

THE ROLE OF INTIMA-MEDIA-THICKNESS, ANKLE-BRACHIAL-INDEX, AND INFLAMMATORY BIOCHEMICAL PARAMETERS FOR STROKE RISK PREDICTION: AN UPDATE SYSTEMATIC REVIEW

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ABSTRACT

Background: Stroke is a leading cause of global mortality and morbidity. The capacity to precisely estimate a person's risk of having a stroke is critical for early intervention and prevention strategies. Researchers are exploring novel predictors beyond traditional risk factors, such as Intima-Media Thickness (IMT), Ankle-Brachial Index (ABI), and inflammatory biochemical parameters, to accurately predict stroke risk.

The aim: This study aims to determine the role of intima-media-thickness, ankle-brachial-index, and inflammatory biochemical parameters for stroke risk prediction.

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SAGEPUB, and ScienceDirect, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Results: In the PubMed database, the results of our search brought up 1,004 articles, whereas the results of our search on SAGEPUB brought up 651 articles, and our search on ScienceDirect brought up 4,254 articles. In the end, we compiled 12 papers, 8 of which came from PubMed, 1 of which came from SAGEPUB, and 3 of which came from ScienceDirect. We included twelve research that met the criteria.

Conclusion: In conclusion, the findings of our study strongly support that Carotid Intima-Media Thickness (CIMT) and Ankle-Brachial Index (ABI) hold significant promise as predictors of stroke risk. This can be helpful to improve stroke prevention and management strategies. However, further research is warranted to clarify the role of inflammatory biochemical parameters in the context of stroke risk prediction.

Keywords: Intima-media-thickness, ankle-brachial-index, inflammatory biochemical parameters, stroke risk

INTRODUCTION

Stroke is a neurological condition that is clinically described as an immediate, focal loss of function in the brain that is caused by vascular injury (hemorrhage, infarction) to the central nervous system.¹ Stroke remains one of the leading causes of mortality and morbidity worldwide, imposing a significant burden on healthcare systems and societal well-being. Stroke is currently the second greatest cause of mortality globally, with vascular diseases accounting for the majority of deaths. Together, ischemic heart disease and stroke claimed 15.2 million lives in 2015 (15–15.6 million). Two Hemorrhagic stroke accounts for a large share of the worldwide burden of stroke, as assessed by mortality and disability-adjusted life years (DALYs), even though ischemic strokes account for the majority of stroke cases. Hemorrhagic stroke mortality rates in low- and middle-income nations are as high as 80%.²

The increasing global burden of stroke strongly implies that current primary preventive measures for cardiovascular disease and stroke are either underutilized or undereffective.³ The ability to accurately predict an individual's risk of experiencing a stroke is of paramount importance for early intervention and prevention strategies. In recent years, researchers and clinicians have increasingly turned their attention towards novel predictors beyond traditional risk factors, seeking more precise and comprehensive approaches to stroke risk assessment.^{1–3} This research delves into the intricate interplay between vascular health markers, specifically Intima-Media Thickness (IMT), Ankle-Brachial Index (ABI), and inflammatory biochemical parameters, in the context of stroke risk prediction. IMT, a measure of the thickness of the arterial walls, reflects the early stages of atherosclerosis and vascular remodeling, whereas ABI serves as a surrogate marker for peripheral arterial disease and systemic atherosclerosis.^{3–5} Additionally, inflammatory biomarkers such as C-reactive protein (CRP), interleukins, and tumor necrosis factor-alpha (TNF- α) signify the inflammatory processes implicated in atherosclerosis and plaque instability, thereby contributing to stroke pathogenesis.^{6,7}

Understanding the significance of these vascular and inflammatory markers in stroke risk assessment offers a promising avenue for enhancing predictive models and refining personalized medicine approaches. Through a comprehensive review and analysis of existing literature, this systematic review aims to determine the role of IMT, ABI, and inflammatory biomarkers for stroke risk prediction.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this systematic review, we compare and contrast the role of intima-media-thickness, ankle-brachial-index, and inflammatory biochemical parameters for stroke risk prediction. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

For researchers to take part in the study, they needed to fulfill the following requirements: 1) The paper needs to be written in English, and it needs to investigate the role of intima-media-thickness, ankle-brachial-index, and inflammatory biochemical parameters for stroke risk prediction. For the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "intima-media-thickness"; "ankle-brachial-index"; "inflammatory biochemical parameters"; and "stroke risk" as keywords. The search for studies to be included in the systematic review was carried out in March, 20th 2024 using the PubMed, SAGEPUB, and ScienceDirect databases by inputting the words: (("intima-media-thickness"[All Fields] OR ("ankle brachial index"[MeSH Terms] OR ("ankle"[All Fields] AND "brachial"[All Fields] AND "index"[All Fields]) OR "ankle brachial index"[All Fields]) OR ("inflammatories"[All Fields] OR "inflammatory"[All Fields]) AND ("biochemical"[All Fields] OR "biochemically"[All Fields] OR "biochemicals"[All Fields]) AND ("parameter"[All Fields] OR "parameter s"[All Fields] OR "parameters"[All Fields]))) AND (("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND ((y_10[Filter]) AND (english[Filter])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers examined to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilize as sources for their article and selected those studies. After looking at several different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't be seen anywhere else.

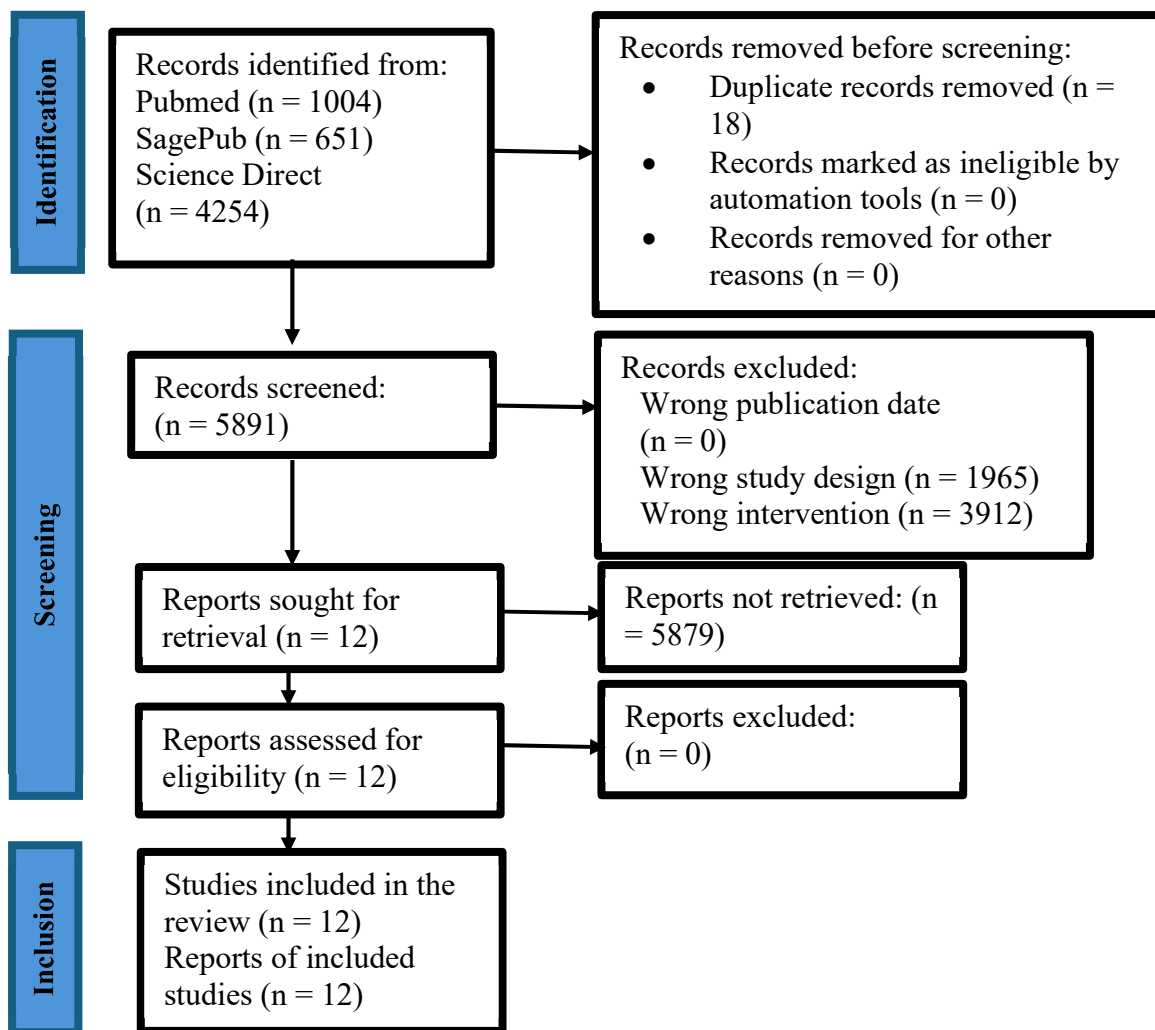


Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before deciding on which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilized in the process of selecting papers for further assessment to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 1,004 articles, whereas the results of our search on SAGEPUB brought up 651 articles, and our search on ScienceDirect brought up 4,254 articles. In the end, we compiled 12 papers, 8 of which came from PubMed, 1 of which came from SAGEPUB, and 3 of which came from ScienceDirect. We included twelve research that met the criteria.

Table 1. The literature included in this study

Author	Origin	Method	Sample Size	Result
Danuaji, 2023 ⁸	Indonesia	Case control	158 patients	Based on the results of CIMT measures, AIS was linked to atherosclerosis in the Indonesian population with respect to age, BMI, sex, T2DM, hypertension, smoking status, dyslipidemia, socioeconomic status, and education level.
Donovan, 2023 ⁹	UK	NA	19,195 participants	The finding of this study showed there was no significant causal relationship between genetically determined FGF-23 levels and atherosclerotic or nonatherosclerotic cardiovascular disorders.
Gronewold, 2014 ¹⁰	Germany	Cohort	3,289 participants	These findings suggested ABI, CIMT, and CAC offer supplementary data regarding the risk of stroke. Predictive value was highest for ABI, which is unique in a small subpopulation, and lowest for CIMT, which is spread across a wider range of values.
Gronewold, 2014 ¹¹	Germany	Cohort	4,299 participants	The results suggested that the general population, ABI is a good predictor of stroke; in particular, it identifies persons who are more at risk of stroke when they have conventional risk factors.
Lee, 2021 ¹²	Taiwan	Retrospective study	84 patients	According to these results, the ankle-brachial index is a highly reliable indicator of ischemic stroke risk in hemodialysis patients.

Shi, 2020 ¹³	China	Observational study	10,750 participants	The findings indicate that in general hypertension individuals, an L-shaped relationship between ABI and the prevalence of stroke was seen, with a turning point at roughly 1.05. Lower ABI values (<1.05), when compared to higher values, would significantly increase the prevalence of stroke (OR: 1.26, 95% CI [1.05-1.50]), particularly in older adults over 65.
Shimoda, 2020 ¹⁴	Japan	Cohort study	2,943 participants	The results suggested that in Asians, the risks of stroke, lacunar infarction, coronary artery disease, and cardiovascular disease were linked to maximum intima-media thicknesses of the internal carotid artery, maximum intima-media thicknesses of the common carotid artery, and heterogeneous plaque.
Sun, 2020 ¹⁵	China	Retrospective study	11,547 participants	This finding suggested that patients with hypertension, there was a strong positive correlation found between baseline cIMT and the likelihood of having a first stroke. Those with greater diastolic or mean arterial pressure values showed an even larger correlation with this.
Wang, 2021 ¹⁶	China	Cohort	1,048 patients	The findings showed that the rs2910164 polymorphism in miR-146a altered the relationships between greater cIMT levels and the IS and LAA subtypes but not the SVO subtype.

Wang, 2021 ¹⁷	USA	Cohort study	5,003 participants	The results suggested regardless of baseline ASCVD status, low ABI was linked to a greater risk of HF and CHD/stroke in individuals without a history of ASCVD. These findings indicate the potential usefulness of ABI in HF risk assessment for older persons as well as its support as a risk enhancer for primary cardiovascular prevention.
Yang, 2021 ¹⁸	Taiwan	Cohort	482 patients	This study found patients diagnosed with type 2 diabetes, low ABI was independently linked to cardiovascular events and diabetic foot ulcers.
Zhou, 2020 ¹⁹	China	Retrospective study	368 patients	The result of this study suggested that increased IMT was associated with TC and sdLDL-C, although sdLDL-C constituted a separate risk factor. A prediction model was developed to screen the population at high risk of AIS, based on IMT and additional characteristics.

Intima-Media-Thickness (IMT)

Six studies^{8,10,14-16,19} suggested that increase in carotid intima-media-thickness (CIMT) was significantly associated with a higher risk of stroke. Danuaji, et al. (2023)⁸ found that Atherosclerotic arteries are a risk factor for acute ischemic stroke (AIS) if their carotid intima-media-thickness (CIMT) value is less than 25% or greater than 1.0 mm. Sun, et al. (2020)¹⁵ showed increase in mean CIMT was linked to a lower risk of first ischemic stroke (HR, 1.10 [95% CI, 1.01-1.20]) and a higher risk of first stroke (hazard ratio [HR], 1.11 [95% CI, 1.03-1.20]). Furthermore, when CIMT was divided into quartiles, individuals in quartiles 2 to 4 (≥ 0.66 mm) had higher chances of having a first stroke (HR, 1.31 [95% CI, 1.06-1.61]) and a first hemorrhagic stroke (HR, 2.25 [95% CI, 1.11-4.58]) than those in quartile 1 (< 0.66 mm).

In addition, Shimoda, et al. (2020)¹⁴ found that hazard ratios (HRs) and 95% CIs for the highest (≥ 1.07 mm) versus lowest (≤ 0.77 mm) quartiles of maximum intima-media thicknesses of the common carotid artery were 1.97 (1.26-3.06) for total stroke, 1.52 (0.67-3.41) for hemorrhagic stroke, 2.45 (1.41-4.27) for ischemic stroke, 3.60 (1.64-7.91) for lacunar infarction, 1.53 (0.69-3.41) for nonlacunar cerebral infarction, 2.68 (1.24-5.76) for coronary artery disease, and 2.11 (1.44-3.12) for cardiovascular disease (similar results were found for maximum intima-media thicknesses of the internal carotid artery) using a multivariate Cox proportional hazard model. Zhou, et al. (2020)¹⁹ showed that the prognostic value of IMT for AIS was still better than that of non-HDL-C and LDL-C. However, Gronewold, et al. (2014)¹⁰ showed that CIMT had the lower predictive value compared with ABI.

Ankle-Brachial-Index (ABI)

Six studies^{10-13,17,18} suggested that patients with a low ABI ≤ 0.9 had higher rates of stroke. Gronewold, et al. (2014)¹⁰ showed that the best prognostic value for stroke was found in ABI. Low ABI values are uncommon in the general population, despite the fact that ABI most significantly influenced stroke risk in the analyses above. Just 4.8% of participants in the HNR research had ABI values less than 0.9. Lee, et al. (2021) showed in univariate Cox regression analysis, compared to abnormal ABI levels, normal ABI levels were linked to a 96.5% lower incidence of IS (HR: 0.035, 95% CI: 0.009-0.145, $p < 0.001$).

Fibroblast Growth Factor-23

Donovan, et al. (2023)⁹ showed that atherosclerotic cardiovascular disease was present in 26,266 (8%) of the UK Biobank individuals. The composite of ischemic stroke (1.04; 95% CI, 0.94 to 1.15; 5992 outcomes) did not show any correlation with genetically predicted FGF-23. Nonatherosclerotic cardiovascular disease was present in 12,652 (4%) of the UK Biobank individuals overall. Hemorrhagic stroke was not associated with genetically predicted FGF-23 (1.05; 95% CI, 0.88 to 1.27; 1745 outcomes). FGF-23, which was genetically predicted, did not correlate with an increased risk of ischemic stroke (0.82; 95% CI, 0.65 to 1.03).

DISCUSSION

The purpose of this research was to review studies published after January of 2014 and up to March of 2024 that investigated the role of intima-media-thickness, ankle-brachial-index, and inflammatory biochemical parameters for stroke risk prediction. With a substantial predictive value for both myocardial infarction and IS, cIMT has been shown to predict cardiovascular risk without the need for conventional cardiovascular risk variables.²⁰ CIMT can be easily accessed by non-invasive B-mode ultrasound.²¹ The European Hypertension Guidelines and the European Prevention Guidelines both identify increased cIMT as an organ damage condition because it is seen by some to be a sign of subclinical atherosclerosis. But genetically and physiologically, cIMT differs from plaque load.²² Mean cIMT values have been suggested as a valuable technique for early detection of systemic atherosclerosis and cardiovascular event risk, including ischemic stroke, as well as a possible surrogate outcome in several clinical trials.²⁰ Sahoo et al. found a greater mean CIMT (0.782 ± 0.19 mm) in stroke cases compared to controls (0.594 ± 0.98 mm; $p < 0.0001$), although in a group residing in south India. The difference was consistent in all age groups, as was found in our study.²¹

According to our research, stroke cases with the identified comorbidities had higher CIMT values, and this difference was statistically significant. A prior study that looked at risk variables like smoking, diabetes, and hypertension found that there was a significant difference between the patient and control groups in the subgroup analysis. In a small group of ischemic stroke cases with age-matched controls, a study on Asian Indian stroke cases found a higher IMT with plaque grades in type II diabetes stroke patients.²⁰ In the Rotterdam Study, 374 participants 55 years of age and older with a history of stroke or MI were followed for an average of 4.2 years in order to assess the impact of CIMT in predicting future CAD. We assessed these participants to see whether CIMT played a role in the novel MI prediction. The traditional risk indicators that were added to the CIMT readings were measured for prognostic value using receiver operating characteristic (ROC) curves. With respect to age and sex, the ROC area was 0.65 (95% CI: 0.62–0.69). Previous MI, stroke, diabetes mellitus, smoking, systolic and diastolic blood pressure, total cholesterol, and HDL cholesterol levels were risk variables that increased the ROC area from 0.65 to 0.72 (95% CI, 0.69–0.75). When CIMT was added to the previous model, the ROC area increased to 0.75 (95% CI, 0.72–0.78).²³

Banerjee et al. recently conducted a topical review in which they noted the high prevalence of multi-territory vascular illness in stroke patients and the significant impact this has on cardiovascular risk, particularly vascular death. The high-risk patients identified can be addressed with multiple tactics to limit the chance of recurrence, such as more aggressive treatment of concurrent vascular risk factors through different drug strategies or encouraging patient adherence in patients, possibly with the use of ABI.²⁴ The ankle-brachial index (ABI), which is the ratio of a patient's systolic blood pressure recorded at their arm and ankle while they are in a supine position, is a cheap, non-invasive, and accurate technique for assessing patients who may have lower extremity peripheral artery disease (PAD).²⁵ ABI screening may be helpful in identifying participants who are extremely high-risk for stroke events; nevertheless, the majority of research has concentrated on the association between low ABI and risk. A low ABI has a high 92.2% specificity in predicting future stroke outcomes, but a low 16.0% sensitivity.²⁶

The Multi-Ethnic Study of Atherosclerosis (MESA) research revealed a stronger correlation between $ABI < 1.0$ and composite endpoints such as stroke, coronary heart disease, and other vascular events, but not just with stroke. With a large cohort size of 14,839 participants, the Atherosclerosis Risk in Communities (ARIC) study found a strong correlation between $ABI < 0.80$ and an increased 7-year risk of ischemic stroke (HR, 5.68 [95% CI, 2.77–11.66]); however, after controlling for major cardiovascular risk factors, the risk became statistically insignificant (HR, 1.93 [95% CI, 0.78–4.78]).²⁷ Moreover, an $ABI < 0.9$ has a strong association with stroke mortality and stroke recurrence during the follow-up period, after additional adjustment for a variety of risk factors.²⁵

Inflammatory biomarkers, such as C-reactive protein (CRP), interleukins, and tumor necrosis factor-alpha (TNF- α), are implicated in the inflammatory processes underlying atherosclerosis and plaque instability, both critical contributors to stroke pathogenesis. Multiple studies have indicated that elevated levels of inflammatory biomarkers are associated with an increased risk of stroke. The findings suggest that inflammation plays a pivotal role in the development and progression of stroke, independent of traditional cardiovascular risk factors. The mechanisms by which inflammation contributes to stroke risk are multifaceted, including endothelial dysfunction, plaque rupture, and thrombosis. Inflammatory processes promote the formation and destabilization of atherosclerotic plaques, increasing the likelihood of embolic events and ischemic stroke. Additionally, inflammation can exacerbate cerebrovascular injury and impair neurological recovery following a stroke event.⁶

CONCLUSION

In conclusion, the findings of our study strongly support that Carotid Intima-Media Thickness (CIMT) and Ankle-Brachial Index (ABI) hold significant promise as predictors of stroke risk. This can be helpful to improve stroke prevention and management strategies. However, further research is warranted to clarify the role of inflammatory biochemical parameters in the context of stroke risk prediction.

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