REVIEW ARTICLE

The Prognostic Power of Blood Biomarkers in Ischemic Stroke: A Systematic Review

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ABSTRACT

Background: Blood biomarkers have emerged as potential indicators of poor outcomes following ischemic stroke, helping to monitor the onset of stroke-related processes. Identifying reliable and accessible biomarkers for assessing the prognosis of ischemic stroke patients remains a significant clinical challenge. One of the most difficult areas of research in cerebrovascular disease is the discovery and validation of dependable biomarkers to track the clinical progression of ischemic stroke and predict patient outcomes. Therefore, this article aims to systematically compile evidence on blood-based biomarkers for ischemic stroke prognosis and their clinical outcomes. **Methods:** Three electronic search engines PubMed, Scopus and Cochrane Library used to search for articles related to the study by following PRISMA-P guidelines using specific keywords covering from January 2018 to December 2023. Seventeen studies were selected from 545 articles based on specific inclusion and exclusion criteria, and their quality was assessed using the Crowe Critical Appraisal Tool (CCAT). **Results:** A total of 545 articles were screened and 17 full-text articles were evaluated. The pathophysiological mechanism(s) involved in ischemic stroke are inflammation marker, angiogenesis marker, oxidative stress marker, neurofilament light chain marker and glial fibrillary acidic protein marker. The clinical outcomes of the biomarkers for ischemic stroke prognosis depend much on the performance of diagnostic accuracy. The study also highlights the importance of the timing of biomarker measurements post-event such as within 24 hours after stroke which is crucial for accurate prognosis. The clinical factors also contribute to the progress of prognostication of ischemic stroke such as age, medical history, particularly hypertension and diabetes which could impact stroke outcomes. **Conclusion:** Blood biomarkers alongside clinical factors, offer valuable insights into ischemic stroke outcomes. This review emphasizes their potential to improve stroke prognosis and management.

INTRODUCTION

Biomarkers are important in supplementing the established prognostic factors and improving outcome prediction of ischemic stroke patients (Whiteley et al., 2009 & Uphaus et al., 2022). Biomarkers in ischemic strokes can provide valuable information about the severity of the stroke, potential complications, and the likelihood of recovery. Identification of reliable and accessible biomarkers to characterize ischemic stroke patients' prognosis remains a clinical challenge. According to Ferrari et al. (2023), one of the most challenging research fields in cerebrovascular disease is to identify and validate reliable biomarkers to characterize the clinical evolution of ischemic stroke and patients' prognosis. They mentioned that ischemic stroke has high inter-individual variability as regards clinical presentation, etiology, infarct size and cerebral localization.

Blood biomarkers have the advantage of being minimally invasive, rapidly obtainable, quantitative and reproducible. Montellano et al. (2021) found that blood-based biomarkers might provide additional information to established prognostic factors. According to Angioni et al. (2022), new blood-based markers have the potential to be accurate. It is also conveniently accessible and cost-effective for extensive clinical applications. Besides, it may help with timely diagnosis and could be employed as pharmacodynamic indicators to determine direct target engagement and disease-modifying effects. Katan and Elkind (2018) mentioned that any measurable substance that evaluates the appearance of a stroke-related process in the context of an acute ischemic stroke might be considered a blood biomarker. Thus, blood biomarkers are used as potential indicators in ischemic stroke prognosis and outcome prediction for the patients.

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Besides that, according to Ishida and Cucchiara (2022), some blood biomarkers have been evaluated for association with stroke outcomes. The prediction of outcome could support decision-making processes in ischemic stroke to tailor management and inform patients and relatives (Montellano et al., 2021). As for that, numerous blood-based ischemic stroke biomarkers have been found and appear to be promising in the treatment of ischemic stroke. The use of biomarkers offers essential insights into the extent of the stroke, possible complications, and prognosis for ischemic stroke patients. Hence, this review goal is to systematically gather information regarding the roles of blood-based biomarkers for ischemic stroke prognosis and their clinical outcomes information.

MATERIALS AND METHODS

This systematic review followed guidelines from Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2020 (Page et al., 2021) and was conducted according to a protocol registered in the International Prospective Register of Systematic Reviews, PROSPERO under registration number CRD42024558197. A comprehensive literature search was conducted utilizing the open-access online databases available through the International Islamic University of Malaysia (IIUM) subscriptions, including PubMed, Scopus, and the Cochrane Library.

Articles were retrieved from the databases of the chosen search engines using specified keywords. The search strategy was applied for each database (PubMed, Scopus and Cochrane Library) to obtain more accurate results for this review. The study employed a study design search method that utilized a combination of words and included MeSH terms as synonyms. All potential variations of these terms were considered. The variations of keywords used were ischemic stroke, prognosis, biomarker, and blood biomarkers.

The articles were evaluated by reviewing the full texts and filtered based on the inclusion and exclusion criteria. Studies were included if they met the following conditions: (1) published in English, (2) released between January 2018 and December 2023, (3) classified as case reports, clinical studies, multicenter studies, randomized controlled trials, evaluation studies, observational studies, prospective studies, or prospective-retrospective studies, and (4) focused on primary human research involving blood biomarkers in patients with ischemic stroke. Studies involving patients diagnosed with transient ischemic attacks or hemorrhagic stroke were excluded from this review.

The quality of the articles was evaluated using the Crowe Critical Appraisal Tool (CCAT) (Crowe, M., 2013) version 1.4 checklist. Only studies that achieved a score of over 75 percent were deemed to be of sufficiently high quality for inclusion in this systematic review.

RESULTS

Data Analysis

According to Figure 1, a total of 545 articles were initially identified for this study using the specified keywords across multiple databases (PubMed, Scopus, and Cochrane Library). After removing 24 duplicate articles, 521 articles remained. These were first screened by title, reducing the number to 256 articles. Further screening based on the abstracts led to the exclusion of 126 articles. The remaining 130 articles were then carefully assessed through full-text reading and filtered according to the inclusion and exclusion criteria, resulting in the removal of 71 irrelevant articles. Ultimately, 59 full-text articles underwent a quality assessment using the CCAT, and only 17 articles met the required quality standards.

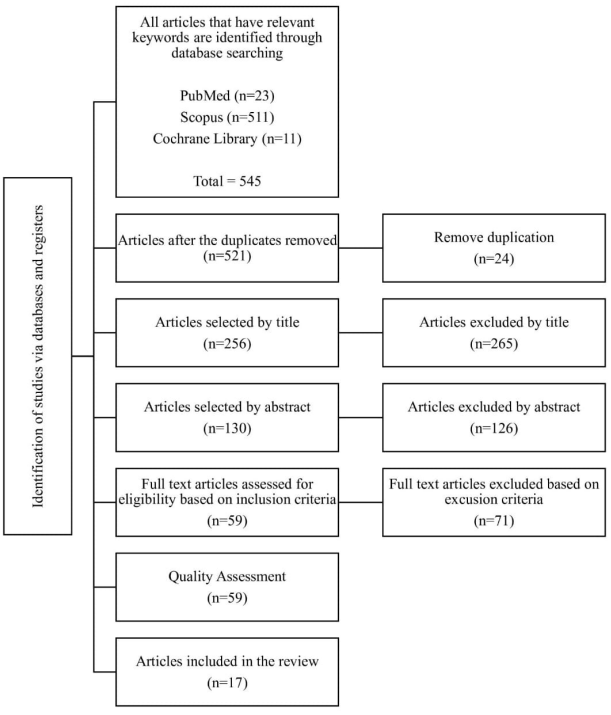

Figure 1: PRISMA 2020 flow diagram

Study Characteristics

The author, study title, country, sample size, study design, and age were extracted and compiled under the study's characteristics based on seventeen relevant full-text articles (Table 2; supplementary data). The review's

included publications, whose sample sizes ranged from 36 to 15,166 patients, were published between 2018 and 2023. The patients' ages ranged from 55 to 68 years old on average. China, Egypt, Italy, and Uzbekistan were the included study countries.

Roles of Blood Biomarkers

All 17 articles published over the past five years (2018-2023) met the inclusion criteria, identifying 17 biomarkers associated with the prognosis of ischemic stroke. Notable roles discussed in this review include markers of inflammation, neuronal injury, glial injury, and anti-inflammatory responses (Table 3; supplementary data).

Blood Biomarkers and the Predicted Outcomes

The seventeen identified blood biomarkers were systematically compiled to determine their predicted outcomes, with all relevant information presented in Table 1. The table includes data on the prognostic outcomes of the biomarkers, along with their diagnostic accuracy in terms of sensitivity, specificity, and area under the curve (AUC). In the context of ischemic stroke prognosis, the timing of blood biomarker measurement post-event is critical, as it affects the accuracy and relevance of the predicted outcomes. Additionally, clinical factors such as age, sex, medical history, smoking habits, and alcohol consumption were also documented.

Table 1: Blood-based biomarkers and the prognosis/predicted clinical outcomes

Biomarker	Clinical Factors	Time measured, post-event	Sensitivity	Specificity	AUC	Prognosis/Clinical outcome
Thioredoxin	Age, sex, smoking, DM, hypertension, dyslipidemia, and carotid stenosis ≥50%.	Within 24 hours from the onset	88%	64%	0.75	A statistically positive correlation between thioredoxin level and clinical outcome after 3 months was measured by mRS.
Copeptin	Age, Sex, DM, hypertension, dyslipidemia, cardiac diseases, carotid stenosis.	Onset within 24 hours	62.2%	84.4%	0.769	Copeptin level was significantly higher in patients with severe stroke (NIHSS > 16) and in patients with unfavorable outcome (mRS 3–6).
Free Triiodothyronine (FT3)	Age, smoking, alcohol consumption, history of stroke, hypertension.	Onset within 48 hours	62.70%	72.03%	0.713	Low FT3 levels at admission are independently associated with poor outcomes in patients with acute ischemic stroke after 3 months.
Serum adiponectin	Age, sex, smoking hypertension, hypercholesterolemia, coronary heart disease, atrial fibrillation, DM	Symptom onset within 48 hours	63.6%	62.4%	0.65	High adiponectin are associated with stroke severity and support the hypothesis that adiponectin can be serve as a biomarker of poor outcome after stroke.

Calprotectin	Age, sex, smoking, medical history (hypertension, hyperlipidemia, hypercholesteremi, atrial fibrillation, DM, family history of stroke).	Within 24 hours after symptom onset	2 weeks after AIS onset (65.63%) During 2 weeks follow-up (81.82%)	2 weeks after AIS onset (66.67%) During 2 weeks follow-up (61.67%)	2 weeks after AIS onset (0.705) During 2 weeks follow-up (0.753)	This study identified calprotectin as a short-term prognostic biomarker of AIS.
Plasma Neurofilament light chain (pNfL)	Age, sex, hyperlipidemia, diabetes, hypertension.	2 days, 7 days and 6 months	2 days (64.3%) 7 days (64.3%) 6 months (82.1%)	2 days (84.6%) 7 days (93%) 6months (54%)	2 days (0.746) 7 days (0.812) 6 months (0.694)	Patients with poor functional outcomes within 6 months after stroke showed have higher pNfL concentration at admission than those with good outcomes.
Serum albumin to globulin ratio (A/G)	Age, sex, smoking, alcohol consumption, medical history (hypertension, dyslipidemia, DM, CHD, atrial fibrillation, family history of stroke).	Within 7 days of the index event of IS or TIA	3 months follow up (53.55%) 1 year follow up (48.56%)	3 months follow up (69.14%) 1 year follow up (69.38%)	3 months follow up (0.6438) 1 year follow up (0.6119)	Lower serum A/G levels were associated with poor functional outcomes and all- cause mortality at 3 months and 1-year follow-up in patients with AIS.
Intercellular adhesion molecule-1 (ICAM-1) and C reactive protein (CRP)	Age, sex, alcohol consumption, medical history (hypertension, DM, CHD, atrial fibrillation, family history of stroke).	Within 24 hours	NA	NA	ICAM (0.829) Hs-CRP (0.748)	Serum concentrations of ICAM-1 and hs-CRP at ED admission could be useful markers for predicting neurological recovery at 3 months after stroke.
Angiopoietin-like protein 4 (ANGPTL-4)	Age, sex, medical history (hypertension, hyperlipidemia, DM, family history of stroke).	Within 48 hours of symptom onset	NA	NA	NA	Increased plasma ANGPTL- 4 concentrations at admission were associated with poor prognosis in ischemic stroke patients.
C1q tumor necrosis factor (TNF)-related protein 9 (CTRP9)	Age, sex, smoking, alcohol consumption, medical history (hypertension, hyperlipidemia, DM).	Within 48 hours of symptom onset	NA	NA	NA	The serum CTRP9 concentration and ratios of CTRP9 to lipids could be promising blood-derived early evaluative biomarkers and a useful tool to predict prognosis in patients with IS at admission.

Eosinophil-to-monocyte ratio (EMR)	Age, sex, medical history of (hyperlipidemia, previous stroke, atrial fibrillation).	The time from the onset of stroke to hospitalization was less than 24 hours	NA	NA	NA	Lower EMR on admission was associated with higher risk of 3-month poor functional outcome, indicating that EMR may be a potential prognostic biomarker for AIS (NIHSS score < 4).
Neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP)	Gender, age, hypertension, smoking habit.	Within 24 hours .	NA	NA	NA	Both biomarkers correlate not only with stroke severity but also with patients' functional recovery assessed through specific motor and disability scales over a 3-month follow-up.
Serum Netrin-1	Age, sex, smoking, alcohol consumption, dyslipidemia, medical history of hypertension.	Within 48 hours of onset	NA	NA	NA	Elevated serum netrin-1 levels were associated with improved prognosis at 3 months after ischemic stroke, suggesting that serum netrin- 1 may be a potential prognostic biomarker for ischemic stroke.
Soluble triggering receptor expressed on myeloid cells (sTREM2)	Age, sex, smoking, alcohol consumption, medical history (hypertension, hyperlipidemia, DM, CHD, family history of stroke)	Within 48 hours	NA	NA	NA	Higher plasma sTREM2 concentrations in the acute phase of ischemic stroke were associated with greater risk of death and cardiovascular events.
Serum Complement C3	Age, sex, smoking, alcohol consumption, medical history (hypertension, DM, hyperlipidemia, family history of stroke)	Within 48 hours of symptom onset	NA	NA	NA	Elevated serum complement C3 levels were associated with increased risks of adverse clinical outcomes among patients with ischemic stroke.

Serum hepatocyte growth factor (HGF)	Age, sex, smoking, alcohol consumption, medical history (hypertension, DM, CHD, family history of stroke)	Within 48 hours of symptom onset	NA	NA	NA	Serum HGF levels were higher in more severe stroke at baseline, and elevated HGF levels were probably associated with 3-month poor prognosis independently of stroke severity among ischemic stroke patients.
Serum Brain-Derived Neurotrophic Factor (BDNF)	Age, sex, smoking, alcohol consumption, medical history (hypertension, hyperlipidemia, DM, CHD, family history of stroke)	Within 48 hours of onset	NA	NA	NA	Elevated serum BDNF levels at baseline are associated with better prognosis at 3 months among Chinese ischemic stroke patients, suggesting that serum BDNF may be a potential biomarker for prognosis after ischemic stroke.

AIS= acute ischemic stroke, AUC= area under curve, CHD= chronic heart disease, DM= Diabetes mellitus, ED= emergency departments, Ischemic stroke, mRS= modified Rankin Scale, NA= Data not available, NIHSS= National Institutes of Health Stroke Scale

DISCUSSIONS

Today's clinical settings depend heavily on blood indicators of ischemic stroke prognosis. Therefore, this review highlights systematically compiled evidence on the potential roles blood biomarkers may play in assisting established prognostic variables in ischemic stroke patients and their functional outcomes.

Blood Biomarkers that Supplement the Established Ischemic Stroke Prognostic Factors

The most notable role of the blood biomarkers is inflammation which involves the biomarkers thioredoxin, serum albumin to globulin ratio (A/G), copeptin, eosinophil-to-monocyte ratio, free triiodothyronine, intercellular adhesion molecule-1 (ICAM-1) and C reactive protein (CRP), calprotectin, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), and serum complement C3. Inflammatory markers play a significant role in the pathophysiology of ischemic stroke and are closely associated with stroke prognosis. After an ischemic stroke, an inflammatory response is triggered in the brain, contributing to both tissue damage and repair. Several inflammatory biomarkers have been studied for their potential to predict the outcomes of ischemic stroke, including the severity of neurological damage, risk of complications, and long-term recovery.

Another proposed role of blood biomarkers is angiogenesis, involving angiopoietin-like protein 4 (ANGPTL-4) and serum hepatocyte growth factor (HGF). Angiogenesis refers to the formation of new blood vessels around the infarct, which is positively associated with stroke patients' survival rate, survival time, and neurological recovery (Zhu et al., 2021). By promoting the development of new blood vessels, ANGPTL-4 and HGF help restore blood flow, reduce the size of the infarct, and support the brain's repair and regeneration processes.

In addition, neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) markers were included in the table. Ferrari et al. (2023) found that GFAP and NfL are brain injury markers detectable in blood using highly sensitive technologies. Among these, sNfL holds a stronger prognostic value, showing better predictive performance compared to sGFAP. Furthermore, elevated blood NfL levels during the acute phase of stroke are associated with a poor prognosis (Wu et al., 2022).

By identifying the roles played by these biomarkers in stroke pathology, a deeper understanding of their contributions can be gained and novel approaches for therapeutic interventions that target the enhancement of their positive effects can be achieved.

Blood Biomarkers and their Clinical Outcomes in Ischemic Stroke Patients

Most of the prognostication outcomes were found to be poor after ischemic stroke. Markers that had poor outcomes were angiopoietin-like protein 4 (ANGPTL-4), serum albumin to globulin ratio, copeptin, eosinophil-to-monocyte ratio, neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), free triiodothyronine, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), serum adiponectin, serum complement C3, and serum hepatocyte growth factor (HGF). However, serum netrin-1 & serum BDNF were found to be associated with better prognosis which has a higher chance of recovery after an ischemic stroke. The remaining biomarkers such as CTRP9, thioredoxin, ICAM-1 & CRP, and calprotectin, were not specified.

The details gathered also discussed the performance of diagnostic accuracy in terms of biomarker's sensitivity, specificity and area under curve (AUC). The biomarkers that provided information on those are thioredoxin, serum albumin to globulin ratio (A/G), copeptin, fT3, ICAM-1 & CRP, calprotectin, pNfL and serum adiponectin. The data on the remaining biomarkers are not available. Thioredoxin, calprotectin and pNfL (at 6 months after stroke) provided good sensitivity between above 80 percent, showing reliable diagnostic capabilities and making it valuable in confirming non-stroke cases. Similarly, copeptin and pNfL (at 2 days & 7 days after stroke) also showed strong performance with high specificity (84.4% and (84.6% & 93%)) respectively. Moreover, ICAM-1 has been identified as the most promising biomarker, demonstrating the highest AUC, which reflects excellent diagnostic accuracy.

The timeframes for post-stroke biomarker measurements, outlined in Table 1, played a pivotal role in understanding the progression and impact of ischemic stroke. Most of the samples were collected within 24 hours (n=6, 35.29%) and 48 hours (n=9, 52.94%) after stroke onset. Montellano et al. (2021) emphasized the importance of sampling biomarkers early, especially those whose concentrations naturally fluctuate during disease progression or are influenced by early complications, such as post-stroke infections and inflammation. Early sampling ensured accurate and timely monitoring of disease progression and potential complications. By providing prompt prognostic information during the initial clinical evaluation, the predictive value of these biomarkers was significantly enhanced.

Clinical factors also serve as predictive outcomes for ischemic stroke, typically reflecting patient characteristics and medical conditions. This review identified several notable clinical factors, including age over 22 years and medical history of conditions such as hypertension (n=16, 94.12%) and diabetes mellitus (n=13, 76.47%). Increased age heightens the risk of ischemic stroke, as aging leads to harder and thicker arterial walls, which raises the likelihood of blockages. Furthermore, McManus & Liebeskind (2016) noted that up to 84% of patients with acute stroke presented with hypertension, while a smaller percentage exhibited blood pressures below normal during episodes of cerebral ischemia. Additionally, individuals with diabetes mellitus (DM) are at risk of developing early atherosclerosis and plaque instability due to endothelial dysfunction, increased thrombogenesis, and monocyte activation (Olesen et al., 2019). Incorporating clinical factors alongside biomarkers improves the predictive accuracy of functional outcomes, such as disability or mortality.

CONCLUSION

This systematic review highlights the findings on the role of blood biomarkers and their clinical outcomes for ischemic stroke prognosis. These blood biomarkers play various roles in ischemic stroke prognosis which are inflammation marker, angiogenesis marker, oxidative stress marker, neurofilament light chain marker and glial fibrillary acidic protein marker. The functional outcomes of the ischemic stroke much relying on the prognostication outcomes, the performance biomarkers' accuracy in terms of sensitivity, specificity and AUC, the timing of biomarker measurements post-event and the clinical factors. This review underscores the importance of blood biomarkers in advancing the prognostication and management of ischemic stroke, ultimately aiming to improve patient outcomes.

One of the systematic review's limitations is the absence of data regarding the diagnostic accuracy of the biomarkers, which could potentially skew the overall results and render them inconclusive. Besides that, the compiled studies were mostly distributed from China caused the dataset may have limited the generalizability of the results to a broader global context. Furthermore, restricting the study to English-language articles might have excluded relevant studies published in other languages. Thus, further research, validation, and standardization are necessary to ensure the clinical utility and integration into routine practice. Additionally, considering factors such as the timing of biomarker measurement, patient heterogeneity, and variability in stroke etiology will be crucial for developing robust predictive models in ischemic stroke management.

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