

## Original Article

# Diagnostic and prognostic value of combined adiponectin, D-dimer, and Framingham Stroke Profile in patients with isolated vertigo and concurrent cerebral infarction

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**Abstract:** Objective: To evaluate the diagnostic and prognostic value of adiponectin (APN), D-dimer (D-D), and the Framingham Stroke Profile (FSP) in patients with isolated vertigo, and further examine the performance of a combined predictive model. Methods: We retrospectively analyzed 270 patients with isolated vertigo and 150 healthy controls admitted between March 2022 and March 2025. Based on imaging data, patients were categorized into two groups: isolated vertigo without infarction ( $n = 184$ ) and isolated vertigo with concurrent cerebral infarction ( $n = 86$ ). Neurological recovery was assessed using the modified Rankin Scale (mRS). Serum levels of APN and D-D, and FSP scores were measured at admission. Group comparisons, correlation analyses, and Receiver Operating Characteristic (ROC) curve analyses were performed. Diagnostic and prognostic efficacy of the markers was compared using the DeLong test, and a combined model was established. Results: Patients with vertigo exhibited significantly lower APN levels and higher D-D and FSP scores than controls (all  $P < 0.001$ ), with more pronounced changes in those with cerebral infarction. APN was the strongest single diagnostic marker (AUC = 0.855), followed by D-D (AUC = 0.821) and FSP score (AUC = 0.816). The combined model achieved the highest diagnostic accuracy (AUC = 0.928; accuracy 89.6%). D-D showed a strong correlation with intracranial atherosclerosis ( $r = 0.551$ ). For prognosis, D-D was the best individual predictor (AUC = 0.854), but the combined model again outperformed all single markers (AUC = 0.861,  $P < 0.05$ ). Conclusions: APN, D-D, and FSP each contribute to the identification of cerebral infarction and the prediction of recovery in patients with isolated vertigo. A combined model integrating all three markers significantly enhanced diagnostic accuracy and prognostic assessment, offering a valuable tool for clinical decision-making.

**Keywords:** Adiponectin, D-dimer, Framingham Stroke Profile (FSP), isolated vertigo, cerebral infarction

## Introduction

Vertigo is a common yet complex symptom with causes ranging from inner-ear disorders to the central nervous system [1]. In older adults, isolated vertigo can sometimes be the first, and only, manifestation of a stroke, particularly a posterior circulation infarction [2]. This situation represents a well-known diagnostic pitfall, since these strokes are often misdiagnosed as benign conditions like BPPV (benign paroxysmal positional vertigo) in the absence of classic warning signs such as muscle weakness or slurred speech, resulting in missing the crucial treatment window [3]. Studies indicate that acute isolated vertigo can be stroke-related, but misdiagnosis remains common due to

vague and nonspecific symptoms [4, 5]. In some cases, vertigo may even signal a transient ischemic attack (TIA), though confirming this is challenging [6]. While tools like the R-cVR algorithm and HINTS exam aid in differentiation, neither is foolproof. The R-cVR algorithm is most effective when paired with additional methods [7], and the HINTS exam can fall short when symptoms are subtle or unclear [8]. These challenges highlight a need for more reliable diagnostic approaches.

Neuroimaging, though standard for stroke diagnosis, has a known blind spot during the first few hours after symptoms start [9]. The problem is especially evident with small infarcts or when the brain changes have not yet visible on

## Diagnostic biomarkers for vertigo-related infarction

scans, posing a significant diagnostic challenge. Even advanced strategies - such as combining diffusion-weighted imaging (DWI) with clinical scoring systems [10], using multimodal magnetic resonance imaging (MRI) [11], or applying high-end techniques like 3D-PCASL [12] - can miss early-stage cases. In practical terms, a patient may show symptoms long before any structural damage is detectable on imaging, underscoring the need for a different approach. Identifying reliable biomarkers may bridge this gap, enabling earlier detection of otherwise hidden strokes.

Adiponectin (APN), a cytokine produced by adipose tissue, plays a role in vascular endothelial function and possesses both anti-inflammatory and anti-atherosclerotic properties [13]. Low levels of APN are associated with an increased risk of cerebrovascular events. Another key indicator, D-dimer, is commonly used to assess thrombotic risk. Elevated D-dimer levels often indicate cerebral infarction and suggest an increased tendency for blood clotting [14]. The Framingham Stroke Risk Score (FSP) is another tool, assessing physical damage like cerebrovascular injury or fibrosis, providing a clearer understanding of the stroke's structural impact [15]. Diagnostic methods continue to evolve. For example, Wang et al. [16] demonstrated that certain circulating lymphocyte subsets can help diagnose ischemic stroke in cases of vertigo.

Each of these markers - APN, D-dimer, and FSP - addresses a different aspect of stroke risk: metabolism, coagulation, and physical structure. Despite their individual relevance, systematic research on combining these markers, especially for identifying strokes in patients presenting with isolated vertigo, is limited. This gap poses a significant clinical challenge. Patients with vertigo may appear to have a benign condition, but standard tests often miss the underlying stroke, leaving clinicians in a difficult position. Considering all three biomarkers together could provide the clarity needed to accurately diagnose these complex cases.

### Materials and methods

#### *Sample size calculation*

To determine the required sample size, we referenced the work of Qian et al. [17], who reported an Area Under the Curve (AUC) of 0.6911 for

APN in distinguishing cerebral infarction cases among patients with isolated vertigo. Using this value, we performed a sample size calculation using the pROC package in R. We aimed for 80% statistical power and a 0.05 significance level ( $\alpha$ ), assuming a 1:0.5 case-to-control ratio. The calculation indicated that a minimum of 33 patients with isolated vertigo and 17 healthy controls were needed.

#### *Study population*

This retrospective study used clinical records from the Yulin City Traditional Chinese Medicine Hospital, covering the period from March 2022 to March 2025. The study included two groups: 270 patients diagnosed with isolated vertigo and a control group of 150 healthy individuals. The study protocol was reviewed and approved by the Ethics Committee of Yulin City Traditional Chinese Medicine Hospital.

#### *Inclusion and exclusion criteria*

Inclusion criteria: (1) Age  $\geq$  18 years; (2) Confirmed diagnosis of isolated vertigo according to the Diagnostic and Therapeutic Guidelines for Vertigo [18]; (3) Symptom onset within 24 hours prior to enrollment; (4) First episode of isolated vertigo with no prior history of recurrent vertigo or cerebral infarction; and (5) Complete clinical and imaging data available for analysis.

Exclusion criteria: (1) Concurrent malignant tumors or severe hepatic or renal dysfunction; (2) History of confirmed cerebral hemorrhage or severe craniocerebral trauma; (3) Pregnancy or lactation status; (4) Substantial data loss that would preclude complete follow-up analysis; or (5) History of major therapeutic interventions (e.g., thrombolysis or stenting procedures) within three months of symptom onset that may influence prognostic evaluation.

#### *Clinical data collection*

Clinical data were systematically retrieved from the hospital's electronic medical record system and outpatient follow-up documentation. Demographic and lifestyle variables included age, sex, body mass index (BMI), ethnicity, smoking status, alcohol consumption, and dietary patterns. Medical history encompassed underlying conditions including hypertension, diabetes mellitus, coronary atherosclerotic heart dis-

## Diagnostic biomarkers for vertigo-related infarction

ease (CAD), and transient ischemic attack (TIA). Cerebrovascular parameters comprised vertebrobasilar artery stenosis or hypoplasia (VBAS/H), decreased cerebral perfusion (DCP), and infarct area (IA). Laboratory assessments were conducted at admission prior to treatment initiation. Hematological markers included APN and D-D. The FSP score was calculated for each patient. Neurological evaluation documented baseline neurological status, with functional outcomes assessed using the modified Rankin Scale (mRS) score.

### *APN and D-D detection*

**Blood sample collection:** Venous blood samples (3 mL) were collected from each enrolled patient on the morning after admission following an overnight fast. **APN Analysis:** Serum APN levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Enzyme-linked Biotechnology Co., Ltd., Cat. No.: APN) according to the manufacturer's protocol. Optical density was measured at 450 nm using a fully automated microplate reader (AMR-100). APN concentrations were calculated from a standard curve. **D-D Analysis:** Blood samples for D-D measurement were collected in sodium citrate anticoagulant tubes and stored at 2-10°C. Samples were centrifuged within 30 minutes of collection to separate plasma. D-D levels were determined using a latex immunoturbidimetric assay.

### *Functional scoring*

**FSP score:** The FSP is a validated risk assessment tool derived from the Framingham Heart Study, designed to estimate the 10-year probability of stroke. It incorporates multiple vascular risk factors, including age, systolic blood pressure (with or without antihypertensive therapy), diabetes mellitus, smoking status, history of cardiovascular disease, atrial fibrillation, and electrocardiographic evidence of left ventricular hypertrophy. Each variable is assigned a weighted point value, and the total score, ranging from 0 to 37, is the sum of all variables. Higher scores indicate a greater predicted 10-year stroke risk. In this study, we used the FSP score as a standardized composite indicator of baseline cerebrovascular risk.

**Modified Rankin scale:** The mRS serves as an internationally recognized tool for assessing neurological outcomes, evaluating functional

independence and the ability to perform activities of daily living following a stroke event [19, 20].

### *Diagnostic criteria for cerebral infarction*

The diagnosis of cerebral infarction in this study was primarily based on MRI with DWI, performed within 24 hours of admission whenever feasible. DWI-MRI is the gold standard for detecting acute infarction, especially in the posterior circulation. For patients who underwent head computed tomography (CT) within the first 24 hours, a follow-up MRI was arranged within 72 hours to confirm or exclude infarction. CT findings alone were not used as the sole diagnostic basis, except in rare cases where MRI was contraindicated (e.g., pacemaker implantation, severe claustrophobia). Cerebral infarction was thus defined by the presence of a new lesion confirmed by DWI-MRI (or CT follow-up in MRI-contraindicated cases), in accordance with the Guidelines for the Diagnosis and Treatment of Ischemic Stroke (2022) [21]. Patients were then categorized into the concurrent cerebral infarction group or the isolated vertigo group according to these imaging results.

### *Prognostic grouping*

Patient outcomes were evaluated through follow-up assessments using the mRS. Functional independence was defined as an mRS score  $\leq 2$ , indicating good prognosis. Conversely, an mRS score  $> 2$  was classified as poor prognosis, reflecting varying degrees of functional disability. The mRS was evaluated at 90 days after symptom onset via outpatient follow-up or structured telephone interviews.

### *Outcome measures*

**Primary outcomes:** (1) the expression levels of APN, D-D, and the FSP score in patients with isolated vertigo were determined; (2) the expression patterns and diagnostic value of these markers in patients with concurrent cerebral infarction were analyzed; and (3) their utility in predicting neurological recovery in patients presenting with vertigo and confirmed infarction was evaluated.

**Secondary outcomes:** (1) baseline characteristics were compared between the patient and control groups, as well as between the isolated vertigo and concurrent cerebral infarction

## Diagnostic biomarkers for vertigo-related infarction

groups; and (2) the correlations between APN, D-D, FSP, and measures of cerebrovascular structure and function were determined.

### *Statistical analysis*

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R language version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean  $\pm$  standard deviation (SD) and compared using the independent samples t-test. Non-normally distributed data were expressed as median and interquartile range [M (Q1, Q3)] and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages [n (%)] and compared using Pearson's chi-square test or the continuity-corrected chi-square test, as appropriate, depending on the minimum expected frequency. Pearson's or Spearman's correlation analysis was performed based on data distribution. Receiver Operating Characteristic (ROC) curve analysis, DeLong test for AUC comparison, confusion matrix construction, combined logistic regression model fitting, lollipop plots, and correlation matrix heatmaps were generated using R software. ROC analysis was used to evaluate the diagnostic/prognostic efficacy of these markers by calculating the AUC, sensitivity, specificity, accuracy, and optimal cut-off values. All tests were two-tailed, and a *P*-value < 0.05 was considered significant.

### **Results**

#### *Comparison of general characteristics between the isolated vertigo group and the control group*

There were no significant differences between the two groups in terms of age, sex, BMI, ethnicity, history of diabetes, alcohol consumption, hypertension, or dietary patterns (all *P* > 0.05, **Table 1**).

#### *Comparison of APN, D-D levels, and FSP scores between the isolated vertigo group and the control group*

Compared to the control group, the isolated vertigo group exhibited significantly lower levels

of APN (*P* < 0.001) and significantly higher levels of D-D and FSP scores (both *P* < 0.001) (**Table 2**).

#### *Comparison of baseline characteristics between isolated vertigo group and concurrent cerebral infarction group*

Compared to the isolated vertigo group, the concurrent cerebral infarction group showed significant differences in the prevalence of diabetes mellitus (DM) (*P* = 0.009), TIA (*P* = 0.009), CAD (*P* = 0.004), VBAS/H (*P* < 0.001), DCP (*P* < 0.001), and history of hypertension (*P* < 0.001). No significant differences were observed between the two groups for other variables, including age, sex, BMI, ethnicity, smoking history, alcohol consumption, or dietary patterns (all *P* > 0.05, **Table 3**).

#### *Comparison of APN, D-D, and FSP scores between the isolated vertigo group and concurrent cerebral infarction group*

Compared to the isolated vertigo group, the concurrent cerebral infarction group had significantly lower APN levels (*P* < 0.001) and significantly higher D-D levels and FSP scores (*P* < 0.001 for both) (**Table 4**).

#### *Diagnostic value of APN, D-D, and FSP score for isolated vertigo with concurrent cerebral infarction*

ROC curve analysis demonstrated that APN, D-D, and FSP all exhibited good diagnostic value for isolated vertigo with concurrent cerebral infarction, with AUCs of 0.855, 0.821, and 0.816, respectively. Among them, APN showed the highest sensitivity (94.19%), while FSP had the highest specificity (75.00%). The diagnostic efficacy of the combined model (Logit(*P*) = 6.420 - 1.307  $\times$  APN + 6.090  $\times$  D-D + 0.431  $\times$  FSP) was further enhanced, achieving an AUC of 0.928 and an accuracy of 89.63%, which was significantly superior to any single marker (*P* < 0.001, **Figure 1; Table 5**). Further comparison of AUCs using the DeLong test showed that the differences between the combined model and each of the individual markers (APN, D-D, and FSP) were statistically significant (all *P* < 0.001), whereas the differences among the three individual markers were not significant (all *P* > 0.05, **Table 6**).

## Diagnostic biomarkers for vertigo-related infarction

**Table 1.** Comparison of baseline characteristics between the isolated vertigo group and control group

Variable	Isolated Vertigo Group (n = 270)	Control Group (n = 150)	Statistic ( $\chi^2$ )	P-value
Age			0.495	0.482
≥ 60	173 (64.07%)	102 (68.00%)		
< 60	97 (35.93%)	48 (32.00%)		
Sex			2.079	0.149
Male	149 (55.19%)	71 (47.33%)		
Female	121 (44.81%)	79 (52.67%)		
BMI (kg/m <sup>2</sup> )			2.092	0.148
≥ 24	98 (36.30%)	66 (44.00%)		
< 24	172 (63.70%)	84 (56.00%)		
Ethnicity			0.706	0.401
Han	260 (96.30%)	141 (94.00%)		
Other	10 (3.70%)	9 (6.00%)		
History of Diabetes			0.216	0.642
Yes	81 (30.00%)	41 (27.33%)		
No	189 (70.00%)	109 (72.67%)		
History of Alcohol Consumption			1.081	0.298
Yes	114 (42.22%)	72 (48.00%)		
No	156 (57.78%)	78 (52.00%)		
Hypertension			0.702	0.402
Yes	108 (40.00%)	53 (35.33%)		
No	162 (60.00%)	97 (64.67%)		
Diabetes			< 0.001	> 0.999
Yes	43 (15.93%)	24 (16.00%)		
No	227 (84.07%)	126 (84.00%)		
Dietary Structure			0.011	0.916
Light	100 (37.04%)	54 (36.00%)		
Heavy/Rich	170 (62.96%)	96 (64.00%)		

Note: BMI: Body Mass Index.

**Table 2.** Comparison of APN, D-dimer levels, and FSP scores between the isolated vertigo group and control group

Variable	Isolated Vertigo Group (n = 270)	Control Group (n = 150)	Statistic	P-value
APN (mg/L)	4.50 ± 1.16	6.91 ± 1.66	17.327	< 0.001
DD (mg/L)	0.60 ± 0.21	0.30 ± 0.07	-17.274	< 0.001
FSP	17.00 [15.00, 18.00]	4.00 [4.00, 4.75]	17.087	< 0.001

Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.

### *Correlation analysis of APN, D-D, FSP, and cerebrovascular indicators*

In patients with isolated vertigo and concurrent cerebral infarction, APN levels showed significant correlations with multiple indicators of cerebrovascular structural and functional abnormalities. Specifically, APN was positively correlated to TIA, CAD, VBAS/H, and DCP (all P

< 0.05). Conversely, APN was negatively correlated with IA (r = -0.301, P = 0.005), indicating that lower APN levels may be associated with larger infarct volumes (**Figure 2A**). D-D exhibited an opposite trend, showing significant negative correlations with TIA, CAD, VBAS/H, and DCP (P < 0.05 for all), but a strong positive correlation with IA (r = 0.551, P < 0.001), suggesting that elevated D-D levels may reflect the

## Diagnostic biomarkers for vertigo-related infarction

**Table 3.** Comparison of baseline characteristics between the isolated vertigo group and concurrent infarction group

Variable	Concurrent Infarction Group (n = 86)	Isolated Vertigo Group (n = 184)	Statistic ( $\chi^2$ )	P-value
Age			0.267	0.606
≥ 60	57 (66.28%)	116 (63.04%)		
< 60	29 (33.72%)	68 (36.96%)		
Sex			0.445	0.505
Male	50 (58.14%)	99 (53.80%)		
Female	36 (41.86%)	85 (46.20%)		
BMI			0.763	0.382
≥ 24	28 (32.56%)	70 (38.04%)		
< 24	58 (67.44%)	114 (61.96%)		
Ethnicity			0.047	0.828
Han	82 (95.35%)	178 (96.74%)		
Other	4 (4.65%)	6 (3.26%)		
History of Diabetes			6.877	0.009
Yes	35 (40.70%)	46 (25.00%)		
No	51 (59.30%)	138 (75.00%)		
History of Hypertension			24.429	< 0.001
Yes	55 (63.95%)	59 (32.07%)		
No	31 (36.05%)	125 (67.93%)		
History of Smoking			0.921	0.337
Yes	38 (44.19%)	70 (38.04%)		
No	48 (55.81%)	114 (61.96%)		
History of Alcohol Consumption			1.391	0.238
Yes	17 (19.77%)	26 (14.13%)		
No	69 (80.23%)	158 (85.87%)		
Dietary Structure			0.251	0.616
Light	30 (34.88%)	70 (38.04%)		
Heavy/Rich	56 (65.12%)	114 (61.96%)		
TIA			6.857	0.009
Yes	30 (34.88%)	37 (20.11%)		
No	56 (65.12%)	147 (79.89%)		
CAD			8.219	0.004
Yes	33 (38.37%)	40 (21.74%)		
No	53 (61.63%)	144 (78.26%)		
VBAS/H			35.134	< 0.001
Yes	43 (50.00%)	29 (15.76%)		
No	43 (50.00%)	155 (84.24%)		
DCP			10.901	< 0.001
Yes	30 (34.88%)	31 (16.85%)		
No	56 (65.12%)	153 (83.15%)		
IA	3.62 ± 1.62			

Note: TIA: Transient Ischemic Attack, CAD: Coronary Atherosclerotic Disease, VBAS/H: Vertebrobasilar Artery Stenosis/Hypoplasia, DCP: Decreased Cerebral Perfusion, IA: Infarct Area.

severity of vascular lesions and cerebral infarction (**Figure 2B**). FSP also showed negative correlations with structural and functional cere-

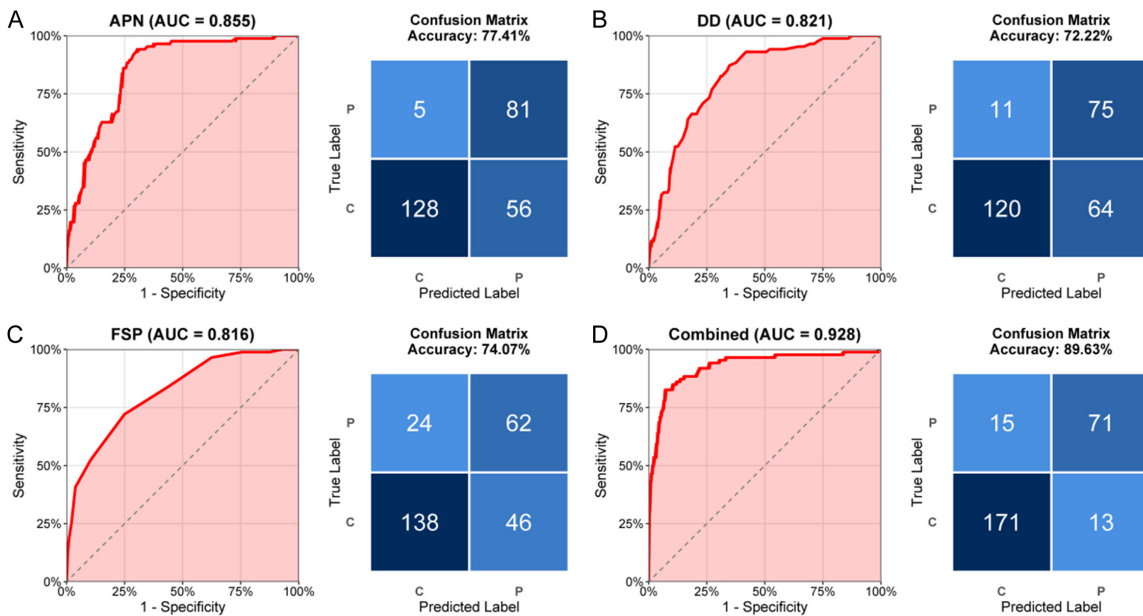
brovascular abnormalities. It was negatively correlated with TIA, CAD, and DCP (all  $P < 0.05$ ) but positively correlated with IA ( $r = 0.234$ ,  $P =$

## Diagnostic biomarkers for vertigo-related infarction

**Table 4.** Comparison of APN, D-dimer, and FSP scores between the isolated vertigo and concurrent infarction groups

Variable	Concurrent Infarction Group (n = 86)	Isolated Vertigo Group (n = 184)	Statistic	P-value
APN (mg/L)	3.74 [2.96, 4.28]	4.96 [4.35, 5.56]	9.406	< 0.001
DD (mg/L)	0.76 ± 0.17	0.53 ± 0.19	-9.761	< 0.001
FSP	19.00 [17.00, 20.75]	16.00 [15.00, 17.25]	8.442	< 0.001

Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.



**Figure 1.** ROC curves and confusion matrices for APN, D-dimer, FSP, and their combination in diagnosing isolated vertigo with concurrent cerebral infarction. A: ROC curve and confusion matrix for APN. B: ROC curve and confusion matrix for D-dimer. C: ROC curve and confusion matrix for FSP. D: ROC curve and confusion matrix for the combined model. Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.

**Table 5.** Performance of individual markers and their combination in diagnosing isolated vertigo with concurrent cerebral infarction

Marker	AUC	95% CI	Specificity	Sensitivity	Cut off	Accuracy
APN	0.855	0.810-0.901	69.57%	94.19%	-4.48	77.41%
DD	0.821	0.770-0.873	65.22%	87.21%	0.585	72.22%
FSP	0.816	0.764-0.869	75.00%	72.09%	17.5	74.07%
Combined	0.928	0.891-0.965	92.93%	82.56%	-0.135	89.63%

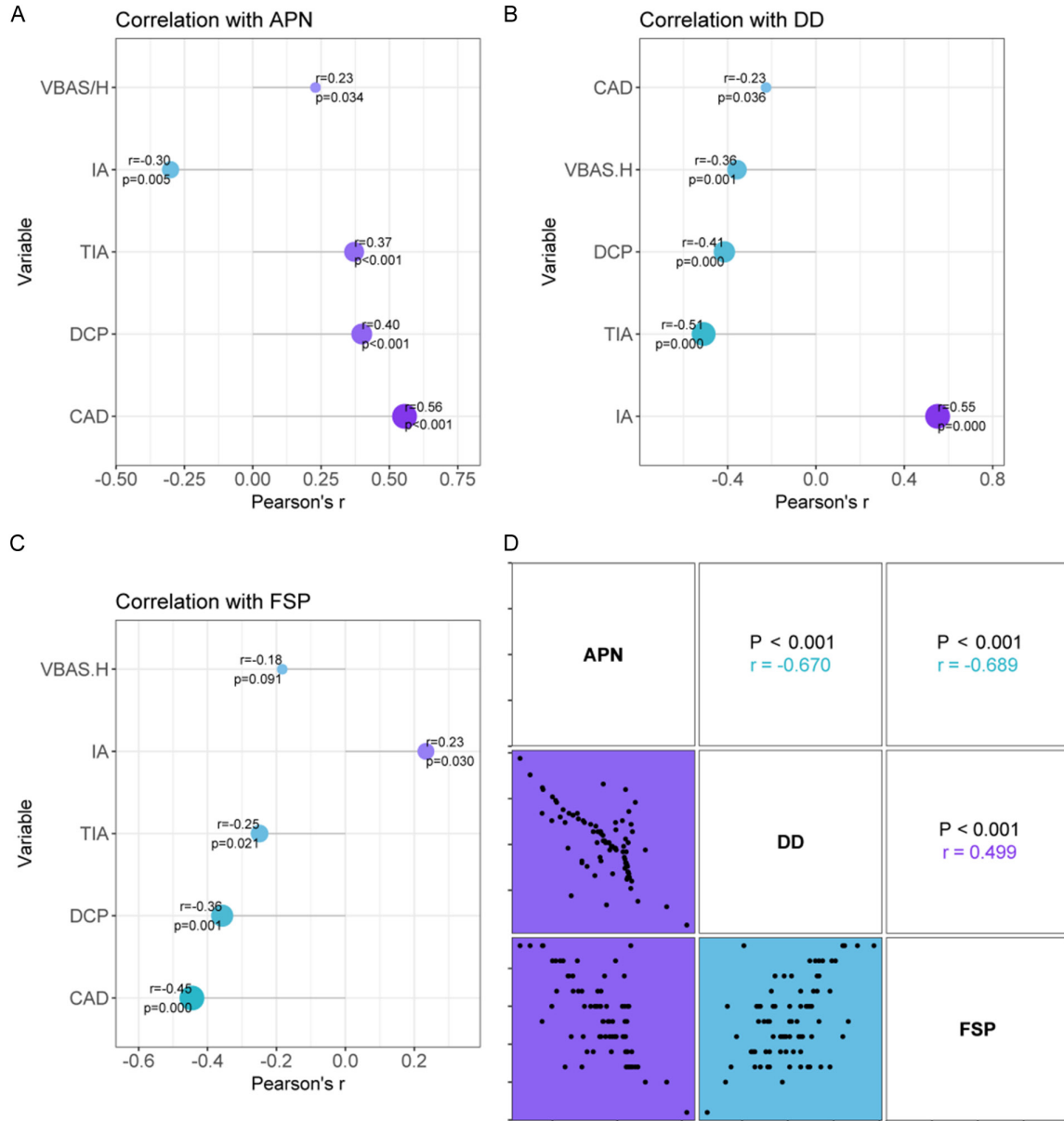
Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile; AUC: Area Under the Curve.

**Table 6.** Comparison of AUCs between different diagnostic markers

Marker 1	Marker 2	Z value	P value	AUC difference	CI lower upper
APN	DD	1.119	0.263	0.034	-0.026 - 0.094
APN	FSP	1.451	0.147	0.039	-0.014 - 0.092
APN	Combined	-4.12	< 0.001	-0.072	-0.107 - -0.038
DD	FSP	0.155	0.877	0.005	-0.058 - 0.067
DD	Combined	-5.132	< 0.001	-0.106	-0.147 - -0.066
FSP	Combined	-5.313	< 0.001	-0.111	-0.152 - -0.070

Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.

## Diagnostic biomarkers for vertigo-related infarction



**Figure 2.** Correlation analysis for APN, D-dimer, FSP, and cerebrovascular structural and functional indicators. A: Correlation analysis of APN with TIA, CAD, VBAS/H, DCP, and IA. B: Correlation analysis of D-dimer with TIA, CAD, VBAS/H, DCP, and IA. C: Correlation analysis of FSP with TIA, CAD, VBAS/H, DCP, and IA. D: Pearson correlation scatter plots and coefficient matrix among APN, D-dimer, and FSP. Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile, TIA: Transient Ischemic Attack, CAD: Coronary Atherosclerotic Disease, VBAS/H: Vertebrobasilar Artery Stenosis/Hypoplasia, DCP: Decreased Cerebral Perfusion, IA: Infarct Area.

0.030) (**Figure 2C**). Furthermore, Pearson correlation analysis revealed a significant negative correlation between APN and both D-D ( $r = -0.670$ ,  $P < 0.001$ ) and FSP ( $r = -0.689$ ,  $P < 0.001$ ). A moderate positive correlation was observed between D-D and FSP ( $r = 0.499$ ,  $P < 0.001$ ) (**Figure 2D**). A correlation matrix for eight variables was also generated (**Figure S1; Table S1**).

### Expression differences of APN, D-D, and FSP in neurological recovery

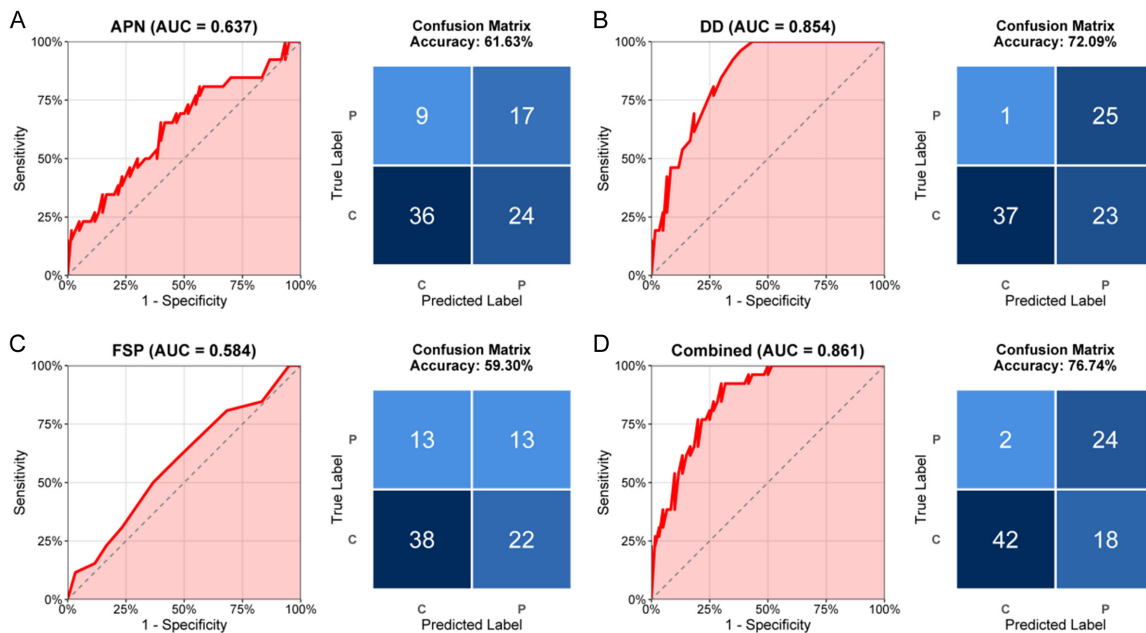
In the poor prognosis group, APN levels were significantly lower than in the good prognosis group ( $P = 0.044$ ), while D-D levels were significantly higher ( $P < 0.001$ ), suggesting an association between these two markers and poor neurological recovery. The FSP score showed

## Diagnostic biomarkers for vertigo-related infarction

**Table 7.** Comparison of APN, D-dimer, and FSP between patients with different neurological recovery status

Variable	Poor Prognosis Group (n = 26)	Good Prognosis Group (n = 60)	Statistic	P-value
APN (mg/L)	3.19 ± 1.04	3.89 [3.30, 4.29]	-2.017	0.044
DD (mg/L)	0.90 ± 0.13	0.70 ± 0.15	6.331	< 0.001
FSP	19.58 ± 2.52	18.83 ± 2.46	1.266	0.212

Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.



**Figure 3.** ROC curves and confusion matrices for APN, D-dimer, FSP, and their combination in predicting neurological recovery. A: ROC curve and confusion matrix for APN. B: ROC curve and confusion matrix for D-dimer. C: ROC curve and confusion matrix for FSP. D: ROC curve and confusion matrix for the combined model. Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.

no significant difference between the two prognosis groups ( $P = 0.212$ ) (Table 7).

### *Prognostic value of APN, D-D, and FSP for neurological recovery*

ROC curve analysis indicated that D-D had high discriminatory power for predicting poor neurological outcome, with an AUC of 0.854, a sensitivity of 96.15%, a specificity of 61.67%, and an accuracy of 72.09%. The predictive ability of APN was lower, with an AUC of 0.637 and an accuracy of 61.63%. The FSP showed weak predictive efficacy, with an AUC of only 0.584 and an accuracy of 59.30%. The combined model ( $\text{Logit}(P) = 11.366 - 0.553 \times \text{APN} - 16.084 \times \text{DD} + 0.227 \times \text{FSP}$ ) demonstrated the best predictive performance, with an AUC of 0.861 and an accuracy of 76.74%, achieving a better balance between sensitivity and specificity (Figure 3; Table 8).

Comparison of AUCs further confirmed that D-D had significantly superior predictive efficacy to both APN ( $P < 0.001$ ) and FSP ( $P < 0.001$ ). The AUC of the combined model was also significantly higher than that of APN ( $P = 0.024$ ) and FSP ( $P = 0.003$ ), but not significantly different from of D-D alone ( $P = 0.909$ ). This suggests that D-D holds high clinical value as a stand-alone prognostic marker, although the combined model may still offer improved accuracy and robustness (Table 9).

### **Discussion**

This study investigated the expression patterns, diagnostic value, and prognostic role of APN, D-D, and the FSP score in patients with isolated vertigo and concurrent cerebral infarction, aiming to provide a more sensitive and practical combined biomarker panel for clinical use. Our results demonstrate that these three

## Diagnostic biomarkers for vertigo-related infarction

**Table 8.** Performance of APN, D-dimer, FSP, and combined model in predicting neurological recovery

Marker	AUC	95% CI	Specificity	Sensitivity	Cut off	Accuracy
APN	0.637	0.504-0.771	60.00%	65.38%	-3.655	61.63%
DD	0.854	0.776-0.931	61.67%	96.15%	0.735	72.09%
FSP	0.584	0.452-0.715	63.33%	50.00%	19.5	59.30%
Combined	0.861	0.785-0.937	70.00%	92.31%	-1.23	76.74%

Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.

**Table 9.** Comparison of AUCs between prognostic markers

Marker 1	Marker 2	Z value	P value	AUC difference	CI lower upper
APN	DD	-3.5	< 0.001	-0.216	-0.337 - -0.095
APN	FSP	1.187	0.235	0.054	-0.035 - 0.143
APN	Combined	-2.26	0.024	-0.223	-0.417 - -0.030
DD	FSP	4.404	< 0.001	0.27	0.150 - 0.390
DD	Combined	-0.114	0.909	-0.007	-0.134 - 0.119
FSP	Combined	-2.996	0.003	-0.277	-0.459 - -0.096

Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile.

markers exhibit significant expression differences across various disease states, showing both independent value and synergistic potential for diagnosis and prognosis.

First, regarding expression differences, compared to healthy controls, patients with isolated vertigo had significantly lower APN levels and significantly higher D-D levels and FSP scores. This trend was even more pronounced in the subgroup with concurrent cerebral infarction. As an anti-inflammatory and anti-atherosclerotic factor, a decrease in APN is often considered a signal of endothelial dysfunction and atherosclerotic progression [22]. A study by Tagawa et al. [23] found that total and high-molecular-weight (HMW) APN levels were significantly reduced in atherosclerotic cerebral infarction, suggesting its association with vasoprotective mechanisms. Furthermore, literature indicates that APN levels are significantly lower in patients with acute isolated vertigo, and combining APN with the ABCD2 score improves the sensitivity and specificity of predicting cerebral infarction [17], which is consistent with the trend of decreased APN in our study. However, a meta-analysis by Xiang et al. [24] pointed out that the correlation between APN levels and the incidence and prognosis of ischemic stroke was not significant, suggesting its mechanism may vary depending on the population or study design. This highlights the complexity of APN's role in cerebrovascular disease.

D-D, a fibrin degradation product, is often elevated in a hypercoagulable state or in individuals at risk for venous thromboembolism [25]. Research by Wang et al. [26] found that plasma D-D levels were significantly elevated in patients with acute cerebral infarction and correlated with mRS and National Institutes of Health Stroke Scale (NIHSS) scores, supporting its clinical value as a high-risk indicator for stroke. Additionally, D-D levels have been shown to significantly decrease after treatment with compound Danshen injection [27], reflecting its sensitivity to the hypercoagulable state in acute cerebral infarction, which aligns with the expression trend of D-D observed in our study. Although FSP is a structural scoring tool rather than a traditional serum biomarker, its ability to quantify the pathologic basis of cerebrovascular sclerosis and perfusion deficits by integrating multiple factors still holds clinical applicability in identifying high-risk populations.

Second, although the individual diagnostic efficacy of the three markers was relatively high (all AUCs > 0.8), the combined model significantly enhanced diagnostic performance, reaching an AUC of 0.928, with a nearly 90% accuracy and a balanced sensitivity and specificity. The superior performance of the combined model over the individual markers validates the complementary roles of APN, D-D, and FSP at the pathophysiological level: APN

## Diagnostic biomarkers for vertigo-related infarction

reflects the metabolic and endothelial function, D-D represents the thrombotic load, and FSP reflects the structural cerebrovascular pathology. Literature shows that combining APN with the ABCD2 score improves prediction of cerebral infarction in patients with isolated vertigo [17], which strongly aligns with the findings of our combined model. Zaharia et al. [28] also found that APN levels correlate with moderate-to-severe NIHSS scores in acute ischemic stroke patients, suggesting its possible diagnostic value. Although their finding of elevated APN contrasts with our results, it supports a discussion on the controversial nature of its expression. Therefore, both theoretical and empirical evidence support the rationale and utility of a combined diagnostic model. Notably, the combined model has the potential to identify patients with subtle symptoms or atypical imaging findings. Literature suggests that plasma APN levels correlate with stroke subtype and neurological severity, which could complement traditional imaging methods in the early diagnosis of cerebral infarction [29].

In the correlation analysis, our study further explored the relationship between these three markers and cerebrovascular function and structure. APN was positively correlated with TIA, CAD, and DCP, but negatively correlated with IA, suggesting its involvement in vasoprotective mechanisms, with lower APN levels predicting a larger infarct area. Sasaki et al. [29] found that APN levels were associated with neurological severity in both atherosclerotic and cardioembolic stroke, supporting the link between APN and vasoprotective mechanisms observed in our study. In contrast, D-D was negatively correlated with TIA and CAD but positively correlated with IA. Literature indicates that D-D level on emergency admission is an independent predictor of symptomatic intracranial hemorrhage after thrombectomy [30], validating its role in reflecting thrombus formation and tissue damage in the acute phase. Furthermore, a meta-analysis by Reda et al. [31] showed that low D-D levels were associated with better functional outcomes and higher recanalization rates post-thrombectomy, further emphasizing its sensitivity to thrombotic burden. FSP also demonstrated negative correlations with several vascular indicators, suggesting that its scoring system may be useful for identifying underlying structural lesions.

The inter-correlations among the three markers are also enlightening: the negative correlations between APN and both D-D and FSP suggest that APN may regulate the disease process by counteracting coagulation and vascular sclerosis, while the positive correlation between D-D and FSP further underscores the interplay between thrombosis and structural vascular damage.

At the prognostic level, D-D demonstrated the best performance for predicting neurological recovery (AUC = 0.854), and the combined model further increased the predictive accuracy to 76.74%. This is consistent with the performance of D-D in other stroke studies, where D-D levels have been significantly correlated with mRS and NIHSS scores in acute cerebral infarction patients, making D-D a risk factor for poor prognosis [26]. A study by Kobata et al. [32] found that elevated D-D levels were associated with acute ischemic lesions and poor outcomes in patients with subarachnoid hemorrhage (AUC = 0.897), indirectly supporting the broad applicability of D-D in stroke prognosis. Although APN showed limited independent predictive efficacy for prognosis, its negative correlation with functional scores is noteworthy. It has been reported that low APN levels are associated with an increased risk of death within 12 months [32], suggesting that APN may play a role in neuroprotection, even at a subclinical level. FSP was the weakest prognostic predictor, likely because, as a structural score, it is less responsive to short-term recovery status. However, as an indicator of long-term structural disease, FSP may still be valuable for assessing the risk of stroke recurrence or chronic cerebral insufficiency.

It is worth noting that while the individual predictive capabilities of the three markers varied, their combined use compensated for individual shortcomings and improved overall performance, demonstrating the value of a multidimensional model for disease identification and risk assessment. Clinically, this finding holds significant implications: it provides a rapid, cost-effective, and relatively stable ancillary tool for diagnosis, particularly in primary care settings with atypical imaging findings or limited access to MRI resources.

It should be noted that our study compared the combined biomarker model only with individual

indicators (APN, D-dimer, and FSP), but not with established bedside diagnostic tools such as HINTS, ABCD2, or the R-cVR algorithm. This is because, at our hospital, neurological outcomes were uniformly assessed using the mRS, which serves as a standardized measure of long-term functional prognosis rather than a tool for acute etiologic differentiation. The mRS differs conceptually from HINTS, ABCD2, and R-cVR, which are designed for rapid diagnosis at the bedside, whereas the mRS reflects long-term functional recovery. Therefore, a direct comparison is not methodologically appropriate. Future studies should aim to integrate biomarker-based models with established diagnostic algorithms to better define their incremental value in clinical decision-making.

Despite the clear and somewhat innovative findings of this study, several limitations must be acknowledged. First, this was a single-center, retrospective study, and despite a relatively adequate sample size, selection bias may exist. Second, although FSP has a clinical basis, it is a relatively novel research variable, and the lack of a standardized definition and scoring system may hinder its widespread adoption. Third, the assessment of neurological recovery relied mainly on the mRS, which, though widely used, may overlook subtle differences in cognitive function. In addition, the role of APN in cerebral infarction remains controversial. Consistent with Qian et al. [17] and Tagawa et al. [23], our study observed significantly decreased APN levels in patients with concurrent infarction, supporting the notion that low APN reflects endothelial dysfunction and increased atherosclerotic burden. However, other studies have reported elevated APN during acute ischemia, which has been attributed to stress- or inflammation-induced compensatory upregulation. These discrepancies may arise from differences in study populations, infarction subtypes, APN isoforms (HMW vs. total APN), and the timing of blood sampling. Therefore, our findings highlight the complex and dynamic nature of APN in cerebrovascular disease, suggesting that while low APN is generally associated with chronic atherosclerotic risk, transient elevations may occur as part of the acute-phase response. Further large-scale, multi-center, prospective studies are needed to clarify these mechanisms and validate the stability and generalizability of this model.

### Conclusion

APN, D-D, and FSP show significant expression changes in patients with isolated vertigo and concurrent cerebral infarction. They hold substantial clinical value for both diagnosis and prognostic assessment. A combined model utilizing these three markers further enhanced diagnostic efficacy.

### Disclosure of conflict of interest

None.

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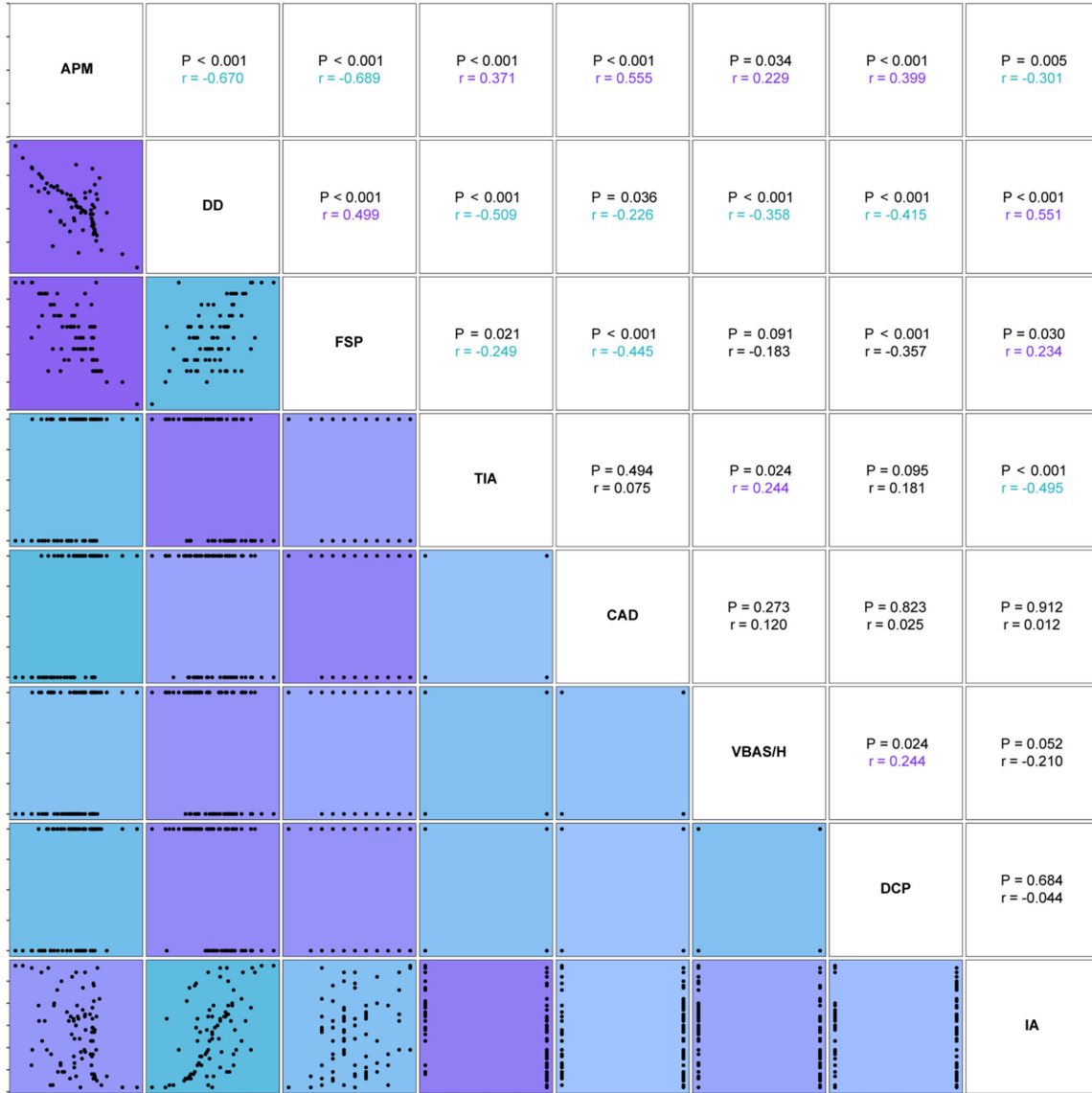
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## Diagnostic biomarkers for vertigo-related infarction



**Figure S1.** Correlation matrix among eight variables. Note: APN: Adiponectin, DD: D-dimer, FSP: Framingham Stroke Profile, TIA: Transient Ischemic Attack, CAD: Coronary Atherosclerotic Disease, VBAS/H: Vertebrobasilar Artery Stenosis/Hypoplasia, DCP: Decreased Cerebral Perfusion, IA: Infarct Area.

## Diagnostic biomarkers for vertigo-related infarction

**Table S1.** Correlation analysis results of each indicator

Base	Variable	Pearson_r	P_value	CI_low	CI_high
APN	FSP	-0.689	0	-0.786	-0.559
APN	DD	-0.67	0	-0.772	-0.533
APN	CAD	0.555	0	0.389	0.686
APN	DCP	0.399	0	0.204	0.563
APN	TIA	0.371	0	0.173	0.54
APN	IA	-0.301	0.005	-0.482	-0.095
APN	VBAS.H	0.229	0.034	0.018	0.421
DD	APN	-0.67	0	-0.772	-0.533
DD	IA	0.551	0	0.384	0.683
DD	TIA	-0.509	0	-0.651	-0.333
DD	FSP	0.499	0	0.322	0.643
DD	DCP	-0.415	0	-0.576	-0.222
DD	VBAS.H	-0.358	0.001	-0.53	-0.158
DD	CAD	-0.226	0.036	-0.418	-0.015
FSP	APN	-0.689	0	-0.786	-0.559
FSP	DD	0.499	0	0.322	0.643
FSP	CAD	-0.445	0	-0.601	-0.258
FSP	DCP	-0.357	0.001	-0.529	-0.158
FSP	TIA	-0.249	0.021	-0.438	-0.039
FSP	IA	0.234	0.03	0.023	0.425
FSP	VBAS.H	-0.183	0.091	-0.38	0.03