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Research Article

An Outline on the Biomarkers Involved in Cardioembolic Stroke

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Abstract

Background: Biomarkers offer promising avenues for improving the diagnosis of cardioembolic strokes and filling gaps in our understanding of stroke mechanisms. Despite the range of biomarkers available, achieving high diagnostic accuracy remains a challenge. In this regard, this review aims to outline unique biomarker associated with cardioembolic stroke to improve diagnostic accuracy, with the goal of enhancing patient care.

Methodology: Data from 2014 to 2023 were gathered from reputable sources like PubMed, PubMed Central, Google Scholar, Research Gate, and Science Direct. Inclusion criteria focused on studies exploring innovative biomarkers used in the diagnosis of cardioembolism.

Results and discussion: The study emphasized the importance of blood-specific biomarkers like NT-proBNP, neuron-specific enolase (NSE), D-dimer, and inflammatory markers such as C-reactive protein (CRP), and Neutrophil-lymphocyte ratio (NLR) in comprehending various aspects of cardioembolic stroke, including cardiac dysfunction, neuronal damage, coagulation activation, inflammatory response, immune imbalance, and genetic predisposition with a sensitivity ranging from 65% to 90% and specificity from 70% to 95%. However, the association of apolipoproteins is yet to be determined. Additionally, genetic biomarkers like microRNAs and gene expression profiles have been extensively researched for diagnostic purposes.

Conclusion: The combination of blood-specific biomarkers and genetic biomarkers holds promise for enhancing diagnostic accuracy, risk assessment, and treatment monitoring in cardioembolic stroke, leading to improved clinical outcomes and personalized management strategies.

Keywords: Cardioembolism; Biomarkers; Stroke; Inflammatory and Genetic Biomarkers; Diagnosis

Introduction

Cardioembolic stroke arises when a blood clot forms in the heart, typically due to conditions like atrial fibrillation (AF), heart valve issues, or heart failure, and subsequently travels to the brain, where it obstructs a blood vessel, causing a stroke [1]. This type of stroke carries an annual incidence rate of approximately 20-30%, with an in-hospital mortality rate of 27.3% for cardioembolic infarctions, significantly higher than the rates for lacunar infarcts (0.8%) and atherothrombotic strokes (21.7%) [2]. The exact incidence varies based on factors like age, comorbidities, and geographic location. These strokes are particularly harmful due to their tendency to result in larger infarcts compared to other ischemic strokes, leading to greater functional impairment [3]. Detection methods for cardioembolic strokes involve assessing

medical history, conducting physical examinations, and utilizing imaging and laboratory tests such as CT scans, MRI scans, angiography, and echocardiography to evaluate heart function and detect risk factors for blood clot formation [4].

The assessment of biomarkers offers significant potential in enhancing the categorization of cardioembolic stroke etiology, such as identifying AF or heart valve abnormalities. Biomarkers, sourced from various cell types and proteins, including B-type natriuretic peptide (BNP), D-dimer, C-reactive protein (CRP), Neutrophil-lymphocyte (NLR), and total cholesterol, can aid in early detection, risk stratification, and monitoring treatment response [5]. However, challenges such as misdiagnosis due to symptom overlap with other stroke types and lack of specificity in current biomarkers lead to estimated misdiagnosis rates ranging from 4% to 64% globally [6]. In this regard, this review aims to outline unique biomarkers associated with cardioembolic stroke to improve diagnostic accuracy, with the goal of enhancing patient care.

Methodology

The reviewed data, spanning from 2017 to 2024, was gathered from various reputable sources such as PubMed, PubMed Central, Google Scholar, Research Gate, and Science Direct. The inclusion criteria focused solely on studies that explored the biomarkers used in the diagnosis of cardioembolism. Consequently, studies that were unrelated to cardioembolism or investigated other disorders and inaccessible studies were excluded. The search was conducted using specific keywords such as "specific type of biomarkers in cardioembolism", "diagnosis patterns for cardioembolism", "clinical trials related to diagnosis of cardioembolism", "biomarkers used for cardioembolism diagnosis", "blood based, genetic and inflammatory markers" and "diagnosis of novel cardiac embolism biomarkers".

Results and Discussion

Blood-based biomarkers

NT-proBNP

Studies investigating potential biomarkers for cardioembolism in ischemic stroke often focus on NT-proBNP, a member of natriuretic peptide family. NT-proBNP is synthesized primarily in the ventricular myocardium of the heart. The precursor molecule is proBNP, which is synthesized and released from cardiomyocytes in response to increased myocardial wall stress and stretching, typically due to conditions such as heart failure or myocardial ischemia [7]. After synthesis, proBNP is cleaved into the biologically active BNP (brain natriuretic peptide) (aa 77-108 and the inactive N-terminal fragment, NT-proBNP (aa 1-76). NT-proBNP levels can be measured in blood samples, with a half-life of 120 minutes. Elevated levels of NT-proBNP are consistently found in cardioembolic stroke associated with AF compared to noncardioembolic stroke cases. NT-proBNP levels in the first 72 hours after cardioembolic stroke show accurate diagnosis, peaking in the initial days and then declining [8]. To one study followed 80 patients with cardioembolic stroke and found paroxysmal AF in 17 during a six-month follow-up, with an NT-proBNP cutoff of 265.5 pg/mL showing 80% sensitivity and specificity for diagnosing AF without any limitations by using blood sample [9]. Another study showed that NT-proBNP can also be elevated in cardioembolic stroke, with a cutoff value of 499pg/mL being indicative of cardiac dysfunction with sensitivity 82% and specificity 80% [10]. Furthermore, a systematic review confirmed that elevated NT-proBNP levels in cardioembolic stroke enhance the sensitivity and specificity of predictive models. The ongoing STROKESTOP II trial utilizes NT-proBNP levels in blood in individuals over 75 years old, where NT-proBNP > 125pg/ml triggers intermittent ECG recordings for further evaluation, aiming to reduce stroke and systemic embolism incidence with sensitivity and specificity 82% [11]. However, various cutoff points have been suggested for diagnosing cardioembolic stroke, and differences in methodologies and assay kits complicate universal adoption. Factors such as age, gender, severity of stroke, physiological fluctuations and certain medical conditions like heart disease, renal failure, and pulmonary disorders can influence NT-proBNP levels, necessitating consideration of confounding factors. Additionally, medications such as Angiotensin-converting enzyme (ACE), Angiotensin II receptor antagonists inhibitors (ARBs), diuretics, and beta-blockers can also affect NT-proBNP levels [12].

Neuron-specific enolase

Neuron-Specific Enolase (NSE) is an enzyme involved in glycolysis, producing phosphoenolpyruvate from 2-phosphoglycerate. It exists as a dimer with three distinct subunits: α, β, and γ. The γ-enolase, known as NSE, is mainly found in neurons and neuroendocrine cells, with minimal presence in normal peripheral blood. However, following brain injury, NSE is released from damaged neurons

due to a compromised blood-brain barrier (BBB). This makes NSE a valuable biomarker for assessing neuronal damage and BBB disruption, aiding in the diagnosis and prognosis of conditions like subarachnoid hemorrhage and ischemic stroke [13]. One study found that a cutoff value of 103ng/mL for NSE showed a sensitivity of 42.1% within 24 hours for diagnosing cardioembolic stroke using blood samples [14]. Another study determined the optimal cutoff value for NSE in diagnosing cardioembolic stroke to be 35.9ng/mL, measured within 24 hours of stroke onset. At this cutoff, the sensitivity of NSE was 68.4% respectively [15]. Similarly, Capoccia et al. observed elevated NSE levels ranging from 15.29 to 23.12ng/mL in the serum of cardioembolic patients after perioperative microembolization during carotid artery stenting, with a specificity and sensitivity of about 80% [16].

D-Dimer

D-dimer, a biomarker resulting from fibrin breakdown, is widely used to assess blood coagulation activation and clot formation, proving valuable in diagnosing conditions like venous thromboembolism and disseminated intravascular coagulation. Several studies have highlighted the link between elevated D-dimer levels and cardioembolic stroke [17]. Takano and colleagues identified a D-dimer threshold of 300ng/mL that effectively distinguishes cardioembolic stroke from atherothrombotic and lacunar infarctions, achieving a sensitivity of 80% and specificity of 77% from blood sample [18]. Conversely, Ageno et al. reported a significantly higher cutoff of 200ng/mL, with a specificity of 93% and sensitivity of 59%, respectively, in detecting a cardioembolic stroke [19]. Analyzing D-dimer levels within 48 hours of stroke onset, Zi and Shuai found significantly higher levels in cardioembolic stroke patients compared to other stroke types, with an optimal cutoff of 910ng/mL for diagnosing cardioembolic strokes, achieving a sensitivity of 83.7% and specificity of 81.5% [18]. The difference in D-dimer values in diagnosing cardioembolic stroke can be attributed to several factors. Firstly, the cardioembolic clots may vary in size, composition, and propensity to produce fibrin degradation products like D-dimer. Additionally, individual patient factors such as age, comorbidities, and medication use can influence D-dimer levels. For instance, older patients or those with conditions like AF (a common cause of cardioembolic stroke) may have higher baseline D-dimer levels due to increased clotting activity. Furthermore, the timing of D-dimer measurement relative to the onset of symptoms can impact its diagnostic accuracy, as D-dimer levels may rise and fall at different rates during the acute phase of stroke. Overall, these complex interplays of clot characteristics, patient factors, and timing contribute to the variability in D-dimer values observed in diagnosing cardioembolic stroke [18].

Inflammatory markers

C-Reactive protein

Elevated levels of C-reactive protein (CRP) are frequently observed in a significant portion of patients following cardioembolic stroke, indicating various factors like a systemic inflammatory response post-stroke, the extent of tissue damage, or concurrent infections. In animal models of focal cerebral ischemia, CRP has been shown to worsen secondary brain damage through complement system activation [20]. One study indicated that detecting cardioembolic stroke via CRP levels > 3 mg/L in serum had 46% sensitivity and 81% specificity using the ELISA method [21]. Another study, utilizing the High-sensitivity CRP (hs-CRP) assay with a CRP cut-off value of < 1 mg/L, achieved 72% sensitivity and 80% specificity through immunoturbidimetry [22]. A commercially available hs-CRP kit measured CRP 6.09 mg/L with 85% sensitivity and 70% specificity. However, different studies may use varying assay methods to measure CRP levels, such as ELISA, immunoturbidimetry, or commercially available high-sensitivity CRP (hs-CRP) kits. Each method may have its own sensitivity and specificity profiles, leading to differences in the reported cutoff values [23].

Apolipoprotein

Apolipoproteins are proteins found in the blood that play a crucial role in transporting cholesterol and other fats throughout the body. They serve as the protein components of various lipoprotein particles present in the blood, including high-density lipoprotein (Type a) (HDL) and low-density lipoprotein (LDL) (Type B) [24]. Donnel et al., discovered that among the subtypes of ischemic stroke, elevated levels of apoB were linked to an increased likelihood of large vessel and undetermined causes, although the association wasn't notably significant in cases of small vessel or cardioembolism [25]. Similarly, Ohtani et al. examined that apoB was not significantly different among the three subtypes, atherothrombotic infraction, cardioembolic stroke, and lacunar infarction [26]. In one study, lipoprotein A levels have shown a

significant difference in cardioembolic stroke (29.2g/L) patients compared to other stroke types (Large artery atherosclerosis; 34.6g/L, Small vessel occlusion; 24.2g/L) with a p-value < 0.001 [27]. However, in a systematic review, no significant associations has been observed between Apo A with cardioembolic strokes [28]. Further research is necessary to consolidate the existing evidence.

Neutrophil-lymphocyte ratio

The NLR is a valuable biomarker in cardioembolism because it reflects the balance and immune activities of neutrophils and lymphocytes. In events like stroke or myocardial infarction caused by cardioembolism, there's typically an inflammatory response marked by increased neutrophils and decreased lymphocytes. A higher NLR indicates a greater imbalance favoring neutrophils, linked with inflammation and tissue damage, while lower lymphocyte levels suggest a weakened immune response. Monitoring NLR levels offers insights into the inflammatory status and immune response in cardioembolic conditions, aiding in risk assessment, prognosis evaluation, and treatment monitoring [29]. A study suggested the NLR value 4.2 from blood samples with sensitivity and specificity 68.7% and 79.6% confirmed cardioembolic stroke [30]. Other studies revealed the NLR value of >3 with 66.19% specificity and 46.58% sensitivity [31] and >4 with specificity and sensitivity of 79% and 68% from blood [32]. The levels of NLR can vary among individuals based on various factors such as age, comorbidities, and inflammatory status. This variability can influence the determination of cutoff values across studies.

Genetic biomarkers

Researchers have investigated the potential of RNAs found in peripheral blood as biomarkers, focusing on how their expression changes in patients with cardioembolic stroke. These changes may indicate specific inflammatory and prothrombotic alterations related to this stroke subtype. Techniques like microarray analysis, RNA sequencing, and reverse transcription PCR have enabled the examination of both noncoding and coding RNA transcripts, such as microRNAs (miRNAs). MiRNAs, which are short non-protein-coding RNAs approximately 22 nucleotides long, have gained attention for their role in regulating post-transcriptional gene expression by binding to target mRNA at the 3′ untranslated region [33]. Changes in miRNA expression levels such as upregulation or downregulation of specific miRNAs, impacting critical signaling cascades have been associated with various pathologies, including cardioembolism. In a discovery-oriented study involving 76 acute cardioembolic stroke patients, whole-genome microarrays identified a 37-gene profile (a gene that code for interleukin I protein) capable of distinguishing cardioembolic stroke due to AF (AF) from other causes with high sensitivity and specificity, exceeding 90% [34]. Another study used genetic biomarkers (mRNA) of AF caused by cardioembolic stroke which showed >0.5 cut off value with sensitivity and specificity of 80% and 75%. Furthermore, a study measured the expression levels of MicroRNA-21 (miR-21) in peripheral blood samples of patients with cardioembolic stroke using quantitative PCR. A fold change of >2.5 in miR-21 expression showed positive results for stroke with 65% sensitivity and 90% specificity [35]. The heterogenous cut-off values are attributable to different causes of cardioembolic stroke, including AF, heart valve disease, and cardiac tumors [36].

Conclusion

This comprehensive review delves into the biomarkers investigated in cardioembolic stroke patients, focusing on their diagnostic accuracy, risk assessment, and treatment monitoring. Our study synthesizes recent research findings, emphasizing the synergistic role of NT-proBNP, neuron-specific enolase (NSE), D-dimer, inflammatory markers (CRP and NLR), and emerging genetic biomarkers (microRNAs and gene expression profiles) in enhancing diagnostic precision. Unlike previous reviews that examined these biomarkers individually, this study presents an integrative approach, highlighting the potential of combining multiple markers to improve sensitivity and specificity.

Additionally, we discuss the variability in biomarker cutoff values, the influence of confounding factors (such as age, comorbidities, and medications), and the necessity for standardized diagnostic criteria. These findings underscore the promise of genetic biomarkers as future diagnostic tools and advocate for their integration into clinical practice to personalize stroke risk assessment. Future research should prioritize validating these biomarkers in larger populations and establishing uniform cutoff values to enhance their clinical utility.

Consent for Publications

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Conflict of Interest

The author(s) declare no conflict of interest, financial or otherwise.

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