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Review Article

Advances in hematological biomarkers of patent foramen ovale-associated stroke

Mengxiang Wang[1,2,3], Jingbo Qie[1,4], Joseph Z Shen[5], Xiaoli Yang[1,2,3], Kaili Cheng[1,2,3], Yufan Luo[1,2,3], Danhong Wu[1,2,3]

[1]Department of Neurology, Shanghai Fifth People's Hospital, Fudan University, Shanghai 200240, China; [2]Joint Center for Translational Medicine, Shanghai Fifth People's Hospital, Fudan University and School of Life Science, East China Normal University, Shanghai 200240, China; [3]Center of Community-Based Health Research, Fudan University, Shanghai 200032, China; [4]Institutes of Biomedical Sciences, Fudan University, Shanghai 200032, China; [5]The University of Chicago, 5801 S Ellis Ave, Chicago, IL 60637, The United States

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Abstract: Patent foramen ovale-associated stroke (PFO-AS) refers to cerebral thromboembolism attributable to an interatrial communication, with paradoxical embolism regarded as a principal mechanism. Discriminating a pathogenic PFO from an incidental finding remains difficult despite echocardiographic assessment and clinical risk stratification. This review examines candidate hematological biomarkers of PFO-AS, focusing on their pathophysiological relevance, potential clinical utility, and limitations within a cardiovascular framework. These candidates reflect interrelated processes including inflammation, hypercoagulability, platelet activation, metabolic dysregulation, and endothelial dysfunction. Potentially relevant markers include the inflammatory response index (IRI), D-dimer, mean platelet volume (MPV), the triglyceride-glucose index (TyG index), B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), homocysteine (Hcy), and osteoprotegerin (OPG). Additional candidates under mechanistic investigation include factor V Leiden and prothrombin G20210A variants, the L-arginine/asymmetric dimethylarginine ratio (L-Arg/ADMA), and plasma protein signatures. Although these biomarkers may offer complementary insights into thrombotic susceptibility and vascular biology, associations with stroke or thrombosis do not establish specificity for PFO-mediated mechanisms. Current evidence is limited by small cohorts, predominantly single-center retrospective designs, insufficient adjustment for confounding, and lack of independent prospective validation. Diagnostic performance and incremental value beyond established clinical and imaging assessments remain inadequately defined, and no biomarker has demonstrated utility in guiding PFO-AS-specific decisions regarding PFO closure or antithrombotic treatment. These candidates therefore remain exploratory rather than established diagnostic or treatment-selection tools. Future research should prioritize standardized measurement, multicenter prospective validation, and proteomic discovery to determine whether individual biomarkers or integrated panels can improve etiological assessment and thromboembolic risk stratification alongside cardiac imaging.

Keywords: Patent foramen ovale, PFO-associated stroke, cryptogenic stroke, hematological biomarkers, paradoxical embolism

Introduction

Stroke is the second leading cause of death worldwide, after ischemic heart disease, and a major cause of disability [1, 2]. Cryptogenic stroke, in which no definite etiology is identified despite a comprehensive evaluation, accounts for approximately 15-30% of ischemic strokes [3] and up to 50% of strokes in young patients [4]. A patent foramen ovale (PFO) is detected in up to half of young patients with cryptogenic cerebrovascular events, supporting an association between persistent interatrial communication and otherwise unexplained cerebral ischemia [5]. PFO-associated stroke (PFO-AS) may account for approximately 5% of all ischemic strokes and 10% of strokes in non-elderly patients [6]. Several studies, including CLOSE [7], REDUCE [8], and DEFENSE-PFO [9], have demonstrated that percutaneous PFO closure significantly reduces recurrent cerebrovascular events in selected patients with

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PFO-AS. The clinical relevance of PFO-AS was further reflected in the 2022 Society for Cardiovascular Angiography and Interventions (SCAI) guidelines, which provided recommendations for its management [10].

The cardiovascular basis of PFO-AS involves interactions among interatrial anatomy, shunt hemodynamics, and thrombotic susceptibility. During fetal life, the foramen ovale permits right-to-left blood flow between the atria. After birth, the rise in left atrial pressure relative to right atrial pressure promotes functional closure by apposing the septum primum to the septum secundum, followed by anatomical fusion in most individuals. Incomplete fusion leaves a potential flap-like interatrial passage, termed a PFO [11], which persists in approximately 25% of adults and is usually clinically silent [12]. The principal proposed mechanism is paradoxical embolism, whereby a venous thrombus traverses the PFO, bypasses the pulmonary vascular bed, and enters the systemic arterial circulation, potentially occluding a cerebral artery [13]. This process is facilitated by transient reversal of the interatrial pressure gradient, as may occur during the release phase of a Valsalva maneuver or with coughing, or by sustained elevation of right-sided pressures, such as in pulmonary hypertension. Embolic risk is further influenced by shunt magnitude and associated septal anatomy: a large right-to-left shunt and an atrial septal aneurysm are clinically relevant high-risk features, whereas a prominent Eustachian valve may direct inferior vena caval flow toward the PFO [14]. Venous stasis and hypercoagulability can provide the thrombotic substrate for paradoxical embolism; local flow stagnation within the PFO tunnel may also favor in situ thrombus formation, although this mechanism is less firmly established [6]. Altered atrial conduction and susceptibility to atrial arrhythmias have also been proposed [15], but their direct mechanistic relationship with PFO remains uncertain. Documented atrial fibrillation should therefore be evaluated as a competing cause of cardioembolic stroke rather than automatically attributed to PFO. Thus, PFO-AS is better understood as the cerebral consequence of an interaction among an anatomical conduit, permissive hemodynamic conditions, and a thrombotic source, rather than anatomical patency alone [16]. This mechanistic framework provides a rationale for investigating circulating biomarkers of coagulation, fibrinolysis, inflammation, and endothelial function as potential adjuncts to etiological assessment.

Diagnosis and evaluation of PFO-AS

According to the SCAI, PFO-AS is defined as a cortical, large white matter, or retinal infarct occurring in the presence of a PFO, with no other identified likely cause [10]. The diagnosis of PFO-AS rests on an integrated assessment that combines PFO detection, characterization of the infarct, and exclusion of alternative etiologies [17]. The determination of an association between PFOs and stroke occurrence is generally based on several characteristics: (1) the individual's age, most notably if they are older than 55 years [18]; (2) imaging features such as the prevalence of cortical or posterior circulation infarcts and concomitant cerebral tissue ischemia in multiple vascular basins [19]; (3) the presence of high-risk anatomical features of PFO which include concomitant atrial septal aneurysms (ASAs), a large number of right-to-left shunts (RLS), or long PFO tunnels [14].

Assessment of PFO and RLS mainly involves contrast-enhanced transcranial Doppler ultrasonography (c-TCD), contrast-enhanced transthoracic echocardiography (c-TTE), and transesophageal echocardiography (TEE) [20]. Although c-TCD is highly sensitive for RLS screening, it cannot directly visualize a PFO or reliably distinguish intracardiac from intrapulmonary shunting. c-TTE permits assessment of intracardiac shunting, while TEE facilitates characterization of PFO anatomy and associated features such as atrial septal aneurysm; its semi-invasive nature and dependence on patient cooperation may nonetheless limit its use [21]. Brain magnetic resonance imaging (MRI), particularly diffusion-weighted imaging, delineates the distribution of infarction; cortical infarcts or infarcts involving multiple vascular territories point toward an embolic mechanism, yet neither finding is specific to PFO-AS. Competing etiologies, including large-artery disease and atrial fibrillation, therefore need to be investigated through imaging of the intracranial and cervical vasculature, cardiac evaluation, and appropriate cardiac rhythm monitoring [21, 22]. **Table 1** summarizes the com-

Table 1. Diagnostic modalities in the evaluation of patients with suspected PFO-AS

Diagnostic Modality	Primary Application	Advantages	Limitations
c-TCD*	Screening for right-to-left shunt	High sensitivity; noninvasive	Cannot differentiate intracardiac from intrapulmonary shunting
c-TTE†	Detection of intracardiac shunting	Noninvasive	Limited visualization of PFO‡ anatomy
TEE§	Characterization of PFO anatomy, including ASA‖ and PFO tunnel morphology	One of the reference imaging modalities for anatomical assessment of PFO	Semi-invasive; dependent on patient cooperation
Brain MRI¶	Assessment of cerebral infarct patterns	Helps identify infarct patterns suggestive of an embolic mechanism	Findings are not specific to PFO-AS**
CTA††/MRA‡‡	Evaluation to exclude large-artery disease	Enables assessment of the cerebral vasculature	Cannot establish a causal relationship between PFO and stroke
Cardiac rhythm monitoring	Detection of atrial fibrillation as an alternative stroke etiology	Helps identify a competing cardioembolic mechanism	Diagnostic yield depends on monitoring duration

Abbreviations: *c-TCD, contrast-enhanced transcranial Doppler ultrasonography; †c-TTE, contrast-enhanced transthoracic echocardiography; ‡PFO, patent foramen ovale; §TEE, transesophageal echocardiography; ‖ASA, atrial septal aneurysm; ¶MRI, magnetic resonance imaging; **PFO-AS, Patent foramen ovale-associated stroke; ††CTA, computed tomography angiography; ‡‡MRA, magnetic resonance angiography. Note: A negative rhythm-monitoring result does not definitively exclude paroxysmal atrial fibrillation.

monly used diagnostic methods for evaluating PFO-AS.

With regard to causal attribution, the Risk of Paradoxical Embolism (RoPE) score [23] estimates the likelihood that a PFO is related to the index stroke on the basis of age, vascular risk factors, and the presence of a cortical infarct. This score, however, does not incorporate PFO anatomical features, and a low score does not exclude PFO-AS. The PFO-Associated Stroke Causal Likelihood (PASCAL) classification builds on the RoPE score by integrating the presence of a large RLS and/or ASA, thereby supporting assessment of the likelihood that the PFO is causally implicated [24, 25]. These approaches form the basis of current diagnostic evaluation, yet causal attribution in individual patients remains uncertain. Such uncertainty underscores the need to explore adjunctive indicators of underlying pathogenic processes beyond clinical and imaging assessment. Hematological biomarkers can be measured in peripheral venous samples by biochemical or immunological assays, which allows convenient sampling and repeated measurement. By offering complementary information on coagulation and fibrinolysis, inflammation, and endothelial function, these biomarkers may help identify a prothrombotic tendency and refine the etiological assessment of PFO-AS [26]. Their measurement is nonetheless influenced by sampling time, treatment, and comorbidities, and no biomarker has been sufficiently validated to independently establish a diagnosis of PFO-AS or to replace imaging. Investigating the associations between hematological biomarkers and PFO-AS, together with the incremental diagnostic value of these biomarkers within existing assessment frameworks, therefore represents an important avenue for improving adjunctive diagnostic assessment.

Hematological biomarkers of patent foramen ovale

Biomarkers with clinical utility potential

The inflammatory response index (IRI): Inflammation is an important mechanism in stroke pathophysiology. Cytokines released from injured brain tissue and activated peripheral immune cells mediate the post-stroke immune-inflammatory response, contributing to infarct progression, disease severity, and clinical outcomes [27, 28]. Inflammatory mediators promote platelet activation and thrombosis, while interactions between platelets and inflammatory factors facilitate neutrophil migration across the blood-brain barrier (BBB)

[29]. This inflammatory cascade may further increase the risk of paradoxical embolism in patients with PFO. In addition, PFO may allow circulating vasoactive or proinflammatory substances to bypass pulmonary metabolic clearance and enter the arterial circulation, potentially promoting hypercoagulability and inflammation [30].

During the hyperacute phase of cerebral ischemia, hypoxia disrupts BBB tight-junction proteins, facilitating neutrophil infiltration into the cerebral parenchyma [29]. Concurrently, upregulated expression of platelet endothelial cell adhesion molecule-1 (PECAM-1) and other junctional proteins further promotes neutrophil transmigration across the BBB [29]. Cerebral infarct volume and neurological deficits are directly associated with neutrophil accumulation [31]. Cerebral ischemia is also characterized by lymphopenia and an elevated neutrophil-to-lymphocyte ratio (NLR), which correlates with ischemic lesion expansion and mortality risk [32]. Patients with PFO-AS have significantly higher NLR and platelet-to-lymphocyte ratio (PLR) values than those in non-PFO stroke cohorts [33], suggesting that these inflammatory indices may serve as early predictors of PFO-AS. An NLR of at least 1.62 showed predictive value for stroke in patients with PFO (sensitivity, 73.4%; specificity, 45.5%; P = 0.042) [33]. Given the lack of prospective validation, further large-scale studies are warranted to evaluate the incremental utility of NLR and PLR for predicting ischemic stroke risk in individuals with PFO.

The D-dimer: Previous research has shown that some patients with cryptogenic stroke have a coexisting hypercoagulable state [34, 35]. A PFO may serve as a conduit for paradoxical embolization of a venous thrombus or as a site of in situ thrombosis [36]. The risk of ischemic stroke in patients with PFO is therefore closely related to venous thromboembolism and underlying hypercoagulability. D-dimer, a fibrin degradation product generated during coagulation and fibrinolysis, is a useful biomarker for identifying prothrombotic conditions and predicting stroke recurrence. Although an isolated PFO provides an anatomical substrate for paradoxical embolism, its coexistence with increased fibrinolytic activity, indicated by D-dimer concentrations above 1,000 ng/mL, was associated with recurrent cerebrovascular events (sensitivity, 42.9%; specificity, 92.5%; P = 0.005) [37]. The relatively long half-life and biochemical stability of D-dimer enhance its reliability as a clinical biomarker [38]. Incorporating D-dimer testing into the evaluation of PFO-AS may improve risk stratification; however, its role in guiding anticoagulation intensity or selecting candidates for PFO closure requires prospective validation.

Mean platelet volume (MPV): Arterial thrombosis, driven by platelet activation and thromboinflammatory interactions, is pivotal to acute cerebrovascular events. Platelets are central mediators of hemostasis and arterial thrombosis, and their immunological reactivity promotes neutrophil-platelet aggregate formation, a process that may be exacerbated by altered shear stress and stasis within the PFO conduit [30, 39, 40].

Mean platelet volume (MPV), a surrogate marker of platelet size and reactivity, is positively associated with prothrombotic potential, reflecting the role of platelets in thromboembolic events [41]. Longitudinal studies comparing MPV levels before and after PFO closure have shown significant postoperative reductions, suggesting dynamic platelet activation related to PFO hemodynamics [42]. MPV levels are also higher in patients with PFO and stroke or transient ischemic attack than in asymptomatic individuals (cutoff, > 9.0 fL; sensitivity, 70%; specificity, 86%), indicating potential value for differentiating thromboembolic risk among patients with PFO [43]. As a readily available and cost-effective routine parameter, MPV may serve as a pragmatic adjunctive biomarker of PFO-AS.

Triglyceride glucose index (TyG index): Metabolic disturbances such as insulin resistance may increase thrombotic risk by promoting venous thromboembolism that is susceptible to paradoxical embolization [44]. Derived from fasting serum triglyceride and glucose concentrations, the triglyceride-glucose (TyG) index is a biochemical surrogate of impaired systemic insulin sensitivity [45]. Elevated TyG index values are strongly associated with arterial stiffness in both normotensive and hypertensive populations [46]. This vascular dysfunction may disrupt hemodynamic balance, impair

venous return, and ultimately increase thrombotic susceptibility. A longitudinal cohort study showed that an elevated TyG index was positively associated with the risk of ischemic stroke and independently predicted cerebrovascular events [47]. A TyG index cutoff of 8.89 yielded a sensitivity of 63.2% and a specificity of 72.3% for predicting cryptogenic stroke in patients with PFO [48]. Consequently, the TyG index may have clinical value as an adjunctive marker of stroke risk in patients with PFO, although its role in treatment planning requires further validation.

B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP): B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) may aid etiological stratification in cryptogenic stroke, particularly by distinguishing PFO-AS from stroke related to atrial cardiopathy. Patients with PFO-AS have lower BNP/NT-proBNP levels, which may reflect paradoxical embolism in the absence of atrial pressure overload. Conversely, an elevated BNP level (cutoff, > 65.0 pg/mL; sensitivity, 55.3%; specificity, 70.9%) [49] may identify patients with non-PFO cryptogenic stroke and underlying cardiac dysfunction, consistent with findings such as an increased E/e' ratio (> 13.0) and reduced left atrial appendage flow velocity (< 46 cm/s). This inverse association has led to the characterization of PFO-AS as a relatively "BNP-negative" entity compared with cardiopathy-related stroke. BNP/NT-proBNP may therefore complement, but should not replace, cardiac imaging and rhythm monitoring in the etiological evaluation of cryptogenic stroke.

Homocysteine (Hcy): Hyperhomocysteinemia is an independent risk factor for cerebrovascular ischemia, and its effects are mediated through endothelial injury and the development of a prothrombotic state via reactive oxygen species-dependent pathways [50]. Deng et al. used mass spectrometry to analyze changes in circulating biomarkers before and after PFO closure and found significant changes in total homocysteine (tHcy) levels in patients with PFO-AS [51]. Specifically, tHcy decreased immediately in patients who achieved complete closure but remained unchanged in those with residual shunting. These findings suggest that RLS associated with PFO may increase tHcy concentrations and that the magnitude of shunting may correlate positively with the severity of hyperhomocysteinemia. The study also demonstrated a sustained long-term reduction in venous tHcy after successful PFO closure, whereas medical management alone did not alter tHcy levels. In addition, serum Hcy levels in patients with PFO were correlated with RoPE scores. An Hcy level above 19.5 μg/dL predicted a RoPE score greater than 7 (OR, 3.21; 95% CI, 2.82-3.26; P < 0.0001), and this association persisted after adjustment for anatomical variations, including persistent RLS and ASA [52]. If confirmed in larger studies, combining Hcy measurements with the RoPE score may improve etiological assessment in patients with suspected PFO-AS.

Osteoprotegerin (OPG): Initially characterized as a regulator of skeletal homeostasis, osteoprotegerin (OPG), a member of the tumor necrosis factor receptor superfamily, has increasingly been investigated as a marker of endothelial dysfunction and related cardiovascular processes [53-55]. OPG levels may be associated with the severity of neurological impairment and functional outcomes. These associations may reflect the pleiotropic involvement of OPG in inflammation, vascular injury, thrombosis, cerebral ischemic injury, and neuronal apoptosis [56, 57]. In patients with stroke, elevated plasma OPG concentrations have been associated with large-artery atherosclerosis and greater initial stroke severity [58] and may predict unfavorable long-term functional outcomes. Beyond its role in atherosclerosis and cardiovascular aging, OPG modulates endothelial cell survival and inflammatory responses by regulating proinflammatory cytokine activity [59]. It also enhances adhesion molecule expression and promotes monocyte-endothelial binding [60], both of which are central to vascular inflammation. The SAFAS study [61] identified an OPG level below 1133 pg/mL as an independent predictor of PFO-AS (OR, 5.007; 95% CI, 1.092-22.958; P = 0.038). Galectin-3, a marker of atrial fibrosis, was inversely associated with PFO-AS. Integrating OPG and galectin-3 with the RoPE score may improve predictive accuracy, although their clinical utility requires external validation.

Biomarkers under mechanistic investigation

Factor V Leiden or prothrombin G20210A mutations: Hereditary procoagulant states are associated with venous embolism [62] and

may contribute to the pathogenesis of PFO-AS. Factor V Leiden or prothrombin G20210A mutations, which underlie inherited thrombophilic disorders, are more prevalent among patients with PFO-associated cryptogenic cerebrovascular events than among non-PFO controls (OR, 12.4; 95% CI, 1.4-105.5; P = 0.008) [63]. The same study found that most affected patients had performed a Valsalva maneuver at stroke onset, providing indirect evidence for a paradoxical embolic mechanism. Screening for hypercoagulability may therefore be appropriate in selected patients with suspected PFO-AS. Although testing for factor V Leiden or the prothrombin G20210A mutation is not routinely indicated in all patients, clinicians should consider coagulation-related risk factors during etiological assessment.

L-Arginine/asymmetric dimethylarginine (L-Arg/ADMA) ratio: Endothelial dysfunction is a pivotal contributor to ischemic stroke pathogenesis. Under physiological conditions, cerebral endothelial cells regulate vascular tone through the basal release of nitric oxide (NO), which exerts vasodilatory effects and inhibits platelet-leukocyte aggregation [64]. However, the passage of microbubbles through a PFO into the arterial circulation may acutely impair endothelial function and disrupt vascular homeostasis [65].

NO is a key mediator of vascular endothelial homeostasis and protects vascular integrity through its vasodilatory and anti-inflammatory effects, including inhibition of platelet aggregation and leukocyte adhesion [66]. L-Arginine (L-Arg), a crucial precursor of NO biosynthesis, supports endothelial function through its role in NO generation. Methylation of L-Arg produces asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) production; ADMA acts as an endogenous competitive inhibitor of nitric oxide synthase (NOS), thereby reducing NO synthesis and aggravating endothelial dysfunction. The L-Arg/ADMA ratio has emerged as a potential marker of endothelial dysfunction and stroke susceptibility in patients with interatrial septal abnormalities. In one study, this ratio was negatively correlated with the PFO tunnel length-to-height ratio ($r = -0.37$; $P < 0.05$) [67]. However, its direct association with PFO-AS requires further validation.

Plasma proteins: Proteomics is a promising approach for characterizing the complex multi-organ changes associated with PFO-AS. The anatomical shunt created by a PFO may expose the cerebral circulation to poorly characterized vasoactive substances, initiating pathophysiological cascades that contribute to cerebrovascular injury and alter systemic hematological profiles [16]. Lopez et al. [68] used high-resolution liquid chromatography-tandem mass spectrometry (LC-MS/MS) to investigate changes in protein profiles in patients undergoing transcatheter PFO closure. They found higher albumin concentrations in samples from patients with cerebral ischemia of embolic origin than in those with noncardioembolic ischemic events. Because albumin carries many circulating molecules, Lopez et al. [69] further investigated the differential expression of serum albumin-binding proteins in patients with stroke who underwent PFO closure. Pathway analysis of high-resolution LC-MS data suggested that PFO closure was associated with increased cholesterol efflux and decreased lipid oxidation. These findings suggest that albumin-binding proteins may help identify PFO-AS and assess biological responses to PFO closure.

However, the translation of these proteomic findings into clinically useful biomarkers faces several challenges, including technical complexity, pre-analytical variability, and a lack of standardization. Current evidence is derived largely from single-center studies without external validation, which may limit the generalizability of the findings. Future multi-center validation efforts integrating anatomical and genetic risk factors would help clarify the clinical utility of these profiles. The development of high-throughput assays could further facilitate prospective evaluation of these markers for predicting stroke recurrence and treatment response.

Discussion

In summary, PFO-AS may arise from the interplay between an anatomical shunt and systemic thrombotic susceptibility. Inflammation-mediated platelet-neutrophil activation, blood stasis, inherited thrombophilia, metabolic dysregulation, and endothelial dysfunction may collectively promote thrombogenesis, with a PFO providing a potential conduit for paradoxical embolism (**Figure 1**). The NLR and PLR reflect inflammatory burden, whereas D-dimer, MPV, and the TyG index provide information on

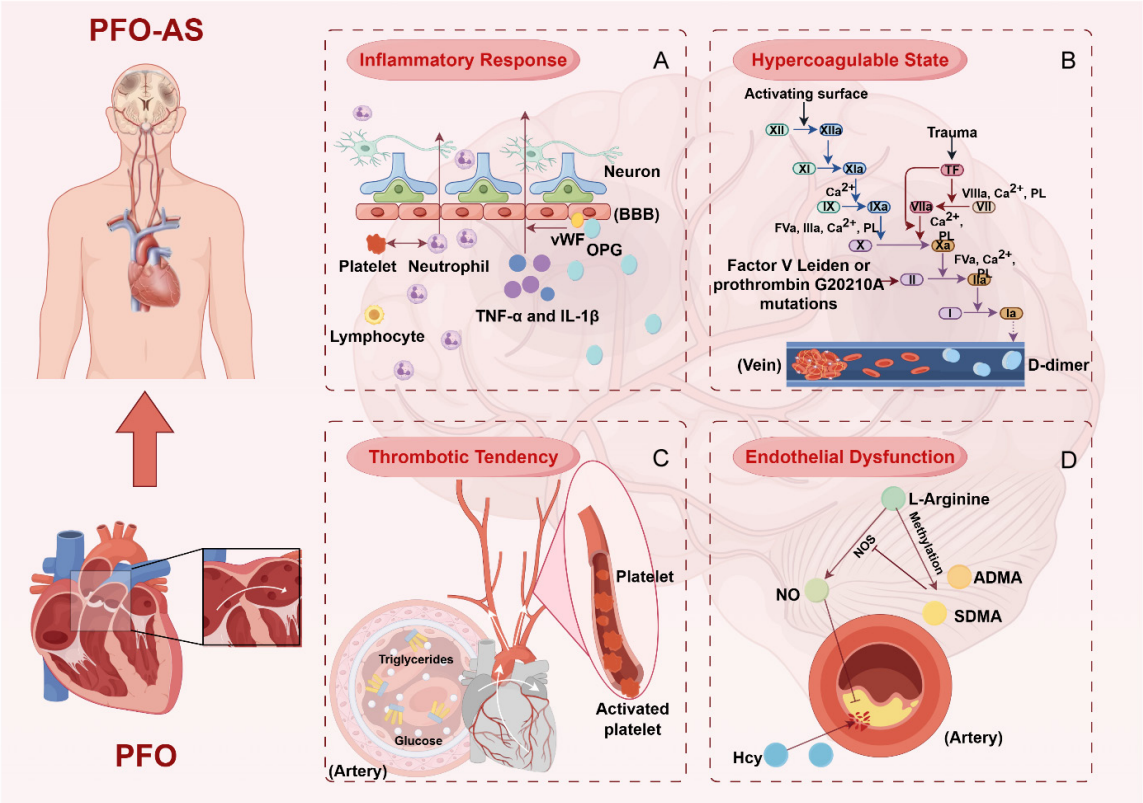


Figure 1. Key hematological biomarkers and pathological pathways in PFO-AS. A. Inflammatory Response: Neuroinflammatory cytokine release activates platelets and neutrophils, exacerbating thromboinflammation and paradoxical embolism via PFO, amplified by OPG-vWF interaction. B. Hemodynamic stasis elevates prothrombotic biomarkers and synergizes with inherited thrombophilias, establishing a hypercoagulable state. C. Thrombotic Tendency: PFO-induced shear stress promotes platelet activation and metabolic dysfunction, increasing thrombotic risk. D. Endothelial Dysfunction: Microbubble-mediated blood flow turbulence generated by RLS impairs endothelial function, exacerbating homocysteine-induced vascular injury. Abbreviations: PFO, patent foramen ovale; PFO-AS, Patent foramen ovale-associated stroke; BBB, the blood-brain barrier; OPG, Osteoprotegerin; vWF, von Willebrand factor; TNF-α, tumor necrosis factor-α; IL-1β, Interleukin-1β; NO, nitric oxide; NOS, nitric oxide synthase; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Hcy, Homocysteine; RLS, right-to-left shunts. This image was created by Figdraw.

fibrin turnover, platelet reactivity, and metabolic status, respectively. Hcy and the L-Arg/ADMA ratio offer insights into endothelial injury and altered NO signaling; these associations, however, do not establish that PFO directly causes the underlying abnormalities. Beyond these mechanistically relevant markers, BNP/NT-proBNP, OPG, and galectin-3 may be particularly informative for etiological differentiation. The relatively lower levels reported in some PFO-AS cohorts may reflect less pronounced cardiac pressure overload, fibrosis, or vascular disease rather than a direct contribution of reduced biomarker levels to stroke pathogenesis [49, 61]. Proteomic alterations involving albumin and albumin-binding proteins further implicate lipid transport and oxidative pathways, although these findings remain exploratory [68, 69]. From a practical perspective, NLR, PLR, MPV, and the TyG index are readily derived from routine laboratory measurements, while D-dimer, Hcy, and BNP/NT-proBNP assays are widely available, supporting further evaluation of their potential as adjunctive assessment tools. In contrast, genetic testing, L-Arg/ADMA measurement, and proteomic profiling are constrained by cost, assay availability, and standardization requirements. Their potential diagnostic contribution lies primarily in refining etiological attribution and risk stratification rather than confirming the presence of PFO or independently establishing its causal

Table 2. Clinical utility and limitations of hematological biomarkers in PFO-AS

Biomarker	Detection Method	Clinical Relevance	limitations	Refs.
IRI*	Complete blood cell counts	Early predictors of PFO-AS† during inflammatory cascades	Low specificity (45.05%); small retrospective cohort (n = 206) without validation	[33]
D-dimer	Latex agglutination assay	High levels suggest hypercoagulability and increased risk of paradoxical thrombosis	uncontrolled confounders (e.g., malignancy)	[37]
MPV‡	Automatic blood counter	Elevated MPV linked to platelet hyperreactivity in PFO-AS	Retrospective design	[43]
TyG Index§	automated blood cell counter and Siemens Healthcare Diagnostic Products kits and calibrators	TyG Index associates with endothelial injury and thrombogenesis in PFO-AS	Moderate diagnostic performance (AUC 0.694); no multicenter validation	[48]
BNP/NT-proBNP‖	/	Elevated BNP indicates non-PFO cardioembolic sources in cryptogenic stroke	Low specificity (AUC 0.66)	[49]
Homocysteine	Enzymatic assay	Hyperhomocysteinemia exacerbates PFO-mediated endothelial damage and stroke risk	High AUC (0.90) derived from pre-selected high-risk cohort without independent validation	[52]
Osteoprotegerin, galectin-3	ELISA¶	Elevated levels correlate with PFO-AS and atrial dysfunction	Small sample (23 cases); single-center; no external validation	[61]
Factor V Leiden and prothrombin G20210A mutations	Genetic testing	Enhances thrombogenic potential of venous clots traversing PFO	Exploratory small sample; unvalidated diagnostic utility	[63]
L-Arg/ADMA**	ELISA	Reduced ratio indicates endothelial dysfunction in PFO	No diagnostic threshold; weak correlation (R^2 = 0.14)	[67]
Albumin	High-resolution LC-MS/MS†† coupled with label-free analysis	Elevated levels predict thrombus stability and embolic potential in PFO	Small sample (n = 14); non-specific signatures; no clinical endpoint linkage	[68]
Albumin-Binding Proteins	Albumin immuno-enrichment and high-resolution LC-MS‡‡	Dysregulation indicates the possibility of PFO associated with stroke and evaluate the therapeutic effect of PFO closure	No diagnostic Receiver Operating Characteristic analysis	[69]

Abbreviations: *IRI, the Inflammatory response index; †PFO-AS, Patent foramen ovale-associated stroke; ‡MPV, Mean platelet volume; §TyG index, Triglyceride glucose index; ‖BNP/NT-proBNP, B-type Natriuretic Peptide/N-terminal pro-BNP; ¶ELISA, Enzyme-Linked Immunosorbent Assay; †PFO, Patent foramen ovale; **L-Arg/ADMA, L-Arginine/asymmetric dimethylarginine; ††LC-MS/MS, Liquid chromatography tandem-mass spectrometry; ‡‡LC-MS, Liquid Chromatography-Mass Spectrometry.

role. For example, the reported NLR threshold yielded a specificity of only 45.5%, limiting its standalone discriminatory performance, whereas D-dimer demonstrated relatively high specificity but a sensitivity of only 42.9% in a recurrence-related analysis, making it insufficient to exclude the risk of subsequent events [33, 37]. Moreover, the evidence is derived predominantly from relatively small observational studies and is susceptible to confounding by the acute response to stroke, infection, renal function, medication use, and blood sampling timing. Assay thresholds also lack harmonization and adequate external validation. **Table 2** summarizes the clinical relevance and limitations of these hematological biomarkers. Integrating hematological biomarkers with echocardiographic anatomical and shunt characteristics and the RoPE score may therefore be more informative than assessing individual markers in isolation. Nevertheless, prospective studies are required to establish their incremental diagnostic performance and clinical net benefit, and current evidence is insufficient to support selecting patients for PFO closure or modifying antithrombotic therapy solely on the basis of these biomarkers.

We consider hematological biomarkers to be adjunctive rather than diagnostic. They may help refine etiological attribution and risk stratification when integrated with echocardiographic anatomy, shunt severity, RoPE/PASCAL, and the exclusion of alternative causes. Among them, D-dimer, MPV, the TyG index, BNP/NT-proBNP, and Hcy are more practical because

they are widely available. However, current evidence is insufficient to support selecting patients for PFO closure or modifying antithrombotic therapy solely on the basis of these markers. Future studies should use standardized sampling and include multicenter prospective validation.

Summary

Hematological biomarkers offer a complementary perspective on PFO-AS by characterizing the thromboinflammatory, metabolic, and endothelial abnormalities that may influence the clinical significance of an anatomical shunt. Combining these biomarkers with clinical and imaging assessments may help improve etiological attribution and risk stratification. However, variable diagnostic performance and limited validation constrain their clinical application, highlighting the need for standardized, multicenter prospective studies to establish their incremental value before these biomarkers can reliably inform diagnostic or therapeutic decisions.

Statistical analysis

This article is a narrative review. No original statistical analysis was performed. All diagnostic performance values, odds ratios, sensitivity, specificity, and AUCs cited in the text and tables were extracted from the original studies. No meta-analysis or pooled analysis was conducted.

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Disclosure of conflict of interest

None.

Address correspondence to: Danhong Wu, Department of Neurology, Shanghai Fifth People's Hospital, Fudan University, Shanghai 200240, China. Tel: +86-18116125596; ORCID: 0000-0002-1132-6669; E-mail: danhongwu@fudan.edu.cn

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