

Association between Carotid Intima-Media Thickness (CIMT) and Alzheimer's Disease Detected by ^{99m}Tc - ECD SPECT of Brain

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ABSTRACT

Background: Single-photon emission computed tomography (SPECT) imaging of brain has emerged as a well-established and non-invasive technique for diagnosing dementia, specifically its primary subtype, Alzheimer's disease (AD). Recent research suggested a potential correlation between the increased intima-media thickness of the carotid artery and the onset of AD. The primary objective of this study is to assess the association between carotid intima-media thickness (CIMT) measured by 2D ultrasound of the carotid artery and AD, detected by Brain SPECT imaging with ^{99m}Tc -Ethyl Cysteinate Dimer (^{99m}Tc ECD).

Patients and Methods: This cross-sectional study was conducted at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS) between March 2021 to June 2022. Ethical approval was obtained from Medical Research Ethics Committee (MREC). The study included 65 patients with suspected or confirmed dementia. Data collection included Mini Mental State Examination (MMSE) score of neurology and associated laboratory reports. All the participants underwent 2D ultrasonography of carotid artery to measure carotid intima-media thickness (CIMT) and a brain SPECT with ^{99m}Tc -ECD followed by image interpretations using the easy Z score imaging system (eZIS).

Result: The mean age of the study population was 63.8 ± 9.5 years, with a male predominance (69.2%). The most prevalent comorbidities were hypertension and dyslipidemia (24.6%) and diabetes mellitus (13.8%). The majority of patients scored in the 25–27 range on the MMSE. Regarding CIMT, 40% of patients had moderate CIMT, 35.4% had normal CIMT, and 24.6% had mildly increased CIMT. Brain SPECT results indicated that 69.2% of patients had Alzheimer's disease (AD), while 30.8% had dementia other than AD. Among AD patients, 71.1% had mild AD, 20.0% had moderate AD, and 8.9% had severe AD. An unpaired t-test revealed a slightly higher mean CIMT value in AD patients (1.28 ± 0.58 mm vs. 1.25 ± 0.60 mm, $p = 0.873$), though this difference was not statistically significant. Conversely, ANOVA and Pearson's correlation tests demonstrated a statistically significant association between CIMT and the severity of AD, as represented by the Z-score ($r = +0.693$, $p < 0.001$).

Conclusion: The study highlights the significance of carotid intima-media thickness (CIMT) in Alzheimer's disease (AD) and non-AD patients, suggesting its use in initial assessment and follow-up measures.

Keywords: Carotid IMT, Brain SPECT, AD, Dementia

Bangladesh J. Nucl. Med. Vol. 27 No. 1 January 2024

DOI: <https://doi.org/10.3329/bjnm.v27i1.71507>

INTRODUCTION

Dementia is a condition characterized by memory loss and significant cognitive decline that disrupts daily functioning. According to the 2021 Alzheimer's Disease Facts and Figures report, 60 to 80 percent of dementia cases stem from Alzheimer's. The prevalence of the disease increases with age, affecting 3% of individuals aged 65 to 75, 17% of those aged 75 to 84, and 32% of individuals beyond 84 years old (1).

The global improvement in healthcare systems has led to a notable demographic shift, particularly in the developed world with an aging population. This trend is also observed in developing nations, as reflected in the increasing life expectancy. For example, the current average life expectancy in Bangladesh is 74.7 years (2). As people live longer, their physiological systems naturally decline, and dementia becomes a significant concern due to its impact on quality of life and identity. The early signs of dementia, such as difficulty recalling simple words, are often subtle.

In 2020, according to World Health Organization (WHO) (3) data, Alzheimer's disease and dementia accounted for

2.09% of all deaths in Bangladesh, with the country ranked 142 globally and an age-adjusted death rate of 13.89 per 100,000 population (4).

To assess the prevalence of dementia in Bangladesh, a survey conducted by the National Institute of Neurosciences and Hospitals (NINS) and the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) from April to September 2019 revealed alarming findings. The study indicated that 1 in every 12 Bangladeshis over 60 years old has dementia. Without adequate intervention, the study predicts a potential increase to 1.37 million cases in 2025, doubling by 2041, and potentially escalating even further.

Beta-amyloid ($A\beta$) plaques and phosphorylated tau neurofibrillary tangles are recognized neuropathological markers of Alzheimer's disease (5, 6). Emerging research suggests that vascular disease may also contribute to Alzheimer's disease (AD) development. A meta-analysis exploring the link between atherosclerosis and AD indicated that, while specific mechanisms remain unclear, vascular pathology might influence AD by diminishing cerebral blood flow and impeding $A\beta$ clearance (7). Carotid intima-media thickness (CIMT), a gauge of carotid atherosclerosis measured through 2D ultrasonography, serves as a sensitive indicator (8). CIMT is often employed in clinical settings due to its simplicity, reproducibility, and non-invasive nature. Numerous studies have demonstrated its effectiveness in predicting cardiovascular disease risk and progression (9, 10).

A comprehensive review and meta-analysis revealed significantly higher CIMT in groups with dementia and mild cognitive impairment (MCI) compared to those without cognitive impairment (7). Additionally, patients with Alzheimer's disease (AD) exhibited considerably higher CIMT than those with non-AD dementia (6, 11).

Single photon emission computed tomography (SPECT) is a nuclear imaging technique that is able to generate three-dimensional images of radiopharmaceutical distribution. When applied to the brain, SPECT measures regional cerebral perfusion. Hypoperfusion in parietal-associated areas and entorhinal atrophy in the preliminary stage have been linked to a rapid conversion to AD. Advances in voxel-based statistical analysis and

the easy Z score imaging system (eZIS) have significantly improved the diagnostic value of brain SPECT in early AD detection (12).

PATIENTS AND METHODS

The main objective of this investigation is to evaluate the correlation between carotid intima-media thickness (CIMT), assessed through 2D ultrasound of the carotid artery, and Alzheimer's disease (AD), detected via brain single-photon emission computed tomography (SPECT) imaging using ^{99m}Tc ECD. The study aims to explore whether CIMT, a marker of atherosclerosis, may indicate or contribute to the development of AD.

This cross-sectional study was conducted at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS) from March 2021 to June 2022. The study included 65 patients with suspected or confirmed dementia. Following MREC approval, each participant submitted written informed consent and received a thorough medical history examination. The neurologist's anticipated Mini Mental State Examination (MMSE) score and biochemical results were recorded on specific data collection sheets. All participants underwent 2D ultrasonography (USG) with a linear probe to determine CIMT. Additionally, each participant underwent a brain SPECT scan using a ^{99m}Tc ECD with a Siemens Symbia Evo dual head gamma camera SPECT scanner. The SPECT DICOM images were processed using the easy Z score imaging system (eZIS) to classify dementia and evaluate the severity of Alzheimer's disease (AD). Statistical analysis was conducted using SPSS 26.0.

Statistical Analysis: Quantitative data were presented as mean and standard deviation, while qualitative data were represented as frequency and percentage. Statistical analyses were conducted using the Statistical Packages for Social Sciences (SPSS Inc., Chicago, IL, USA). Unpaired t-tests, ANOVA tests, and Pearson's correlation tests were employed for the analysis. A p-value less than 0.05 was regarded as significant.

RESULT

Of the 65 patients included in the study, 45 (69.2%) were males and 20 (30.8%) females with a male-to-female ratio of 2.3:1. Mean age was 63.8 (\pm 9.5) years with a range of 50 to 90 years.

22 patients (33.8%) belonged to 50–59 years group and 16 (24.6%) in 60–69 years age group. 5 patients (7.7%) were older than 80 years. The age distribution of the research population is displayed in Table 1. Risk factors like dyslipidemia and hypertension were the most common. Figure 1 shows the distribution of the study population by risk factors. Regarding the distribution of MMSE scores among the study population, the majority of patients (73.8%) scored in the range of 25–27 on the Mini-Mental State Examination (MMSE). Following this, 13 patients (20%) scored above 27, and 4 patients (6.2%) scored in the range of 21–24. Notably, no participant had an MMSE score lower than 21. Table 2 shows the distribution of the MMSE score among the study population. 26 patients (40%) had moderately increased CIMT (T2). Following this, 23 patients (35.4%) had normal CIMT (T0), and 16 patients (24.6%) had mildly increased CIMT (T1). Table 3 shows the distribution of the study population by different values of CIMT. The distribution of areas of brain perfusion deficit among the study population revealed that out of 65 patients, a majority of (73.8%) had it in the temporo-parietal region, posterior cingulate gyri, and precuneus areas respectively. These regions are known to show reduced blood flow in cases of (AD). Additionally, 37 patients (56.7%) displayed a perfusion deficit in the frontal lobe area, 23 patients (35.4%) in the occipital lobe areas, and 7 patients (10.8%) in discrete areas. Table 4 shows the distribution of areas of brain perfusion deficit among the study population.

Among the 65 individuals examined, 45 patients (69.2%) were diagnosed with Alzheimer's disease, while 20 patients (30.8%) exhibited causes of dementia other than Alzheimer's disease (non-AD). The distribution of the severity of Alzheimer's disease (AD) within the study population was determined by applying the easy Z-score imaging software to brain Single-Photon Emission Computed Tomography (SPECT) DICOM data. The software measures the degree of decreased regional cerebral blood flow (rCBF) in specific voxels of the image, focusing on the temporo-parietal lobes, precuneus, and posterior cingulate gyri. According to the Z-score classification, a score between 0 and 1 was considered normal cognition, 1 to 2 as mild AD, 2 to 3 as moderate AD, and more than 3 as severe AD. Figure 4 shows the processed SPECT DICOM data after the eZIS application. In this study population, the majority of patients with AD (71.1%) had mild AD, followed by moderate AD in 09 patients (20.0%), and severe AD in 04 patients (8.9%). Figure 2 shows the distribution of the severity of AD, which was determined by applying easy Z-score imaging software to brain SPECT DICOM data. The association between carotid intima-media thickness (CIMT) and the presence of Alzheimer's disease (AD) was examined through an unpaired t-test. The mean value of CIMT in AD patients was observed to be 1.28 ± 0.58 mm, while in non-AD patients, it was 1.25 ± 0.60 mm, as shown in Table 5. The severity of AD was measured by applying the eZIS to brain SPECT DICOM data. Figure 3 shows a strong positive correlation between CIMT and Z score ($r = +0.639$, $p < 0.001$)

Table 1: Age distribution of the study patients (n=65)

Age (years)	Number	Percentage (%)
50-59	22	33.8
60-69	22	33.8
70-79	16	24.6
>80	5	7.7

Mean age = (63.8 ± 9.5) years; range: (50-90) years

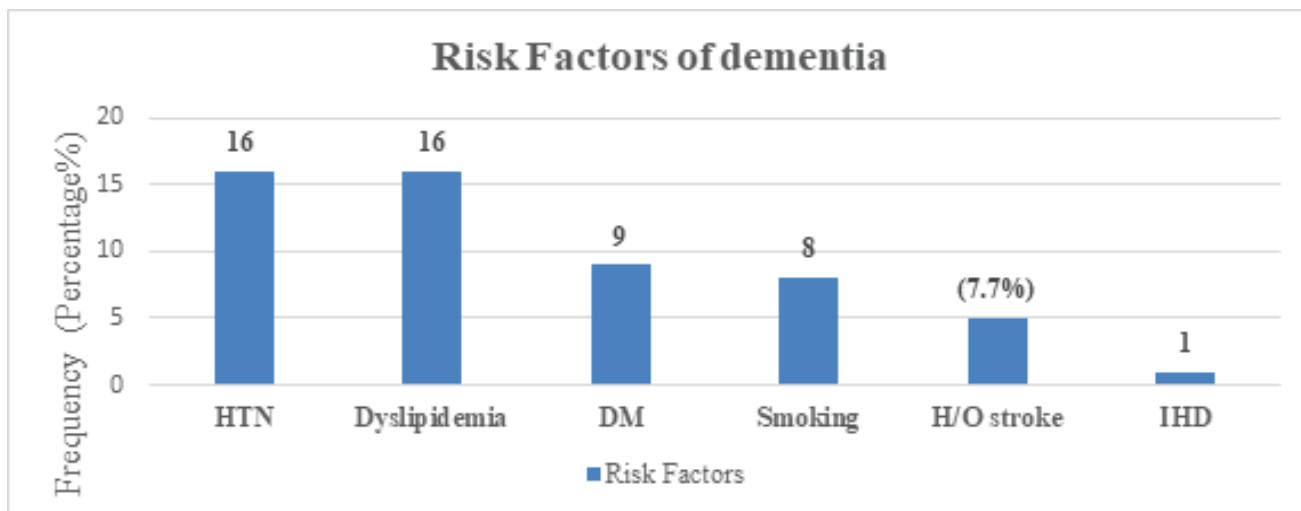


Figure 1: Risk factors of Study population having dementia (n=65)

Table -2: Mimi mental state examination score of the study population (n= 65)

MMSE Score	Number	Percentage
<21	0	0.0
21-24	4	6.2
25-27	48	73.8
>27	13	20.0

Table-3: Carotid Intima medial thickness (CIMT) values of the study population (n=65)

CIMT	No of patients	Percent
T ₀ : Normal (<1mm)	23	35.4
T ₁ : Mild (1 to <1.3)	16	24.6
T ₂ : Moderate (1.3 to <3)	26	40.0

CIMT=Carotid intima-media thickness

Table-4: Areas of brain perfusion deficit among study population (n=65)

Areas of Perfusion Deficit	No of patients	Percent (%)
Frontal Lobe	37	56.7
Temporo-parietal lobe, Posterior cingulate gyri, Precuneus	48	73.8
Occipital Lobe	23	35.4
Discrete areas	7	10.8

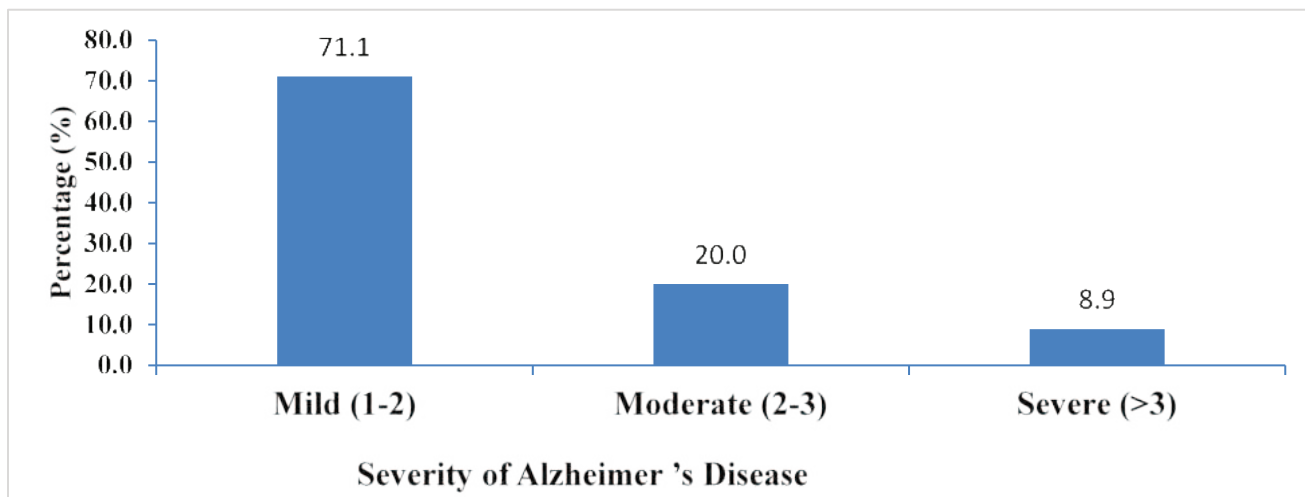


Figure-2: Severity of Alzheimer's disease (n=45)

Table-5: Association of CIMT with presence of Alzheimer's Disease (n=45)

	AD (n=45) (mean±SD)	Non AD (n=20) (mean±SD)	p value
CIMT (mm)	1.28±0.58	1.25±0.60	0.873

Values are expressed as Mean ± SD over column in total
 **Unpaired t-test was performed to determine p-value.

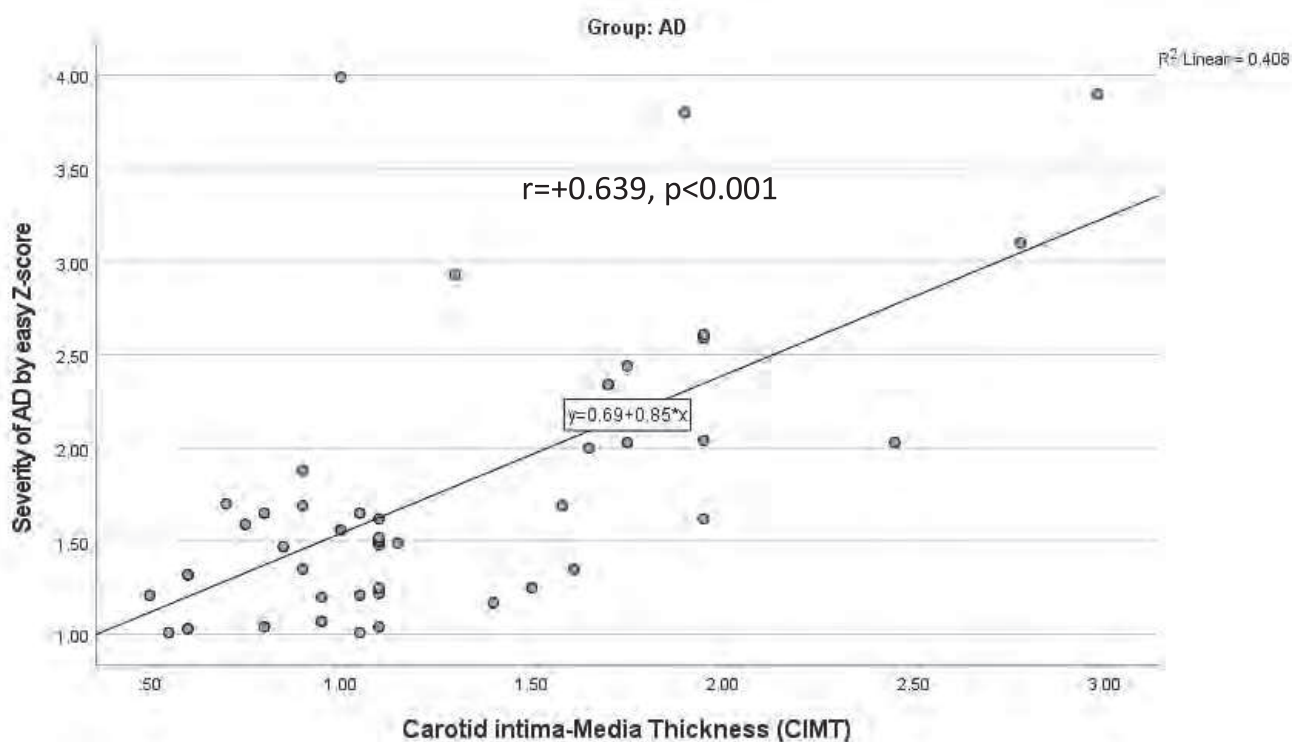


Figure: 3: A strong positive correlation between CIMT and Z score in patients (n=45)

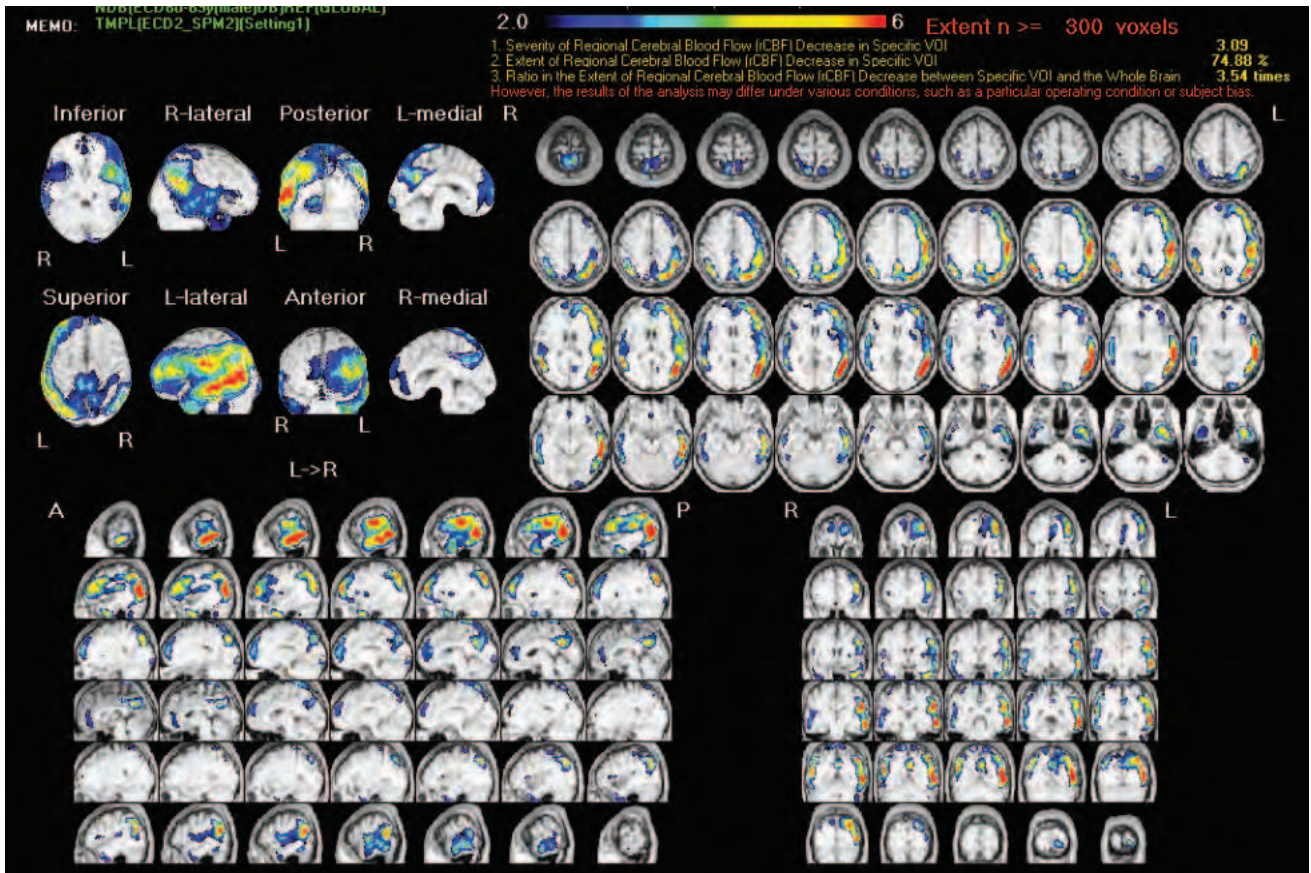


Figure: 4. Severe form of Alzheimer’s disease in a 69 years old Male with history of forgetfulness and Z score 3.09. Hypoperfusion was noted in both posterior cingulate gyri, both precuneus, both parietal lobes more on left side and also both frontal lobes.

DISCUSSION

AD is predominantly a neurodegenerative disorder that constitutes a significant portion of dementia cases, making early identification quite challenging. There is an increasing need to identify this particular form of dementia due to new developments in drugs that target early-stage Alzheimer's disease (1). Radionuclide imaging techniques, such as SPECT and PET of the brain, have been extensively employed in the early diagnosis of Alzheimer's, consistently revealing specific patterns of brain perfusion or metabolic abnormalities (13). Epidemiological studies suggest that vascular risk factors like hypertension, diabetes, smoking, hypercholesterolemia, and atherosclerosis elevate the risk of dementia. However, there is a shortage of clinical techniques to assess the degree of atherosclerosis and the vascular mechanisms contributing to dementia. The Fazekas scale in magnetic resonance imaging (MRI) and

computed tomography (CT) of the brain is one such technique, but it has limitations (10). Carotid intima-media thickness (CIMT), being a precise and objective measurement, is proposed as a potentially useful marker for predicting cognitive impairment risk (10). While increased CIMT has been identified as a risk factor for cognitive impairment and vascular dementia, its association with Alzheimer's disease remains inconclusive. Researchers are actively exploring vascular pathology in various types of dementia (10). This cross-sectional study aimed to assess the association between CIMT and Alzheimer’s disease (AD) detected by brain SPECT. A total of 65 patients with known or suspected dementia underwent clinical evaluation by neurologists to determine dementia levels using the MMSE score and exclude psychiatric disorders or organic brain pathology. The mean age of the study patients was 63.8 ± 9.5 years, with a notable male predominance (69.2%). Most patients (73.8%) had an

MMSE score in the range of 25–27. Common risk factors observed included hypertension, dyslipidemia, diabetes mellitus, smoking, a history of stroke, and a family history of ischemic heart disease (IHD). CIMT measurements classified patients into normal, mildly increased, moderately increased, and severely increased CIMT categories. Brain SPECT identified reduced blood flow in areas associated with AD. Forty-five patients (69.2%) were diagnosed with Alzheimer's disease, and twenty (30.8%) had dementia other than AD. Severity assessment using the easy Z score imaging system (eZIS) indicated that the majority of AD patients had mild severity (71.1%), followed by moderate (20.0%) and severe (8.9%) cases. The association between CIMT and AD was examined through an unpaired t-test, revealing a slight increase in mean CIMT in AD patients (1.28 ± 0.58 mm) compared to non-AD patients (1.25 ± 0.60 mm), though not statistically significant (p value 0.873). While the study found no conclusive association between CIMT and AD, it did establish a strong positive correlation between CIMT and AD severity, measured by eZIS, with a Pearson's r of 0.639 (p value < 0.001). This correlation sheds light on a potential relationship between CIMT and the severity of Alzheimer's disease, paving the way for further investigations in this area.

CONCLUSION

The findings of this study suggest that CIMT plays a role in both AD and non-AD patients. Therefore, it is wise to consider this vascular marker while evaluating AD patients initially. Furthermore, CIMT may be employed as a surveillance study to assess the advancement of AD and possibly prevent subsequent cerebrovascular incidents, e.g., strokes. However, a more extensive multi-center investigation with a larger sample size is highly recommended to bolster the validity of these observations.

Conflict of interest: The authors have no conflict of interest regarding this work.

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