

Common Carotid Artery Intima–Media Thickness and Intracranial Atherosclerotic Disease (ICAD) as Predictors of Short-Term Major Adverse Cardiovascular Events (MACE) in Non-Hemorrhagic Stroke

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ABSTRACT

Background: Non-hemorrhagic stroke (NHS) is a leading cause of global morbidity and mortality, with intracranial atherosclerotic disease (ICAD) as an important etiology. Intima–media thickness (IMT) is widely used as an early marker of atherosclerosis in both cerebral and coronary circulation. However, evidence on IMT and ICAD as predictors of short-term major adverse cardiovascular events (MACE) after NHS, and their mutual relationship, remains limited and inconsistent. **Objective:** This study aimed to evaluate the ability of common carotid artery IMT and ICAD to predict 90-day MACE in NHS patients, to determine a reliable IMT cutoff, and to assess the association between IMT and ICAD in this population. **Methods:** This prospective cohort study enrolled NHS inpatients at RSUP Prof. dr. I.G.N.G. Ngoerah. IMT was measured at admission by carotid ultrasonography, and ICAD was assessed with angiography imaging according to the hospital's clinical protocol. Patients were followed for 90 days for MACE. The optimal IMT cutoff was identified using receiver operating characteristic (ROC) analysis. Associations of IMT and ICAD with MACE, and IMT with ICAD, were tested using proportion comparisons. Survival was analyzed with Kaplan–Meier curves and the log-rank test. Independent predictors were identified using multivariable Cox regression and reported as adjusted hazard ratios (AHRs). **Results:** 52 patients were included in this study. The optimal IMT cutoff to predict MACE was 0.82 mm (AUC 0.717; sensitivity 72.7%; specificity 68.3%). On chi-square analysis, higher IMT (RR 3.9; 95% CI 1.17–13.14; $p=0.014$) and ICAD (RR 4.6; 95% CI 1.34–15.39; $p=0.005$) were associated with 90-day MACE. IMT was not significantly associated with ICAD (RR 1.64; 95% CI 0.80–3.33; $p=0.172$). In multivariable analysis, elevated IMT was an independent predictor of short-term MACE (AHR 13.10; 95% CI 1.03–166.93; $p=0.047$), whereas ICAD was not an independent risk factor after adjustment (AHR 5.06; 95% CI 0.76–33.68; $p=0.094$). Additional independent predictors were atrial fibrillation (AHR 20.81; $p=0.008$), NIHSS severity (AHR 6.99; $p=0.040$), left-ventricular ejection fraction (AHR 0.89 per 1%; $p=0.007$; protective), and leukocyte count (AHR 1.42 per $10^9/L$; $p=0.028$). **Conclusion:** IMT at admission is an independent predictor of 90-day MACE in NHS patients. ICAD shows clinical relevance but is not an independent risk factor after adjustment, likely due to the limited number of events and collinearity with other covariates. No significant association between IMT and ICAD was observed. These findings support IMT for early risk stratification and underline the need for larger studies to validate the role of ICAD as a short-term MACE risk factor in the NHS.

Keywords: intima-media thickness; intracranial atherosclerotic disease; major adverse cardiovascular events

INTRODUCTION

Atherosclerosis is the primary pathophysiological process behind most cardiovascular diseases, including coronary and carotid vascular events. The transition from atherosclerotic plaque to vulnerable plaque prone to thrombosis is recognized as a leading cause of mortality and disability worldwide,

accounting for almost 46% of deaths in developed nations [1,2]. The disease often begins early in life, remaining asymptomatic and undetected for extended periods before advancing to critical stages [1]. Early identification and management are therefore key to reducing its global health impact.

Atherosclerotic lesions are characterized by the accumulation and transformation of lipids, inflammatory mediators, smooth muscle cells, and necrotic debris in the tunica intima beneath endothelial cells that line blood vessels [3]. These changes are marked by pathological intimal thickening, extensive macrophage infiltration, and formation of advanced atheromatous plaques with a necrotic core, which increases the risk of plaque rupture and acute arterial thrombosis, potentially causing myocardial infarction or cerebral stroke [3,4]. Imaging modalities such as 2D ultrasonography, MDCT, and MRI are crucial for evaluating rupture-prone plaques [3].

Stroke, representing the cerebrovascular endpoint of atherosclerosis, is the second leading cause of disability and death globally, with non-hemorrhagic (ischemic) stroke as the predominant subtype [5,6]. Recent years have seen an increasing incidence and economic burden from stroke, notably in Southeast Asia and Indonesia, where stroke prevalence and related costs for younger adults are significant [7]. Ischemic stroke and intracerebral hemorrhage remain the major causes, showing high prevalence in population-based studies [8].

One major cause of ischemic stroke is Intracranial Atherosclerotic Disease (ICAD), with higher prevalence noted in East Asian populations and non-white groups in the United States [9,10]. ICAD not only raises stroke risk, including recurrence rates over 20% in those with severe stenosis, but also increases risk for dementia and cognitive decline. Stroke recurrence is frequent even with maximal medical therapy [11]. Mechanisms include plaque rupture, in situ thrombosis, embolization, hemodynamic compromise, and branch artery occlusion [9].

Carotid artery Intima-Media Thickness (IMT), measured by 2D ultrasound, is a validated tool for predicting cardiovascular risk. Increased IMT strongly correlates with future cardiovascular events and is recommended for risk stratification in asymptomatic moderate-risk individuals [12,13]. IMT also enables therapy monitoring, such as assessing statin effects, which helps guide prevention strategies. Despite this, the relationship among IMT, ICAD, and major adverse cardiovascular events (MACE) after non-hemorrhagic stroke remains limited and sometimes contradictory, warranting further investigation into their predictive value [14–17].

METHOD

This study utilized a prospective cohort observational design, conducted at RSUP Prof. dr. I.G.N.G. Ngoerah Denpasar between February and August 2025. The primary variables assessed at initial admission were the common carotid artery

Intima-Media Thickness (IMT) and presence of Intracranial Atherosclerotic Disease (ICAD), with no prior major adverse cardiovascular events (MACE) or ICAD diagnosis in participants. Patients were followed longitudinally during hospitalization and for 90 days post-discharge to monitor the occurrence of MACE.

The target population included all patients diagnosed with non-hemorrhagic stroke (NHS) admitted during April–May 2025. Using consecutive non-probability sampling, 52 patients meeting the inclusion criteria (age >18 years, first-time NHS admission) were enrolled after informed consent. Exclusion criteria eliminated patients with hemorrhagic stroke history, prior NHS or transient ischemic attack, acute coronary syndrome, significant coronary artery disease, severe valve disease, high NYHA class heart failure, severe infection, advanced chronic kidney disease or dialysis, malignancy, autoimmune diseases, pregnancy, or refusal to participate.

IMT measurements were obtained via Doppler ultrasound at both carotid arteries during the first emergency room contact, using automated digital measurement software. ICAD was diagnosed from clinical imaging (CT angiography, MR angiography, DSA, or transcranial Doppler). MACE outcomes, defined as all-cause mortality, unstable angina, acute myocardial infarction, stroke, and acute heart failure, were monitored and confirmed through medical records, laboratory tests, imaging, and clinical exams.

Data analysis included descriptive statistics to characterize sociodemographic and clinical variables. Receiver Operating Characteristic (ROC) curves determined optimal IMT cutoff values for predicting MACE and ICAD. Chi-square tests compared MACE incidence across IMT and ICAD categories, expressed as relative risk. Kaplan-Meier survival analysis and log-rank tests evaluated time-to-event differences. Multivariable Cox regression adjusted for confounders, identifying independent predictors reported as adjusted hazard ratios. Statistical significance was set at $p < 0.05$, using SPSS 27 for computations. This methodological approach ensured robust assessment of IMT and ICAD predictive value for short-term cardiovascular events post-NHS.

RESULT

Receiver Operating Characteristic (ROC) Curve Analysis

To determine the optimal cut-off value for Intima-Media Thickness (IMT), a Receiver Operating Characteristic (ROC) curve analysis was performed. The cut-off value distinguishes high (abnormal) IMT based on data from this study (see Figure 1).

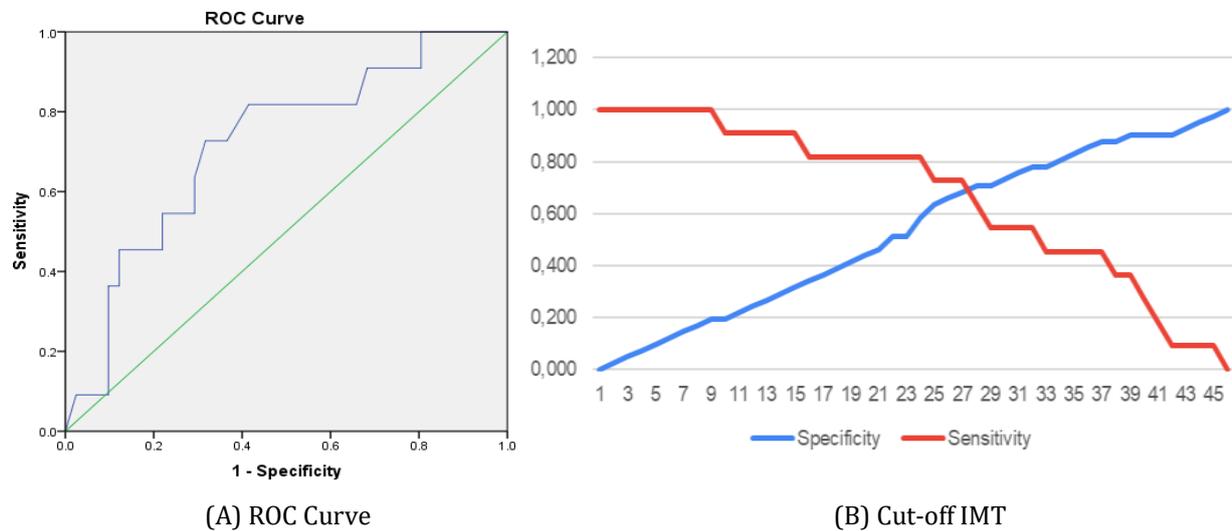


FIGURE 1: (A) ROC curve analysis result; (B) Graph of IMT cut-off point determination.

Based on the ROC curve analysis, the optimal cut-off point for defining high IMT to predict outcome was 0.82 mm, balancing sensitivity and specificity. At this cut-off, sensitivity was 72.7%, specificity 68.3%, with an Area Under the Curve (AUC) of 0.717 (Table 1). Using this cut-off, 21 patients were classified as high IMT, and 31 as low IMT.

TABLE 1: AUC, Sensitivity, and Specificity of IMT as Predictor of MACE.

Variable	AUC	95% CI	Sensitivity (%)	Specificity (%)	p-value
Intima-Media Thickness	0.717	0.550 - 0.885	72.7	68.3	0.028*

*Statistically significant.

Subject Characteristics by IMT Category

Subjects were divided into two groups based on the IMT cut-off of 0.82 mm. Descriptive analysis of sociodemographic, clinical history, and supporting examinations was performed.

Basic Characteristics

TABLE 2: Basic Characteristics by IMT Category.

Variable	IMT High (≥ 0.82) n=21	IMT Low (< 0.82) n=31	p-value
Age (mean \pm SD)	59.76 \pm 11.03	55.9 \pm 15.24	0.328
Male sex, n (%)	15 (44.1)	19 (55.9)	0.451
Hypertension history, n (%)	18 (51.4)	17 (48.6)	0.020**
Diabetes Mellitus, n (%)	6 (60.6)	4 (40.0)	0.160
Dyslipidemia, n (%)	1 (33.3)	2 (66.7)	0.798
Smoking history, n (%)	10 (43.5)	13 (56.5)	0.686
Alcohol consumption, n (%)	2 (100.0)	0 (0)	0.080
Family history, n (%)	10 (40.0)	15 (60.0)	0.957
BMI (mean \pm SD)	23.27 \pm 3.35	24.95 \pm 4.63	0.160

*p \leq 0.05; ** significant.

Hypertension was significantly more common in the high IMT group (p=0.020).

Clinical Characteristics

TABLE 3: Clinical Characteristics by IMT Category.

Variable	IMT High (≥ 0.82)	IMT Low (< 0.82)	p-value
Stroke onset (hours) Median (Range)	14 (1-96)	22 (1-145)	0.291
NIHSS score (moderate-severe) n (%)	4 (57.1)	3 (42.9)	0.420
Glasgow Coma Scale (GCS) Median (Range)	15 (5-15)	15 (10-15)	0.070
Mean Arterial Pressure (MAP) Mean \pm SD	127.00 \pm 21.93	109.83 \pm 21.62	0.007**
Atrial fibrillation, n (%)	3 (30.0)	7 (70.0)	0.456

Higher MAP was significantly associated with higher IMT (p=0.007).

Supporting Examination Characteristics

TABLE 4: Laboratory, Echocardiography, and Ultrasound by IMT Category.

Variable	IMT High (≥ 0.82) Mean/Median	IMT Low (< 0.82) Mean/Median	p-value
Hemoglobin (g/dL)	13.19 \pm 3.09	13.79 \pm 1.71	0.427
White blood cell count ($\times 10^3$)	11.16 \pm 3.06	9.95 \pm 4.14	0.259
Platelet count ($\times 10^3$)	297 (173-548)	257 (58-706)	0.233
LDL Cholesterol (mg/dL)	133 (35-251)	118 (33-263)	0.259
Triglycerides (mg/dL)	114 (59-336)	88 (40-218)	0.062
Fasting Blood Glucose (mg/dL)	100 (65-370)	84 (44-260)	0.095
Left ventricular ejection fraction (LVEF) %	56 (19-68)	58 (23.5-70)	0.556
Carotid plaque present, n (%)	14 (66.7)	12 (38.7)	0.048**

Presence of carotid plaques was significantly higher in the high IMT group (p=0.048).

Major Cardiovascular Events (MACE) by Subject Characteristics
MACE by Basic Characteristics

TABLE 5: MACE Incidence by Basic Characteristics.

Variable	With MACE (n=11)	Without MACE (n=41)	p-value
Age (mean \pm SD)	62.45 \pm 10.03	56.14 \pm 14.35	0.178
Male sex, n (%)	8 (23.5)	26 (76.5)	0.727
Hypertension, n (%)	10 (28.6)	25 (71.4)	0.078
Diabetes Mellitus	3 (30.0)	7 (70.0)	0.424
Dyslipidemia	1 (33.3)	2 (66.7)	0.518
Smoking	7 (30.4)	16 (69.6)	0.182
BMI (mean \pm SD)	22.06 \pm 1.40	24.87 \pm 4.51	0.010**

BMI was significantly lower in the MACE group (p=0.010).

MACE by Clinical Characteristics

TABLE 6: MACE by Clinical Parameters.

Variable	With MACE (n=11)	Without MACE (n=41)	p-value
NIHSS severity (moderate-severe) n (%)	5 (71.4)	2 (28.6)	0.003**
Glasgow Coma Scale (median)	13 (5-15)	15 (1-15)	0.004**
MAP (mean \pm SD)	122.36 \pm 28.67	115.26 \pm 21.61	0.372
Atrial Fibrillation	4 (40.0)	6 (60.0)	0.190

MACE by Supporting Examinations

TABLE 7: MACE by Laboratory and Imaging.

Variable	With MACE (n=11)	Without MACE (n=41)	p-value
White blood cells (mean)	12.43 \pm 4.60	9.90 \pm 3.36	0.047**
Hemoglobin	12.97 \pm 3.01	13.70 \pm 2.17	0.364
LDL Cholesterol	108 (35-242)	123 (33-263)	0.335
Carotid plaque present	4 (15.4)	22 (84.6)	0.308

Correlation of MACE with High IMT and ICAD Status

TABLE 8: MACE Incidence by IMT and ICAD.

Variable	With MACE (n=11)	Without MACE (n=41)	Relative Risk (RR)	95% CI	p-value
IMT ≥ 0.82 mm	8 (38.1%)	13 (61.9%)	3.9	1.17 - 13.14	0.014**
IMT < 0.82 mm	3 (9.7%)	28 (90.3%)			
ICAD significant stenosis	8 (42.1%)	11 (57.9%)	4.6	1.34 - 15.39	0.005**
ICAD non-significant stenosis	3 (9.1%)	30 (90.9%)			

Both high IMT and significant ICAD stenosis are associated with increased MACE risk.

ICAD Status According to IMT

TABLE 9: ICAD by IMT Category.

Variable	Significant ICAD Stenosis (n=19)	Non-significant Stenosis (n=33)	RR	95% CI	p-value
IMT ≥ 0.82 mm	10 (47.6%)	11 (52.4%)	1.64	0.80 – 3.33	0.172
IMT < 0.82 mm	9 (29.0%)	22 (71.0%)			

The trend of higher ICAD in the high IMT group is present but not statistically significant.

Survival Analysis for MACE by IMT

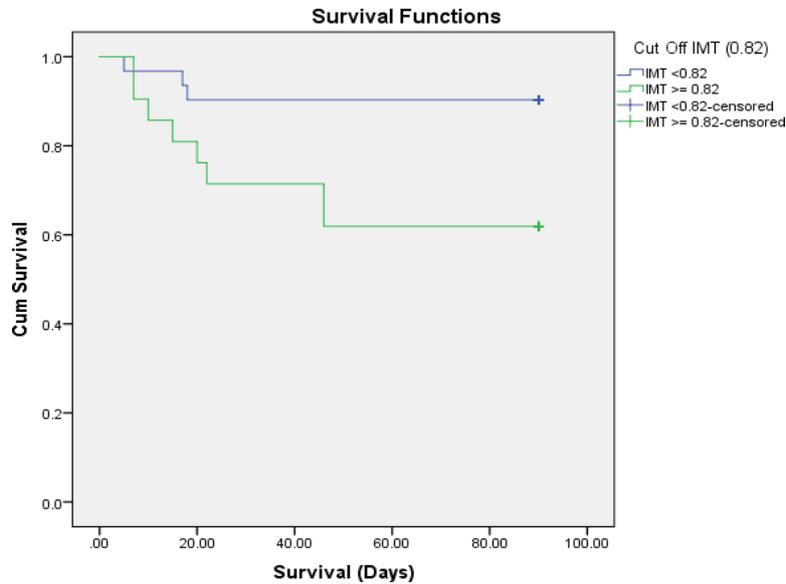


FIGURE 2: Kaplan-Meier survival estimation curve of major cardiovascular events (MACE) occurrence in non-hemorrhagic stroke patients based on Intima-Media Thickness (IMT) values.

TABLE 10: Mean Survival Time by IMT.

Variable	Mean Survival Time (days)	95% CI	90-day Survival Rate	p-value
IMT ≥ 0.82 mm	63.95	49.21 – 78.69	61.9%	0.016*
IMT < 0.82 mm	82.58	74.57 – 90.58	90.3%	

High IMT significantly correlates with shorter MACE-free survival.

Survival Analysis for MACE by ICAD

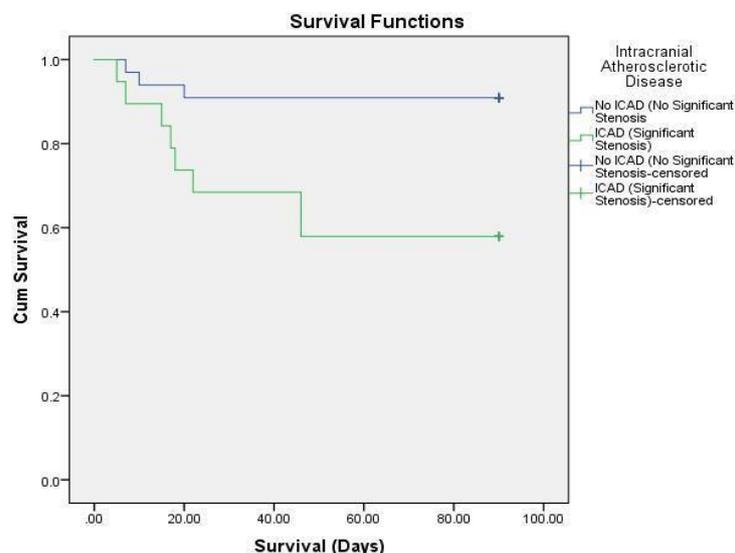


FIGURE 3: Kaplan-Meier survival estimation curve of major cardiovascular events (MACE) occurrence in non-hemorrhagic stroke patients based on the presence or absence of Intracranial Atherosclerotic Disease (ICAD).

TABLE 11: Mean Survival Time by ICAD.

Variable	Mean Survival Time (days)	95% CI	90-day Survival Rate	p-value
Significant stenosis	61.37	45.65 – 77.07	57.9%	0.005*
Non-significant stenosis	82.94	75.30 – 90.58	90.9%	

ICAD significantly reduces survival free of MACE.

Types of MACE by IMT Category

TABLE 12: MACE Types by IMT.

Variable	IMT \geq 0.82 (n=21)	IMT < 0.82 (n=31)	p-value
All-cause mortality	5 (23.8%)	3 (9.7%)	0.026**
Recurrent stroke	3 (14.3%)	0 (0%)	
Unstable angina	0 (0%)	0 (0%)	
Acute heart failure	0 (0%)	0 (0%)	
Myocardial infarction	0 (0%)	0 (0%)	

Multivariate Cox Regression Analysis of IMT, ICAD, and MACE

After controlling for covariates (age, gender, family history, hypertension, smoking, dyslipidemia, alcohol, diabetes), high IMT independently predicted MACE with an adjusted hazard ratio (HR) of 13.10 (95% CI: 1.03–166.93; p=0.047).

TABLE 13: Multivariate Cox Regression Analysis of IMT, ICAD, and MACE.

Variable	Adjusted HR	95% CI	p-value
Atrial fibrillation	20.81	2.17 – 199.28	0.008
Leukocyte count	1.42	1.04 – 1.94	0.028
NIHSS severity	6.99	1.09 – 44.80	0.040
Left ventricular ejection fraction (LVEF)	0.89	0.82 – 0.96	0.007
ICAD	5.06	0.76 – 33.68	0.094

DISCUSSION

This study used ROC curve analysis to assess the value of common carotid artery Intima-Media Thickness (IMT) in predicting short-term major cardiovascular events (MCE) in non-hemorrhagic stroke patients over 90 days. The analysis found an AUC of 0.717 with an optimal IMT cut-off of 0.82 mm, yielding a sensitivity of 72.7% and specificity of 68.3%. According to Hosmer, Lemeshow, and Sturdivant (2013), this AUC reflects a fair level of discrimination, indicating that IMT moderately identifies patients at risk of major cardiovascular events in this clinical setting [18]. These findings align with earlier studies, such as Nambi et al. (2012) in the ARIC study, which reported an AUC of 0.68 for IMT in predicting coronary events, and Polak et al. (2011), who found a similar AUC of 0.70 for cardiovascular outcomes [19–21]. Additionally, Asian populations show comparable results, with Chien et al. (2008) reporting an AUC of 0.79, and Kasliwal et al. (2016) an AUC of 0.75, affirming IMT's consistent predictive value despite minor differences due to ethnicity, risk factors, and imaging techniques [22,23]. Overall, despite not reaching an excellent predictive threshold (>0.8), IMT remains a valuable non-invasive screening tool for stratifying stroke patients' vascular risk and guiding preventive therapy.

The study included 52 patients newly diagnosed with non-hemorrhagic stroke, revealing that those with higher IMT (\geq 0.82 mm) had higher prevalence of hypertension and elevated mean arterial pressure on admission, consistent with the association of blood pressure and arterial wall remodeling documented by Lim et al. (2009) and others [24]. Higher IMT also corresponded with more frequent carotid plaques, evidencing progression from early vascular thickening to advanced atherosclerosis, supporting prior research by Polak et al. (2011) and Nambi et al. (2012) on the linked nature of IMT increase and plaque formation [20,21].

Among the cohort, 21.2% experienced major cardiovascular events during follow-up, and those with events were generally older, had lower BMI consistent with the "obesity paradox" noted in vascular literature [25], and exhibited more severe neurological deficits reflected by higher NIHSS and lower Glasgow Coma Scale (GCS) scores. Elevated white blood cell counts in this group underscored the inflammatory role in cardiovascular pathology and poorer stroke outcomes.

The study demonstrated that high IMT and the presence of significant intracranial atherosclerotic disease (ICAD) were strongly associated with higher risk of major cardiovascular events, mirroring

results from large-scale cohort studies such as the Cardiovascular Health Study and meta-analyses establishing IMT as a systemic atherosclerosis marker predictive of myocardial infarction and stroke [26,27]. ICAD's significance aligns with clinical trials such as WASID and SAMMPRIS, emphasizing intracranial stenosis as a potent risk enhancer for recurrent events.

Although a greater proportion of ICAD was observed in patients with higher IMT, this link did not reach statistical significance, likely due to small sample size, varied imaging modalities, and the cross-sectional nature of ICAD assessment. Survival analysis via Kaplan–Meier curves revealed significantly shorter event-free survival in patients with higher IMT, reinforcing IMT's prognostic value in the acute stroke period. Similarly, significant ICAD is related to poorer short-term survival, reinforcing the high-risk nature of intracranial stenosis.

Multivariate Cox regression analysis found that high IMT independently predicted major cardiovascular events with an adjusted hazard ratio of 13.10 after adjusting for confounders, including age, hypertension, atrial fibrillation, leukocytosis, and left ventricular ejection fraction. Atrial fibrillation and NIHSS severity also independently increased risk, while higher ejection fraction was protective, underscoring the multifactorial nature of risk in this population.

Notable limitations include the small sample size and low event count, increasing the risk of overfitting and broad confidence intervals, coupled with single-center recruitment, limiting generalizability. Additionally, ICAD was assessed only on admission without longitudinal imaging, and varied imaging techniques could reduce lesion detection accuracy. The 90-day follow-up period limits understanding of the longer-term prognostic implications of IMT. Accordingly, future studies with larger multicenter cohorts, standardized imaging protocols, and extended follow-up are needed to validate these findings and better delineate IMT's and ICAD's roles in stroke prognosis.

CONCLUSION

This prospective cohort study evaluated the value of Intima-Media Thickness (IMT) and Intracranial Atherosclerotic Disease (ICAD) as predictors of short-term major adverse cardiovascular events (MACE) within 90 days in non-hemorrhagic stroke patients admitted to RSUP Prof. dr. I.G.N.G. Ngoerah. The study found that IMT measured at admission was an independent predictor of short-term MACE, while ICAD showed clinical relevance but lacked a statistically significant association. Furthermore, no significant relationship was found between IMT values and ICAD findings in these patients.

Based on these findings, IMT can be effectively applied for risk stratification of non-hemorrhagic stroke patients during hospitalization, whether under conventional therapy or percutaneous intervention, as a predictor of short-term MACE.

Although ICAD may also aid risk stratification and therapeutic decision-making, further research with larger multicenter samples, longer follow-up, standardized ICAD assessment, and more precise IMT categorizations is recommended to better confirm these roles and improve prognostic accuracy.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

FUNDING

This research did not receive funding from the government or other private sectors.

ETHICS IN RESEARCH

This research received approval from the research ethics committee of Prof. Dr. IGNG Ngoerah Hospital/Faculty of Medicine, Udayana University.

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