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Original article

Correlation of brain imaging scale, comorbidities, and cognitive decline

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Abstract. *Background and aim:* Aging and increased life expectancy contribute to the rising prevalence of cognitive decline. Various diagnostic screening tools have been developed to assess cognitive function. While the impact of comorbidities on cognitive decline is well-established, further research is needed to understand their influence on diagnostic methods. This study explores the correlation among the MTA scale, Fazekas scale, and MoCA-INA, and the relationship between comorbidities and these scales. *Research design and Methods:* This cross-sectional study used MRI scans to assess the Fazekas scale and MTA scale, while the MoCA-INA test was administered by a certified neurologist. Statistical analyses, including Spearman and ANOVA tests, were conducted to evaluate correlations among the MTA scale, Fazekas scale, and MoCA-INA scores. Chi-square and Pearson tests were applied to examine the relationship between comorbidities and cognitive decline. *Results:* The study sample included 18 males and 19 females. The MTA scale showed a significant negative correlation with cognitive decline ($r = -0.513$, $p = 0.001$). A combined analysis of MTA and Fazekas scale also yielded a significant negative correlation with cognitive decline ($r = -0.551$, $p = 0.002$). Additionally, a significant correlation was found between stroke and small vessel disease with Fazekas scale ($r = 0.342$, $p = 0.038$). *Conclusion*: The MTA is a reliable scale for assessing cognitive decline. The combination of the Fazekas and MTA scales have a significant effect on cognitive decline. Stroke and small vessel disease influenced the Fazekas scale significantly. Further research is needed to explore the combined impact of brain imaging scales and comorbidities in cognitive decline. (www.actabiomedica.it)

Key words: cognitive decline, comorbidities, fazekas, medial temporal lobe atrophy, montreal cognitive assessment-indonesian version

Introduction

Aging cannot currently be stopped, but certain therapies can inhibit its progression and extend lifespan (1). As the healthcare system improves, life expectancy has increased (2), resulting in the rise in age-related diseases, including cognitive decline. In Europe, the prevalence of cognitive decline is increasing, particularly among women. In individuals under 75 years old, the incidence is less than 1%, but it increases threefold in those over 75 years old (3). Morbidity increases the risk of cognitive decline, particularly in the presence of multiple comorbidities, such as dyslipidemia, hypertension (HT), stroke, diabetes mellitus (DM), heart disease, atrial fibrillation (AF), normal pressure hydrocephalus (NPH), white matter hyperintensities (WMH), previous history stroke, and Parkinson's disease (PD) (4,5). These comorbidities are typically found in individuals over 75 years old (5). Cognitive decline not only affects the health of individuals but also has significant social, psychological, caregiving (including the burden on carers and healthcare professionals), and financial impacts (6). Thus, early detection of cognitive decline is essential to differentiate it from normal aging.

Alzheimer's is the most common cause of cognitive decline. To distinguish Alzheimer's disease (AD) from Vascular Cognitive decline, various scoring systems have been developed based on clinical assessments and imaging, including the Medial Temporal Lobe Atrophy (MTA) scale, Fazekas scale, and Montreal Cognitive Assessment-Indonesian Version (MoCA-INA) (7,8). A previous study in India examined the correlation between the Fazekas scale and the MTA scale, revealing a strong association with cognitive decline as measured by the Mini-Mental State Examination (MMSE). The Fazekas scale demonstrated a sensitivity of 87.5% and specificity of 83.3%. In comparison, the MTA score showed a sensitivity of 83.3% and specificity of 86.4% for individuals under 65 years of age with a cutoff ≥1, a sensitivity of 73.7% and specificity of 84.6% for those aged 65-74 years with a cutoff ≥1.5, and a sensitivity of 73.7% and specificity of 76.2% for those aged 75-84 years with a cutoff ≥2 in diagnosing cognitive decline (9). While the MoCA-INA did not report sensitivity and specificity values, the original MoCA, with a cutoff of ≤26, demonstrated a sensitivity of 97.5% and specificity of 73.7% in diagnosing cognitive decline (10). Although the risk factors for cognitive decline are well-established and the role of the MTA scale in identifying cognitive decline is clear (11), the correlation between cognitive decline as assessed by the MoCA-INA and brain imaging scales, as well as the relationship with comorbidities, remains unclear. This study is the first to investigate cognitive decline as assessed by the MoCA-INA and to explore the correlation between brain imaging scales, including the MTA scale and the Fazekas scale. Additionally, the study examines the influence of common comorbidities, such as diabetes, hypertension, stroke, and small vessel disease, on cognitive decline and brain imaging markers. The research aims to establish the relationship between these diagnostic scales and cognitive decline, with a particular focus on how comorbidities affect brain imaging results.

Patients and Methods

Study design

The cross-sectional study was conducted at Premier Hospital in Surabaya, Indonesia, using purposive sampling from January 1, 2023, to January 31, 2024. Ethical approval was obtained from Premier Hospital's ethics committee (03/RSPS/KERS/XII/2023). The inclusion criteria are patients who are either outpatients or inpatients at Premier Hospital during this period, report subjective complaints of forgetfulness (either self-reported or by family members), consent to undergo MoCA-INA cognitive screening, and have no comorbidities or one or more of the following comorbidities: DM, coronary heart disease (CHD), HT, PD, stroke (including ischemic stroke, intracerebral haemorrhage), small vessel cerebral ischemia, dyslipidemia, NPH, or AF. Patients are excluded if they have pain, visual or hearing impairments, brain tumors, autoimmune disorders, or active infections and other conditions that prevent the patient from undergoing the MoCA-INA cognitive screening test.

Data collection

Sociodemographic data (age and gender) and medical history were collected through electronic medical records. T2DM is defined based on American Diabetes Association classification (12) or the consumption of diabetes drug, CHD, PD, dyslipidemia, stroke (ischemic stroke, intracerebral haemorrhage) and small vessel cerebral ischemia, and atrial fibrillation based on previous medical history and the latest brain MRI results. HT is defined as having systolic blood pressure readings of ≥140 mmHg and/or diastolic blood pressure readings of ≥90 mmHg on both days, or a previous history of hypertension. NPH is diagnosed based on the latest brain MRI results.

Brain imaging, MTA score, Fazekas score and MoCA-INA assessment

MRI scanning of the brain was performed with 3-Tesla Images 3D scans of the entire brain (TR = 7.0 ms, TE = 3.3 ms, flip angle = 9°, FOV = 230 mm, isotropic voxels=0.7 mm.) were acquired as anatomical references. WMH were quantified using the Fazekas scale based on 3D T2 Fluid-Attenuated Inversion Recovery (FLAIR) imaging, with a grading system ranging from 0 to 3. The Fazekas scale was applied to axial T2-weighted or T2 FLAIR images to evaluate WMH burden across the whole brain. The scale consists of

four distinct grades: Grade 0 represents no or occasional punctate white matter changes; Grade 1 denotes multiple punctate white matter changes; Grade 2 indicates the early confluence or bridging of punctate lesions, and Grade 3 corresponds to confluent white matter changes (13). The MTA scale was assessed using T1-weighted inversion recovery (T1IR) MR images, specifically focusing on the coronal slice aligned with the brainstem axis and passing through the aqueduct of Sylvius. Both hemispheres were assessed on this slice, with scores ranging from 0 to 4, where MTA 0 and MTA 1 are considered normal, while MTA 2–4 indicates increasing severity of atrophy. MTA 2 is characterized by a widened choroid fissure and temporal horn, along with a slight reduction in hippocampal height. MTA 3 is present with a severely widened choroid fissure and temporal horn, accompanied by a more pronounced reduction in hippocampal height. MTA 4 represents extensive widening of the choroid fissure and temporal horn, along with a severe reduction in hippocampal height. The MTA scale score of 0-1 is considered normal in individuals under 75 years of age, while a score of 0-2 is considered normal for those aged 75 and older. MTA 4 is always considered pathological, regardless of age (13,14). MRI scans were randomly assigned to an experienced radiologist who was blind to the specific diagnosis to rate the scale. An experienced neurologist, certified in neurobehavioral assessment, administered neuropsychological tests using the MoCA-INA was used to assess cognitive decline in all patients, with a cutoff score of <26 indicating cognitive impairment. An education level adjustment is applied by adding 1 point for patients with less than 12 years of education (10,15).

Statistical analysis

The characteristics of the subjects were analyzed descriptively based on gender, the Fazekas scale, and the MTA scale. Analytical tests were conducted using the Spearman test to examine the correlation between the MTA scale and the MoCA-INA scores, and that between the Fazekas scale and the MoCA-INA scores. These analyses were followed by an ANOVA test to determine the correlation between the MTA scale and the Fazekas scale with the MoCA-INA scores. Additionally, analytical tests were performed using Chi-Square test, followed by Spearman and Pearson tests, to evaluate the correlation between each comorbidity and the MTA scale, as well as the correlation between each comorbidity and the Fazekas scale. The comorbidities include T2DM, CHD, HT, PD, stroke (ischemic stroke, intracerebral hemorrhage), and small vessel cerebral ischemia, dyslipidemia, NPH, and atrial fibrillation.

Results

Subject characteristics

The study comprised 18 males and 19 females (Table 1). Analysis by age revealed that the predominant age group was those over 70 years old, with a count of 19 individuals. This was followed by the 60–70-year age group, which included 16 individuals, while the remainder, aged between 50-60 years, represented the smallest group. In the assessment using MoCA-Ina, out of 37 patients, 27 of them (73%) fell into the abnormal category, whereas 10 of them (27%) were classified as normal. The mean of the MoCA-INA score among the patients was 20.03, which was notably below the established cutoff value of 26, indicating a general trend toward cognitive decline.

We depict the representative examples of the Fazekas scale and MTA scale in the following Figure 1. In the Fazekas scale, the most frequently observed score was 1 – present in 16 individuals (43.2%), followed by score 2 – present in 19 individuals (51.4%). A score of 3 was notably rare: it was recorded in only 2 individuals (5.4%). In the case of the MTA scale, the majority of the sample, 26 individuals (70.3%), were categorized as abnormal. Conversely, 11 individuals (29.7%) were considered normal. Within the abnormal group, 16 individuals (43.2%) had an MTA score of 2, and 12 (32.4%) had a score of 3.

Patient profile based on cognitive decline based on MoCA-INA results and MTA scale showed that a high percentage of both male and female patients predominantly had cognitive decline, with 61.1% of males and 84.2% of females falling into this category, while the distribution of MTA scores indicated a significant prevalence of abnormalities across age groups, with 48.6% of patients under 75 years and 21.6% of

Table 1. Patient Characteristics in the Study

Profile	N	%	Min	Max	Mean	SD
Gender						
Male	18	48.6				
Female	19	51.4				
Age						
50 – 60 Years	2	5.4	57	59	58.0	1.41
60 – 70 Years	16	43.2	63	70	66.6	2.22
> 70 Years	19	51.4	71	87	77.3	4.46
MoCA-INA (Cognitive Status)						
Normal	10	27.0	26	29	27.8	1.23
Abnormal	27	73.0	2	24	17.2	5.12
Fazekas						
1	16	43.2				
2	19	51.4				
3	2	5.4				
MTA						
Normal	11	29.7				
Abnormal	26	70.3				
0	1	2.7				
1	5	13.6				
2	16	43.2				
3	12	32.4				
4	3	8.1				

Abbreviations: MoCA-INA: Montreal Cognitive Assessment; MTA: Medial Temporal Lobe Atrophy; SD: Standard Deviation.

those 75 years and older exhibiting abnormal scores (Table 2).

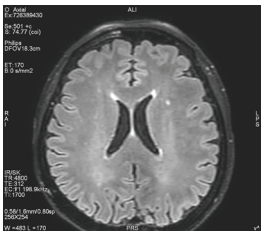
Association of Fazekas Scale and MTA Score with Cognitive Decline

Correlation analysis between the Fazekas and MTA scale with MoCA-INA scores revealed that the Fazekas parameter alone did not exhibit a significant negative association with cognitive decline in patients (Figure 2a). However, the MTA scale independently showed a strong and significant negative correlation with cognitive decline, with a correlation coefficient of -0.513 (p=0.001) (Figure 2b). Additionally, the combined analysis of the Fazekas and MTA parameters yielded a correlation coefficient of -0.551 (p=0.002), indicating a significant and meaningful negative correlation with cognitive decline as assessed by MoCA-INA (Table 3). This underscores the combined impact of these parameters on cognitive assessment outcomes.

The correlation between comorbidities and Fazekas scores was generally positive, but not statistically significant. The only significant correlation was observed between the comorbidity of Stroke and Small Vessels Disease with Fazekas scale, with a correlation coefficient of 0.342 (p=0.038) (Table 4). This suggests that patients with stroke and SVD comorbidity are likely to have higher Fazekas scores.

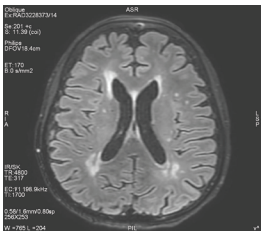
The correlation between comorbidities and MTA scores showed a positive trend in Table 5, but it was not statistically significant for conditions, such as T2DM, HT, and Parkinson's disease. In contrast, a

Fazekas Scale 1



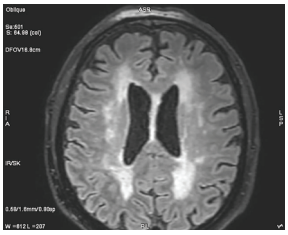
A 64-year-old female with a Fazekas scale of 1, an MTA scale of 2, and a MoCA-INA score of 29.

Fazekas Scale 2



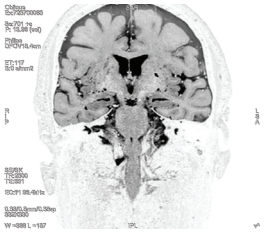
A 71-year-old female with a Fazekas scale of 2, an MTA scale of 3, and a MoCA-INA score of 17.

Fazekas Scale 3



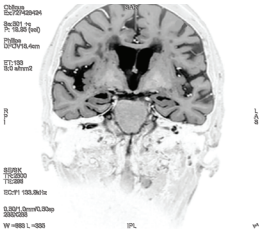
A 74-year-old male with a Fazekas scale of 3, an MTA scale of 2, and a MoCA-INA score of 16.

MTA Scale 1



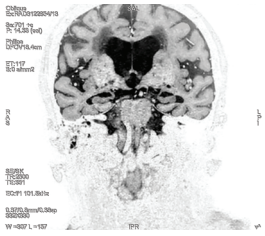
A 68-year-old female with a Fazekas scale of 1, an MTA scale of 1, and a MoCA-INA score of 28.

MTA Scale 2



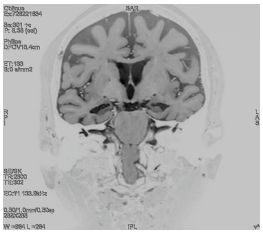
A 71-year-old female with a Fazekas scale of 2, an MTA scale of 2, and a MoCA-INA score of 22.

MTA Scale 3



A 83-year-old female with a Fazekas scale of 2, an MTA scale of 3, and a MoCA-INA score of 13.

MTA Scale 4



A 65-year-old female with a Fazekas scale of 1, an MTA scale of 4, and a MoCA-INA score of 11.

Figure 1. Representative examples of Fazekas (1–3) and MTA (1–4) scale classifications from our study.

Table 2. Patient Profile Based on Cognitive Status and MTA scale

Profile	Cognitive Status	n (%)	Min	Max	Mean	SD
Male	Normal	7 (18.9)				
	Decline	11 (29.7)				
Female	Normal	3 (8.1)				
	Decline	16 (43.2)				
Age	Normal	10 (27.0)	59	81	68.6	6.54
	Decline	27 (73.0)	57	87	72.8	7.09
	MTA	**n (%)**				
Age (< 75)	Normal	6 (16.2)				
	Decline	18 (48.6)				
Age (≥ 75)	Normal	5 (13.5)				
	Decline	8 (21.6)				

Abbreviations: MTA: Medial temporal lobe atrophy; SD: standard deviation.

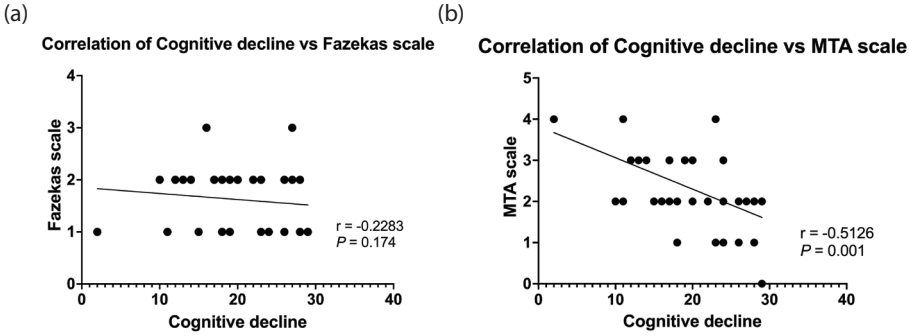


Figure 2. Correlation of the Fazekas scale, the MTA scale, and cognitive decline. (a) Correlation between cognitive decline and the Fazekas scale. (b) Correlation between cognitive decline and the MTA scale.

Table 3. Correlation Analysis of Fazekas, MTA, and Cognitive Decline

	Cognitive Decline	
	Coefficient Correlation (r)	**Statistic Significancy (p)**
Fazekas	-0.228	0.174
MTA	-0.513	**0.001**
Fazekas & MTA	-0.551	**0.002**

negative correlation was observed between comorbidities and Fazekas scores in patients with CHD, stroke and SVD, dyslipidemia, NPH, and AF. The correlations between patient comorbidities and MTA scores were all statistically insignificant ($p \geq 0.05$).

Discussion

During normal aging, a reduction in whole brain volume, or brain atrophy, of approximately 0.4% is typically observed, with the rate of atrophy ranging from 0.3% per year in individuals in their 40s to 0.5% per year in those in their 80s (16). In contrast, cognitive decline is associated with a greater rate of brain atrophy, ranging from 1.1% to 3.8% per year (17,18). While WMH are also found in normal aging without cognitive decline (19), WMH can develop into cognitive decline over an estimate of 8 years (20). Brain atrophy and WMH require a long period to develop cognitive decline. Thus, to screen, to diagnose early, and to differentiate normal aging from cognitive

Table 4. Correlation Analysis of Patient Comorbidities with Fazekas scale

	Fazekas (%)			Fazekas	
	1	**2**	**3**	**Rs**	**P**
Diabetes	18.9	18.9	0.0	-0.144	0.394
CHD	10.8	8.1	0.0	-0.153	0.365
HT	24.3	35.1	2.7	0.083	0.627
Parkinson	10.8	16.2	5.4	0.214	0.204
Stroke & SVD	21.6	40.5	5.4	0.342	**0.038**
Dyslipidaemia	10.8	24.3	0.0	0.126	0.458
NPH	2.7	5.4	0.0	0.037	0.829
AF	2.7	10.8	0.0	0.146	0.387

Table 5. Correlation Analysis of Patient Comorbidities with MTA scale

Variable 2 / Variable 1	MTA (%)		MTA	
	Normal	**Abnormal**	**Rs**	**p**
T2DM	24.3	13.5	0.102	0.547
CHD	13.5	5.4	-0.012	0.943
HT	37.8	24.3	0.264	0.115
Parkinson	18.9	13.5	0.181	0.284
Stroke & SVD	51.4	16.2	-0.181	0.284
Dyslipidaemia	29.7	5.4	-0.231	0.169
NPH	8.1	0.0	-0.193	0.252
AF	10.8	2.7	-0.084	0.620

decline, several scoring systems have been developed, including the MTA scale and Fazekas scale. Brain atrophy and WMH are observed in cognitive decline and serve as independent factors contributing to the condition. However, the combination of brain atrophy and WMH presence exerts a synergistic effect, accelerating cognitive decline (21). Brain atrophy can be assessed using the MTA scale, while WMH are assessed using the Fazekas scale. In our study, we found a significant negative correlation between the MTA scale and cognitive decline as assessed by MoCA-INA. This is consistent with previously reported data from Indonesia, where a similar method was used in Central Java with 61 patients. That study also found that higher MTA scores were associated with worsening cognitive decline (22). Furthermore, the MTA scale can differentiate among normal aging, MCI, prodromal AD, and AD (23,24), suggesting that the MTA scale could serve as an early marker for screening cognitive decline. As widely discussed, the medial temporal lobe, which includes the hippocampus as the central hub for memory consolidation, plays a critical role in these conditions (25). In cognitive decline and correlation with Fazekas scores, we did not find significant correlation, suggesting that WMH may not be associated with cognitive status in our study. In contrast, a study conducted in China with 64 patients found a significant negative correlation between WMH and cognitive decline (26). A similar result was observed in Spain with 976 patients (27). The discrepancy between these studies and ours may be due to our smaller sample size, which might not have reached statistical significance. Additionally, the difference in the scoring methods used to assess cognitive decline could be a factor. For example, a similar study in India with 40 patients found statistically significant results using the MMSE (28). In Asians, the sensitivity and specificity of MMSE and MoCA differ in detecting cognitive

decline. MoCA is better for screening MCI, while MMSE is more effective for screening dementia (29). However, our study did not differentiate between the types of cognitive decline. No significant association was found in the correlation between the Fazekas scale and comorbidities. A previous study with a larger sample size (1,763 patients) in Switzerland demonstrated a significant correlation between the Fazekas scale and AF (30). However, a study in Sweden with a sample size similar to ours (43 patients) did not find a significant correlation (31), suggesting that a larger sample size is a crucial factor. A significant correlation of the Fazekas scale with comorbidities including stroke, SVD, dyslipidemia, CHD, and diabetes) were observed in studies with larger sample sizes (32–34). However, no correlation was found with PD occurrence, and no association was identified in NPH. A previous study only reported a correlation between an increased Fazekas scale and cognitive function decline (35). We also identified the relationship between comorbidities and Fazekas scores, specifically in patients with a history of stroke and SVD. This finding is consistent with the understanding that stroke and SVD are associated with WMH, as hyperintensities on MRI are often indicative of hemorrhages seen in both stroke and SVD. Additionally, more severe SVD correlated with worse cognitive decline (23,26). Interestingly, our data did not show a significant correlation between the Fazekas scale and hypertension despite HT being a high risk factor for stroke and SVD. Our findings contrast with a previous study conducted in China involving 333 patients, which reported a significant positive correlation (36). No significant correlation was found between comorbidities and MTA scores, despite a positive trend being observed. Previous studies have shown that HT does not correlate with MTA occurrence but is associated with diabetes, stroke, CHD, Parkinson's disease, and AF (37–40), while NPH has not been reported as being associated with the MTA scale in previous studies despite NPH being known as a risk factor for cognitive decline (41). This indicates the need for further study to elucidate comorbidities of cognitive decline and MTA. Our study has several limitations. One of them is a small sample size, being a single-center study. Additionally, the study did not classify cognitive decline into categories, such as MCI, AD, or other forms of AD and did not explore biological markers, such as *APOε4* carrier. Further studies with larger sample sizes, multicenter involvement, and the use of biological markers are essential to address these limitations.

Conclusion

This study found a significant negative correlation between the MTA score and cognitive decline, indicating its potential as an early marker for cognitive decline. The combination of the Fazekas and MTA scales have a significant effect with cognitive decline. Stroke and small vessel disease influenced the Fazekas scale significantly. Further research is needed to explore the combined effects of brain imaging markers and comorbidities in cognitive decline.

Ethical Approval: Ethical approval was obtained from Premier Hospital's ethics committee (03/RSPS/KERS/XII/2023)

Conflict of Interest: Each author declares that they have no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc).

Authors' Contribution: VB, CS Conceptualized the idea for the article, conducted the literature search, and performed the data analysis; FMH drafted the manuscript; VB, FMH, CS thoroughly revised the work.

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