

Intracranial atherosclerosis: Cerebral angiography findings, clinical phenotypes, and associated risk factors in a retrospective study

Muhammad Yunus Amran^{1,2,3*}, Irbab Hawari⁴, M Fajrin Hidayah⁵

¹Division of Interventional Neurology and Neuroendovascular Therapy, Department of Neurology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; ²Brain Centre, Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia; ³Hasanuddin University Teaching Hospital, Makassar, Indonesia; ⁴Department of Neurology, Al- Azhar Islamic University, Mataram, Indonesia; ⁵Department of Neurology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Abstract. *Background and aim:* Intracranial atherosclerosis (ICAS) is a significant contributor to global stroke incidence and is associated with a substantially higher risk of stroke recurrence compared to other stroke types. The annual recurrence rate of ischemic stroke in ICAS ranges from 10% to 50%, with a two-year recurrence rate of 38.2% in the affected arterial territory. Identifying the risk factors associated with ICAS is essential to improving prevention and management strategies. *Methods:* This retrospective descriptive study analyzed medical records of ischemic stroke patients at Wahidin Sudirohusodo Hospital who underwent cerebral angiography from January 2021 to December 2022. Variables studied included demographic characteristics (age, sex), risk factors, and the location of ICAS within intracranial vessels. *Results:* A total of 106 ICAS patients were identified during the study period. The majority were male (58.40%), with an average age of 54.7 years. The highest prevalence was observed in the 50–60 age group (45.28%). Hypertension was the most frequent risk factor (70.75%), followed by dyslipidemia (46.22%), diabetes mellitus (22.64%), prior stroke or transient ischemic attack (17.92%), extracranial carotid artery stenosis (7.54%), and cardiac disease (5.66%). The middle cerebral artery (MCA) was the most commonly affected site (57.46%). *Conclusions:* Hypertension and dyslipidemia were the leading modifiable risk factors for ICAS, emphasizing the need for targeted management strategies. Effective control of these conditions could serve as a primary and secondary preventive approach to reduce ICAS incidence and associated complications. (www.actabiomedica.it)

Key words: intracranial atherosclerosis, large artery disease, ischemic stroke, hypertension, dyslipidemia, cerebral angiography, risk factors, clinical phenotypes, retrospective cohort study

Introduction

Intracranial atherosclerosis (ICAS) is a notable global cause of stroke and is particularly linked to a heightened risk of stroke recurrence. This condition has a high prevalence among various demographic groups, including Black, Asian, Hispanic, Indian, and several Arab populations, indicating a significant public health concern. The increasing population in these regions suggests that the burden of strokes attributable

to ICAS will continue to rise. Key risk factors for ICAS encompass several interconnected elements, including age, which naturally predisposes individuals to vascular changes, along with hypertension, dyslipidemia, diabetes, and lifestyle choices such as smoking. Collectively, these risk factors underline the importance of early identification and management to mitigate the incidence and progression of this condition (1-3). Stroke patients with ICAS can have a poor prognosis, including poor functional outcomes and increased morbidity

and mortality. The annual recurrence rate of ischemic stroke in ICAS ranges from 10% to 50%, with a two-year recurrence rate of 38.2% in the territory of the stenosed artery. Another study reported annual mortality rates from ICAS as 12.4% per year for internal carotid artery (ICA) stenosis, 6.8% for middle cerebral artery (MCA) stenosis, and 11.6% for vertebrobasilar artery (VBA) stenosis. The location of ICAS in influencing clinical outcomes and management strategies. Specific arterial locations, such as the MCA and ICA, are identified as sites where plaque development occurs with distinct implications for stroke risk. For example, MCA lesions are frequently associated with acute ischemic strokes, while lesions in the ICA are linked to transient ischemic attacks and an increased risk of recurrent strokes. The understanding of these locational differences is essential for enhancing diagnostic imaging techniques and developing targeted treatment approaches for cerebrovascular diseases (3–5). Therefore, it is crucial to identify the risk factors associated with the occurrence of ICAS in the stroke patient population. Considering the lack of research on the characteristics of ICAS patients in Makassar, we conducted a study to determine the demographic profile, risks, and characteristics of ICAS patients who underwent cerebral digital subtraction angiography (C-DSA) procedures at Wahidin Sudirohusodo Central General Hospital, Makassar, from January 2021 to December 2022.

Material and Methods

Study design

This descriptive study was performed at Wahidin Sudirohusodo Hospital in Makassar, covering the timeframe from January 2021 to December 2022. Following the acquisition of ethics approval which was obtained from the Health Research Ethics Committee of the Faculty of Medicine at Hasanuddin University in Makassar, as indicated by letter number 10794/UN4.6.8/PT.01.04/2023, we conducted a retrospective analysis of the medical records and angiograms for all patients diagnosed with intracranial atherosclerotic disease (ICAS).

Patient selection and research procedure

We documented the clinical manifestations, angiographic findings, and treatment approaches. All neuroendovascular procedures were executed and evaluated by a consultant specializing in neurointerventional and neuroradiology at Wahidin Sudirohusodo Hospital in Makassar. The angiographic suite utilized for these procedures was the Allura Monoplane Unit from Philips Corporation, USA. Each patient underwent cerebral digital subtraction angiography (C-DSA), with arterial access primarily achieved through the right femoral artery, while some cases required access from the left femoral artery. The C-DSA was performed using various catheters, including the 5F Judkins Right (JR) 3.5 catheter from Merit Medical Systems, as well as the 5F Vertebral and 5F Headhunter catheters from Terumo Radio focus, Japan. The angiography procedure was conducted as follows, after the patient was diagnosed with ischemic stroke using a non-contrast computed tomography (CT) scan, catheter-based digital subtraction angiography (C-DSA) was performed. Access was typically obtained through the right or left femoral artery. Cerebral blood vessels were examined using an iodine-based contrast agent, with a concentration of approximately 320–370 mg iodine/mL, administered through a catheter. The radiation dose for cerebral angiographic procedures was generally maintained at approximately 250 milligray (mGy) per series, with imaging acquired at a rate of 2 frames per second. This dosage was carefully monitored to ensure patient safety. In cases involving more complex cerebral vasculature, the imaging frame rate was increased to 4–6 frames per second to enhance visualization. For particularly challenging vascular anatomy, roadmap guidance was employed using pedal fluoroscopy, which facilitated navigation while minimizing radiation exposure. Additionally, three-dimensional (3D) rotational angiography was performed in cases where standard imaging was insufficient to adequately analyze the cerebral vasculature. Contrast injection rates varied based on the target vessel. For the internal carotid artery (ICA) and middle cerebral artery (MCA), the injection rate was 4–6 mL/second, with a total volume of 8–10 mL. For the anterior cerebral artery (ACA), posterior cerebral

artery (PCA), basilar artery (BA), and vertebral artery (VA), the injection rate was 3–5 mL/second, with a total volume of 6–8 mL. After completing the C-DSA procedure, we assessed the degree of stenosis in the following arterial segments: the intracranial segment of the ICA, the proximal segments (M1 and M2) of the MCA, the A1 and A2 segments of the ACA, the P1 and P2 segments of the PCA, the BA, and the V4 segment of the VA. Stenosis was quantified by measuring the luminal diameter of the affected cerebral blood vessels. The study population comprised all patients diagnosed with ischemic stroke at Wahidin Sudirohusodo Hospital in Makassar who underwent C-DSA. To ensure a focused analysis, individuals diagnosed with hemorrhagic stroke and those with incomplete medical records were excluded from the study. This exclusion criteria were implemented to enhance the reliability of the findings by concentrating solely on ischemic stroke cases, which exhibit different clinical presentations and treatment pathways compared to hemorrhagic strokes. The research variables investigated in this study included age, gender, known risk factors, and the anatomical locations of ICAS within the intracranial vasculature. These variables are critical for understanding the demographic and clinical profiles associated with ICAS and their implications for stroke management. A detailed study flow is illustrated in Figure 1 below.

Results

A total of 236 patients who underwent C-DSA at the Neurology Catheterization Laboratory of Wahidin Sudirohusodo Hospital, Makassar, met the study criteria. In the retrospective study conducted in February 2023, out of 236 patients who underwent C-DSA between January 2021 and December 2022, 106 patients (44.9%) were found to have ICAS stenosis. The demographic characteristics of the study subjects showed an average age of 54.7 years (age range 35–80 years). The age distribution indicated that 20 patients (18.86%) were under 50 years old, 82 patients (77.35%) were between 50–70 years old, and 4 patients (3.77%) were over 70 years old. The majority of the subjects were males, with 62 males (58.4%) and 44 females (41.50%).

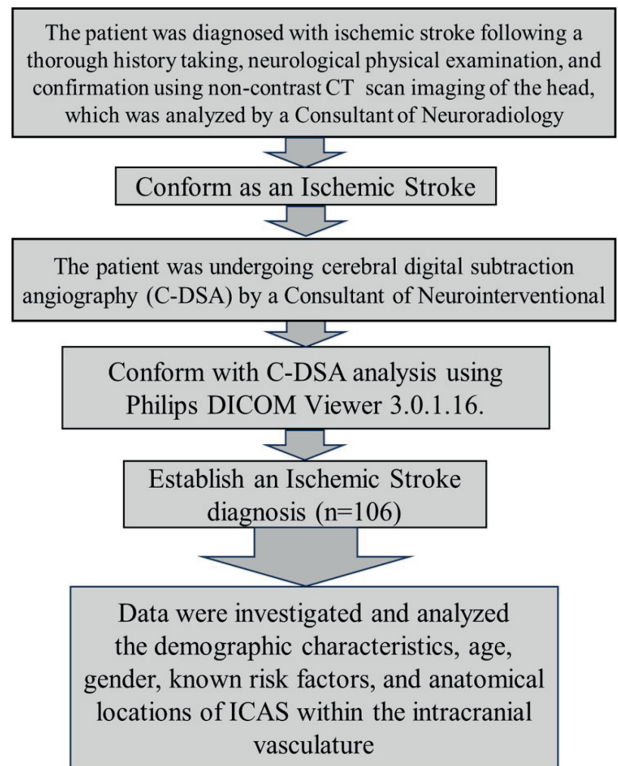


Figure 1. Study flow of clinical characterization and risk factor analysis of ICAS

Table 1. Age and Gender Distribution of ICAS Patients at Wahidin Sudirohusodo Central General Hospital, Makassar

Age Group	Number of Patients	Percentage (%)
<50 years	20	18.86
50-60 years	48	45.28
60-70 years	34	32.07
>70 years	4	3.77
Gender	Number of Patients	Percentage (%)
Male	62	58.40
Female	44	41.50

Table 1 presents the distribution of age and gender among ICAS patients at Wahidin Sudirohusodo Central General Hospital, Makassar. Among all the subjects in this study, the most prevalent stroke risk factor was hypertension, found in 75 patients (70.75%), followed by dyslipidemia in 49 patients (46.62%), diabetes mellitus (DM) in 24 patients (22.64%),

Table 2. Risk Factors for ICAS Patients at Wahidin Sudirohusodo Central General Hospital, Makassar

Risk Factor	Number of Patients	Percentage (%)
Hypertension	75	70.75
Diabetes Mellitus	24	22.64
Dyslipidemia	49	46.22
History of Previous Stroke/ transient ischemic attack (TIA)	19	17.92
History of Heart Disease	6	5.66
Comorbidity with ECAS	8	7.54

Table 3. Locations of ICAS in Intracranial Blood Vessels

Vessel	Number of Stenoses	Percentage (%)
ICA (Internal Carotid Artery)	17	12.68
MCA (Middle Cerebral Artery)	77	57.46*
ACA (Anterior Cerebral Artery)	4	2.98
PCA (Posterior Cerebral Artery)	9	6.71
BA (Basilar Artery)	23	17.16
VA (Vertebral Artery)	4	6.71

a history of previous stroke/ Transient ischemic attack (TIA) in 19 patients (17.92%), comorbidity with extracranial artery stenosis (ECAS) in 8 patients (7.54%), and a history of heart disease in 6 patients (5.66%).

Table 2 outlines the risk factors identified among ICAS patients at Wahidin Sudirohusodo Central General Hospital, Makassar. In this study, a total of 134 stenotic plaques were identified. Based on their locations, the highest number of stenoses was found in the MCA (77 plaques, 57.46%), followed by stenoses in the ICA (17 plaques, 12.68%), BA (17 plaques, 12.68%), posterior cerebral artery (PCA) (9 plaques, 6.71%), and Anterior cerebral artery (ACA) and vertebral artery (VA), each with 4 plaques (3.2%).

Table 3 shows the distribution of ICAS locations among various intracranial blood vessels.

This retrospective study involved patients with ICAS and revealed several cases illustrating the distribution of ICAS locations across various intracranial blood vessels (Figure 2, 3 and 4).

Discussion

Age is a non-modifiable traditional risk factor for ICAS and is associated with increased prevalence and severity of the condition. In this study, the majority of ICAS plaques were found in the age range of 50-60 years (45.28%), followed by 60-70 years (32.07%), <50 years (18.86%), and >70 years (3.77%). A cross-sectional study by Bae et al. involving patients aged 40 and above with cerebrovascular events found that age is an independent predictor of ICAS severity. As age increases, intracranial arteries become more susceptible to oxidative stress and inflammatory reactions due to hemodynamic, histological, and metabolic changes, leading to an increased buildup of plaques in the elderly. Atherosclerosis development follows a linear trend throughout the age spectrum. As age progresses, intracranial arteries respond to a gradual loss of elastic fibers and tunica media by forming collagenous tissue that replaces the muscle fibers in the vessel walls. In the fifth and sixth decades of life, necrosis and intimal thickening become prominent manifestations of ICAS. In the proximal segments of intracranial arteries, erythrocyte leakage, plaques with neovascularization, and intraplaque hemorrhage are observed, accompanied by the expansion of vasa vasorum in the vessel walls (4). In our study, we found that increasing age is not directly proportional to the incidence of intracranial atherosclerotic stenosis (ICAS). The lack of a direct correlation between increasing age and ICAS incidence in Makassar likely reflects a complex interplay of genetic predispositions, lifestyle and dietary habits, regional differences in vascular disease patterns, and study limitations. In this study, the number of males was 62 (52.40%), slightly more than the number of females at 44 (41.50%). These results align with several studies that show a gender disparity in the prevalence of atherosclerosis and stroke. Most studies indicate a higher prevalence of intracranial atherosclerosis in males compared to females. A retrospective multicenter study by Song et al. found a risk ratio of 1.5 (95% CI, 1.0-2.1) for males compared to females among treated patients. This is often linked to other demographic factors in males, such as smoking habits (5,6). The higher incidence of ICAS among males in Makassar can be attributed to a combination of

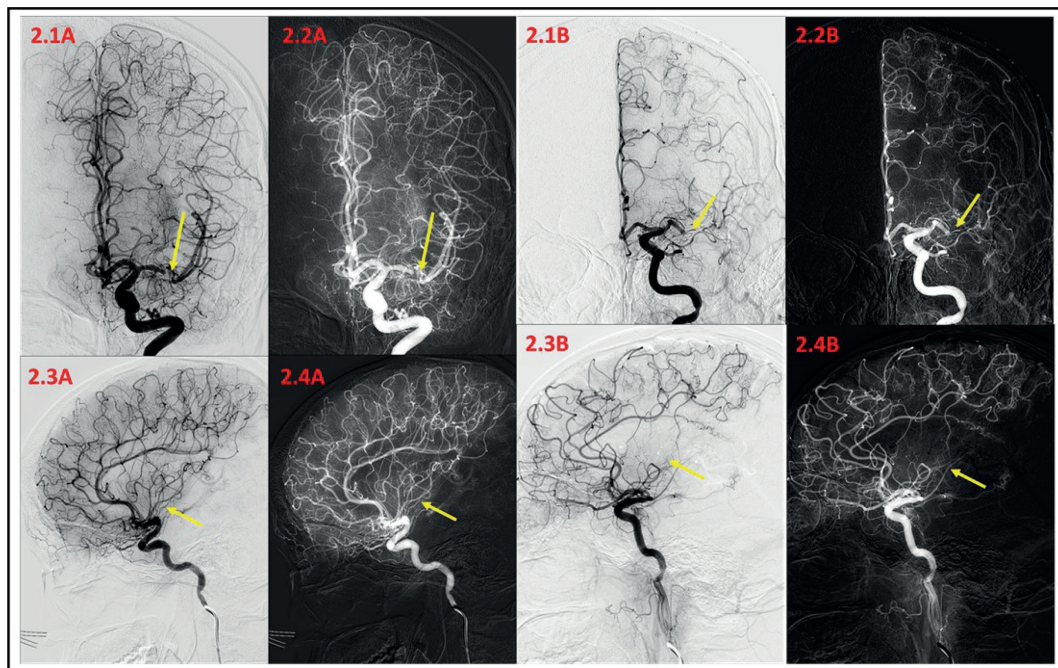


Figure 2. Cerebral Digital Subtraction Angiography of the Left Internal Carotid Artery (Lt-ICA). 2.1A. Anterior-posterior (AP) view of the Lt-ICA in the arterial phase, showing stenosis at the M1 segment of the Lt-MCA with sufficient collateral flow (indicated by yellow arrow); 2.2A. AP view of the Lt-ICA in the arterial phase, with stenosis at the M1 segment of the Lt-MCA and adequate collateral circulation visible in Roadmap imaging (yellow arrow); 2.3A. Lateral (Lat) view of the Lt-ICA in the arterial phase, demonstrating stenosis at the Lt-MCA M1 segment with adequate collateral flow (yellow arrow); 2.4A. Lat view of the Lt-ICA in the arterial phase, highlighting stenosis at the M1 segment of the Lt-MCA with good collateral flow on Roadmap imaging (yellow arrow); 2.1B. AP view of the Lt-ICA in the arterial phase, showing stenosis at the Lt-MCA M1 segment without significant collateral flow (yellow arrow); 2.2B. AP view of the Lt-ICA in the arterial phase, with stenosis at the Lt-MCA M1 segment and inadequate collateral flow, as shown in Roadmap imaging (yellow arrow); 2.3B. Lat view of the Lt-ICA in the arterial phase, illustrating stenosis at the M1 segment of the Lt-MCA without adequate collateral flow (yellow arrow); 2.4B. Lat view of the Lt-ICA in the arterial phase, depicting stenosis at the Lt-MCA M1 segment with insufficient collateral flow in Roadmap imaging (yellow arrow).

biological, lifestyle, and social factors. Habits such as smoking, dietary patterns, and stress are more prevalent among men, increasing their risk of ICAS. In this study, hypertension was identified as the most common risk factor among patients with ICAS. Numerous previous studies have shown a strong association between hypertension and ICAS. A retrospective multicenter case-control study by Hong et al., involving six hospitals in China, demonstrated elevated systolic blood pressure, diastolic blood pressure, and pulse pressure in patients with ICAS subtype stroke compared to non-ICAS patients. Specifically, systolic blood pressure (151.3 ± 23.9 mmHg), diastolic blood

pressure (85.2 ± 12.2 mmHg), and pulse pressure (66.1 ± 19.4 mmHg) were significantly higher in the ICAS group compared to the non-ICAS group (138.2 ± 17.6 mmHg, 82.0 ± 10.7 mmHg, and 56.1 ± 14.6 mmHg, respectively, with $p < 0.001$). The study also showed that for each 10 mmHg increase in systolic blood pressure, the unadjusted odds ratio for ICAS increased by 0.36 (OR = 1.36, 95% CI = 1.30-1.42, $p < 0.001$). After multivariate adjustment, the risk for ICAS increased by 0.32 (OR = 1.32, 95% CI = 1.26-1.38, $p < 0.001$) (6-8). The high rates of hypertension in Makassar align with the region's salt-heavy dietary patterns and its coastal nature, which

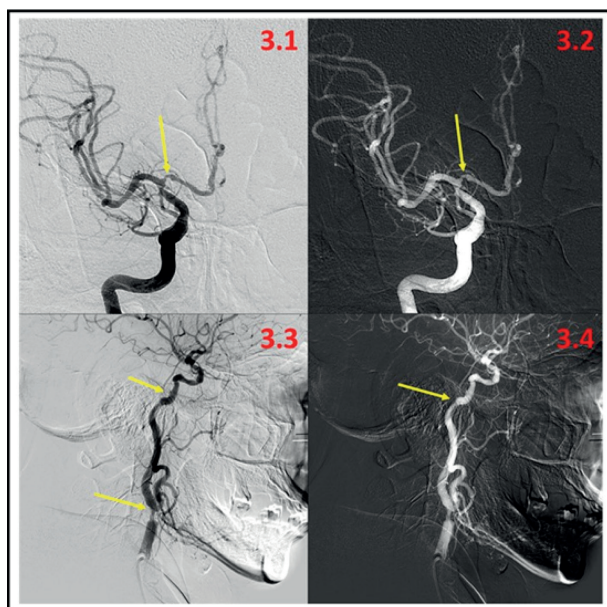


Figure 3. Cerebral Digital Subtraction Angiography of the Right Internal Carotid Artery (Rt-ICA). 3.1. AP view of the Rt-ICA in the arterial phase, showing stenosis at the A1 segment of the Rt-ICA with sufficient distal flow (indicated by yellow arrow); 3.2. AP view of the Rt-ICA in the arterial phase, highlighting stenosis at the A1 segment with adequate distal flow, as seen in Roadmap view (yellow arrow); 3.3. Lat view of the Rt-ICA in the arterial phase, demonstrating stenosis at the C1 segment and along the C3 segment of the Rt-ICA with adequate flow (yellow arrow); 3.4. Lat view of the Rt-ICA in the arterial phase, again showing stenosis at the C1 and C3 segments with sufficient flow (yellow arrow).

promotes the consumption of preserved and salty foods. Dyslipidemia was the second most common risk factor in this study, identified in 49 patients (46.22%). Dyslipidemia is defined based on levels of total cholesterol, triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and a history of lipid-lowering medication use. A meta-analysis conducted by Ma et al. on 131 studies concerning ICAS risk factors and demographic characteristics found that dyslipidemia is associated with a higher risk of ICAS (OR = 1.29, 95% CI = 1.04-1.59, $I^2 = 20\%$, $p = 0.29$). Elevated LDL levels were also linked to ICAS in the overall analysis (OR = 1.06, 95% CI = 1.00-1.12; $I^2 = 63\%$, $p = 0.04$). However, no association was found between ICAS risk and low HDL levels in that study. Another study by Jianxia et al. supported the relationship between dyslipidemia

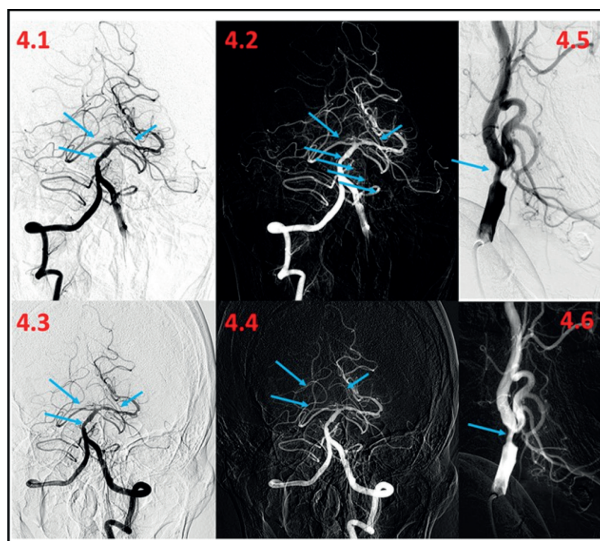


Figure 4. Cerebral Digital Subtraction Angiography of the Right and Left Vertebral Arteries (Rt-VA and Lt-VA). 4.1. AP view of the Rt-VA in the arterial phase, showing stenosis at the distal portion of the Rt-VA, along the basilar artery (BA), and in the right and left posterior cerebral arteries (Rt-PCA and Lt-PCA), with sufficient distal flow (indicated by blue arrow); 4.2. AP view of the Rt-VA in the arterial phase, highlighting stenosis at the distal Rt-VA, the BA, and Rt-PCA and Lt-PCA, with adequate distal flow shown in Roadmap view (blue arrow); 4.3. AP view of the Lt-VA in the arterial phase, showing stenosis at the distal Lt-VA, along the BA, and in the Rt-PCA and Lt-PCA, with sufficient distal flow (blue arrow); 4.4. AP view of the Lt-VA in the arterial phase, again demonstrating stenosis at the distal Lt-VA, the BA, and both posterior cerebral arteries (Rt-PCA and Lt-PCA) with sufficient distal flow in Roadmap view (blue arrow); 4.5. Lateral (Lat) view of the Rt-ICA in the arterial phase, showing stenosis at the C1 segment with adequate flow (blue arrow); 4.6. Lat view of the Rt-ICA in the arterial phase, demonstrating stenosis at the C1 segment with sufficient flow (blue arrow).

and ICAS. In a study of 110 patients with intracranial plaques, high LDL levels were associated with overall ischemic stroke incidence. When stratified by plaque enhancement grading, LDL levels were correlated with grade 1 plaque enhancement (OR = 6.778, 95% CI = 2.122-21.649, $p = 0.001$). LDL accumulation in the intima initiates the formation and progression of atherosclerosis. HDL plays a protective role as an anti-atherosclerotic agent by promoting cholesterol efflux from macrophages, inhibiting LDL oxidation, and reducing smooth muscle cell migration and platelet aggregation (9). DM is also a traditional risk factor for

ICAS. In this study, 24 patients (22.64%) had DM as a risk factor. According to a meta-analysis conducted by Ma et al., patients with DM have a 1.98-fold increased risk of developing ICAS compared to non-DM patients. Additionally, glycemic status and the duration of DM also influence the degree of stenosis. A cross-sectional study involving 1,644 participants from the Atherosclerosis Risk in Communities Study, who underwent magnetic resonance imaging (MRA), demonstrated this relationship. Regression analysis categorized ICAS into no stenosis, stenosis <50%, or stenosis >50%, showing that patients with DM duration exceeding 20 years had a higher degree of stenosis compared to non-DM patients. Furthermore, higher stenosis grades were observed in patients with diabetes duration of 10 to 20 years and >20 years compared to those with a duration of <10 years (OR 1.32 and 2.52, respectively). Several mechanisms are thought to contribute to the relationship between DM and ICAS. In hyperglycemic conditions, advanced glycation end products (AGEs) form through a non-enzymatic reaction between reducing sugar aldehyde groups and proteins, lipids, and nucleic acids. AGEs cause vascular damage and accelerate atherosclerotic plaque formation by altering the functional properties of extracellular matrix molecules in blood vessels or by activating cell-dependent receptor signaling pathways (10-14). The high prevalence of DM and dyslipidemia in Makassar is driven by an interplay of dietary habits, urbanization, genetic predispositions, and socio-economic factors. Addressing these issues will require targeted public health interventions, including dietary education, promotion of physical activity, and accessible healthcare services to encourage routine screening and early management of these conditions. This study also describes the number of patients with a history of stroke or TIA and comorbidities with ECAS in ICAS patients. It was found that 19 patients (17.92%) had a history of stroke, and 8 patients (7.54%) had comorbid ECAS. In a study by Nidawi et al. involving 123 ICAS patients, 44 patients (35.8%) had a history of stroke/TIA, and 28 patients (22.8%) had comorbid ECAS. These numbers are higher than those found in the current study. ICAS is a significant risk factor for stroke recurrence in patients with ischemic stroke or TIA. The WASID study identified modifiable risk factors

related to ICAS for recurrence, such as increased blood pressure and cholesterol levels. Specifically, blood pressure >140 mmHg and cholesterol levels >200 mg/dL were most strongly correlated with stroke recurrence. Patients with ECAS are also thought to have a higher prevalence of ICAS. This is due to atherosclerotic disease being a systemic condition that affects multiple blood vessels in different locations (15,16). In this study, the distribution of plaque locations, from highest to lowest frequency, was as follows: MCA, basilar artery (BA), ICA, PCA, and then ACA and VA with equal numbers. These findings are consistent with research on ICAS in Asian populations, where the MCA is the most frequently involved vessel. In contrast, in European populations, where ICAS prevalence is much lower than in Asia, the ICA is the vessel most commonly affected. The history of TIA provides a critical clue or warning that the likelihood of developing ICAS is a comorbid factor that should not be underestimated. Most of the plaques in these cases are formed in the MCA. This raises significant questions and presents an opportunity for further research to better understand this phenomenon. However, a notable limitation of our study is that it involved only a single center. Future studies should include a broader scope, particularly investigating the genetic predispositions of the population in our city regarding the incidence of ICAS.

Conclusion

This study underscores the multifaceted risk factors contributing to the development of ICAS, highlighting age as a pivotal non-modifiable factor, with the highest prevalence observed among individuals aged 50–70 years due to vascular alterations driven by oxidative stress and inflammation. Male predominance in ICAS cases may be linked to lifestyle factors such as smoking and hypertension. Among modifiable risk factors, hypertension emerged as the most significant contributor, as even minor blood pressure elevations can markedly accelerate plaque formation. Dyslipidemia further exacerbates the condition, with elevated LDL levels fostering plaque accumulation and HDL providing a protective effect. Diabetes mellitus also plays a critical

role, as prolonged disease duration and poor glycemic control promote vascular stenosis through mechanisms such as advanced glycation end-product formation. Plaque formation predominantly affects the MCA, particularly in Asian populations, suggesting the influence of genetic and environmental factors on disease distribution. These findings emphasize the intricate interplay between modifiable and non-modifiable risk factors in ICAS pathogenesis, underscoring the need for targeted prevention and management strategies.

Ethic Approval: All research designs were reviewed and approved by the Health Research Ethics Committee of Dr Wahidin Sudirhusodo Hospital – Faculty of Medicine, Hasanuddin University (10794/UN4.6.8/PT.01.04/2023) on May 8, 2023.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: MYA (Concept, Design, Supervision, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript), IH (Concept, Design, Analysis and Interpretation, Literature Search), and MFH (Concept, Design, Analysis and Interpretation, Literature Search). All authors read and approved the final version of the manuscript.

Declaration on the Use of AI: none.

Consent for Publication: All subjects have provided consent for publication.

Acknowledgments: Not applicable.

Funding: This research received no external funding.

Data Availability Statement: All the data are available from the corresponding author upon a reasonable request [MYA].

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Correspondence:

Received: 21 November 2024

Accepted: 23 December 2024

Muhammad Yunus Amran, M.D., Ph.D., FIPM, FINR, FINA

Division of Interventional Neurology and Neuroendovascular Therapy, Department of Neurology, Faculty of Medicine, Hasanuddin University,

Brain Centre, Dr. Wahidin Sudirohusodo General Hospital, and Hasanuddin University Teaching Hospital, Jl. Perintis Kemerdekaan KM 11, 90245, Makassar, South Sulawesi, Indonesia.

E-mail: muhyunusamran@med.unhas.ac.id;

yunusamran10@gmail.com

ORCID: 0000-0001-5079-7490