] = 0.76, 95% CI 0.68–0.84; optimal cutoff = 5.2, sensitivity 54.1%, and specificity 94.2%). Diagonal reference line represents chance prediction (AUC = 0.5).

cognitive deficits particularly in memory consolidation and executive function[39]. Meta-analyses have demonstrated a bidirectional association between IR and depression[40]. Elevated plasma cortisol (CORT) concentrations are consistently observed in depression cohorts[41]. The increased secretion of CORT leads to a decrease in glucose utilization, an increase in glucose isomerization, and an antagonistic effect on insulin suppression of blood glucose, increasing insulin IR. Progressive IR culminates in β-cell dysfunction, ultimately manifesting as overt diabetes mellitus through pancreatic islet decompensation. This reciprocal interaction forms a vicious cycle mediated through neuroendocrine and metabolic pathways. Although epidemiological studies have reported associations between IR, depression, and diabetes, the specific causal relationship of IR with PSD in diabetic populations remains understudied.

In this study, multivariable logistic regression analysis identified the HOMA-IR as an independent risk factor for PSD

Table 5 | Risk factors of PSD in multivariate logistic regression

Variable	Original estimate				Bootstrap validation		
	B (SE)	P-value	Wald	OR [95% CI]	Bias	P-value	95% CI
HOMA-IR	0.562 (0.130)	<0.001	18.753	1.755 [1.360–2.263]	0.037	0.001*	0.383–0.894*
HbA1c (%)	0.142 (0.098)	0.145	2.121	1.153 [0.952–1.397]	0.026	0.182	−0.066 to 0.512
Smoking	0.723 (0.521)	0.165	1.930	2.061 [0.743–5.716]	0.071	0.185	−0.379 to 2.021
Constant	−3.840 (1.133)	0.001	11.494	0.021 [–]	−0.395	0.002	−7.807 to −1.699

Multivariate logistic regression analysis was carried out with smoking, BMI, HbA1c, and HOMA-IR. *P < 0.01. HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 6 | NIHSS scores at baseline and 3-month follow-up

Time points	Groups	Number of cases	NIHSS scores	*P*
Baseline	IR	96	3 (2, 4)	0.215
	Control	28	2 (1, 4)	
3 months	IR	96	0 (0, 2)**	0.138
	Control	28	0 (0, 1)**	

Data are presented as [M (*P25*, *P75*)]. **$P < 0.01$ for intragroup comparisons. NIHSS, National Institutes of Health Stroke Scale.

(OR = 1.755, 95% CI: 1.136–2.263, $P < 0.001$). The robustness of the results was further supported by bootstrap resampling analysis. ROC analysis demonstrated that at a HOMA-IR cutoff value >5.2, the prediction of PSD achieved a sensitivity of 51.4% and specificity of 94.2% (AUC = 0.76, 95% CI: 0.68–0.84). The finding suggests HOMA-IR could serve as follows: (1) a rule-out factor for PSD in clinical screening protocols; (2) a component of composite risk scores rather than an isolated diagnostic criterion for PSD; (3) a therapeutic target for preventive interventions in high-risk populations. Although we used inverse probability treatment weighting (IPTW) to mitigate selection bias and performed sensitivity analyses to verify the stability of the results, the limited sample size ($n = 124$), particularly the small control group ($n = 28$), remains a constraint. However, generalizability remains limited by the single-center design, necessitating larger, population-representative multicenter studies to confirm these findings.

In recent years, clinical studies have suggested that insulin-like growth factor-1 (IGF-1) is a potential biomarker for predicting the risk of developing PSD[42]. IGF-1 crosses the blood–brain barrier and activates IGF-1 receptors (IGF-1Rs), which are widely expressed in hippocampal neurons, to regulate key neuropsychiatric functions, including mood regulation and cognitive processing. IGF-1 contributes to PSD through multiple mechanisms: (1) modulating HPA axis activity, (2) regulating inflammatory factors and glutamic acid (Glu) levels, and (3) enhancing brain-derived neurotrophic factor (BDNF) activity[43–46]. Contrary to theoretical expectations, our univariate analysis in this diabetic stroke cohort demonstrated no significant association between IGF-1 serum levels and PSD incidence ($P = 0.835$). The limited sample size and resultant statistical power constraints may explain this discrepancy. To evaluate neurological recovery trajectories, we conducted serial NIHSS assessments at baseline (i.e., acute phase) and 3-month follow-up in both IR and control groups. Longitudinal analysis revealed significant neurological improvement in both cohorts with no intergroup difference in improvement magnitude. These findings suggest that while HOMA-IR predicts PSD development to a certain extent, it does not appear to influence short-term neurological recovery in diabetic stroke patients.

In conclusion, while HOMA-IR showed no significant association with functional neurological outcomes in diabetic stroke patients, it was identified as an independent risk factor for PSD. Given its high specificity and low sensitivity, IR demonstrates greater clinical utility as a rule-out tool rather than a standalone screening indicator. Otherwise, early identification of patients with elevated IR (e.g., HOMA-IR ≥ 5.2) enables targeted interventions such as metformin, which enhances insulin sensitivity. This approach may reduce the risk of PSD in high-IR populations, particularly those with metabolic comorbidities. Study limitations include the following: (1) single-center design with a moderate sample size ($n = 124$); (2) the 3-month observation period was insufficient to assess long-term outcomes; (3) potential residual confounding may arise from unmeasured variables such as the use of insulin sensitizers. Although bootstrap resampling and E-value analyses support the robustness of our findings, future investigations require multicenter validation with larger sample sizes. Subsequent studies should extend beyond the 3-month follow-up period by incorporating serial assessments at 3, 6, and 12 months to characterize dynamic relationships between metabolic parameters and PSD development, while rigorously documenting all psychiatric/metabolic medications (e.g., antidepressants, insulin sensitizers) to enhance reliability.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted ethics committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Biomedical Research Ethics Review Committee of the Weihai Municipal Hospital affiliated to Shandong University, Approval No. 2019002.

Informed consent: All informed consent was obtained from the subjects.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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