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Original Article

Association Between Periventricular and Subcortical White Matter Hyperintensities and Cognition in a Local Population

Fadi Esttaifo[1], Lawrence Mbuagbaw[2] and Crystal Fong[3]

[1]Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada, [2]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada and [3]Department of Medical Imaging, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

ABSTRACT: ***Background:*** White matter hyperintensities (WMH) on fluid-attenuated inversion recovery MRI sequence are regions where fluid from supplying vessels leaks into brain tissue. Some studies have demonstrated an association between WMH and cognitive decline. Given the common WMH risk factors in our local population, the aim of this study is to examine the relationship of overall and regional WMH with cognition in Hamilton, Canada. ***Methods:*** Adults presenting to Hamilton General Hospital in 2020 with a head MRI and cognitive assessment within 6 months of the MRI were included in our cross-sectional study. MRIs were reviewed, assigning a periventricular (PV), a subcortical (SC) and an overall severity score to each based on the Fazekas scale, ranging from 0 to 3. Montreal Cognitive Assessment (MoCA) scores were used as a measure of cognitive function. Patients with confounding diagnoses were excluded. Multiple regression analyses were conducted between WMH and cognitive scores, adjusting for hypertension, diabetes and smoking. ***Results:*** Multiple regression models revealed R^2 values of 0.097, 0.050 and 0.036 for overall, PV and SC WMH with MoCA, respectively. There were negative associations between overall Fazekas scores and MoCA ($B = -2.11$, $p < 0.001$), PV scores and MoCA ($B = -1.46$, $p < 0.001$) and SC scores and MoCA ($B = -1.21$, $p = 0.002$). ***Conclusion:*** The association between MRI WMH and cognition supports prognostic use for cognitive decline to limit/delay deterioration. Specifically, stronger PV associations prompt research and perhaps development of revised scales prioritizing PV changes. Implementing this into the field of radiology whereby WMH severity and location assessment becomes a standard within brain MRI reports could improve patient outcomes.

RÉSUMÉ: **Association entre les hyper-intensités de la substance blanche des régions périventriculaire et sous-corticale et les fonctions cognitives au sein d'une population locale.** ***Contexte :*** Les hyper-intensités de la substance blanche (HISB) observées dans des séquences d'IRM de type FLAIR (« *flow-attenuated inversion recovery* ») sont des régions où le liquide provenant des vaisseaux sanguins s'infiltre dans le tissu cérébral. Certaines études ont démontré une association entre les HISB et le déclin cognitif. Compte tenu des facteurs de risque courants des HISB dans notre population locale, l'objectif de cette étude était d'examiner la relation entre les HISB globales et de régions du cerveau et la fonction cognitive à Hamilton, au Canada. ***Méthodes :*** Les adultes qui se sont présentés à l'hôpital général de Hamilton en 2020 avec un examen d'IRM de la tête et une évaluation cognitive dans les 6 mois suivant cet examen ont été inclus dans notre étude transversale. Les examens d'IRM ont été examinés et un score de gravité périventriculaire (PV), sous-corticale (SC) et générale a été attribué à chacun d'entre eux sur la base de l'échelle de Fazekas (score de 0 à 3). Les scores au MoCA ont aussi été utilisés comme mesure de la fonction cognitive. À noter que les patients présentant des diagnostics confondants ont été exclus. Des analyses de régression multiple ont été effectuées entre les HISB et les scores cognitifs, et ce, en tenant compte de l'hypertension, du diabète et du tabagisme. ***Résultats :*** Les modèles de régression multiple ont révélé respectivement des valeurs R^2 de 0,097, 0,050 et 0,036 pour les HISB globales, de la région PV et de la région SC avec le MoCA. Il existait par ailleurs des associations négatives entre les scores à l'échelle de Fazekas visant les HISB globales et le MoCA (B = −2,11 ; p < 0,001), les HISB de la région PV et le MoCA (B = −1,46 ; p < 0,001) et les HISB de la région SC et le MoCA (B = −1,21 ; p = 0,002). ***Conclusion :*** L'association entre les HISB observées dans le cadre d'un examen d'IRM et la fonction cognitive justifie une utilisation pronostique pour le déclin cognitif afin de limiter ou de retarder la détérioration. Plus précisément, des associations plus fortes avec la région SC incitent à la recherche et peut-être au développement d'échelles révisées donnant la priorité aux changements dans cette région du cerveau. La mise en œuvre de cette approche dans le domaine de la radiologie, où l'évaluation de la gravité et de la localisation des HISB devient une norme dans les rapports d'examens d'IRM, pourrait améliorer l'évolution de l'état de santé des patients.

Keywords: white matter hyperintensities; periventricular white matter changes; subcortical white matter changes; cognitive impairment; cognitive function

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Corresponding author: Crystal Fong; Email: crystal.fong@medportal.ca

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Highlights

- Higher MRI white matter hyperintensity (WMH) severity is associated with lower cognitive function in the local Hamilton, Canada population.
- Adjusting for hypertension, diabetes and smoking, periventricular WMH have a greater association with cognition compared to subcortical WMH.
- Routine neuroradiologist reporting of WMH location and severity can potentially improve patient outcomes.

Introduction

MRI is a commonly used screening tool to identify and diagnose brain lesions and pathologies.[1]The fluid-attenuated inversion recovery (FLAIR) sequence highlights the tissue fluid signal while suppressing the signal from free fluid, such as the CSF in the ventricles and surrounding the brain. FLAIR imaging can thus be a very helpful diagnostic and investigative tool as the image it produces is more sensitive to excess fluid within the brain parenchyma, which is usually indicative of cognitive dysfunction or pathology.[1]

White matter hyperintensities (WMH) are readily identified on the FLAIR sequence, presenting as bright lesions on the image.[1–3] These changes, also termed leukaraiosis, commonly occur in the periventricular (PV) white matter or the subcortical (SC) white matter deep to the cerebral cortex.[1-3] In this setting, WMH have a vascular etiology; they represent areas where the supplying vessels have decreased integrity, resulting in fluid leakage from the blood plasma into the tissues due to a compromised blood-brain barrier.[3–5] Even though some plasma fluid leakage with resulting WMH can occur as a by-product of aging,[2] many studies have associated WMH with hypoperfusion to the white matter leading to tissue death, demyelination and axonal degeneration.[1,2,4] Patients with WMH detected on the FLAIR sequence are also at an increased risk of developing stroke and neurodegenerative disorders due to vascular risk factors and loss of neural connections following tissue death.[1,4,5] The volume of WMH is associated with cognitive decline, specifically decreased brain executive function and processing speeds;[5] this decline is thought to be caused by SC damage to the white matter making up the neural networks of the brain.[4]

The MRI FLAIR sequence is therefore a valuable radiological tool for early detection of white matter changes before extensive tissue damage has occurred, allowing for potential interventions aimed at slowing down or controlling the progression to severe cognitive dysfunction.[1] Early radiological evidence of WMH would encourage stricter physician recommendations and facilitate improved patient adherence to modifications, such as lifestyle factors and smoking cessation, which have been shown to mitigate vascular risk factors and slow down progression of white matter lesions.[6]

Previous studies have demonstrated a correlation between the volume of WMH on MRI and cognitive functioning in patients.[7]When evaluating different MRI features associated with cognitive function – including white matter lesions, number of cerebral microbleeds and overall brain volume – WMH have been shown to be one of the strongest MRI predictors of cognitive impairment.[7,8] Outside of MRI assessment, the main predictor of cognitive decline is vascular risk factors, with the biggest risk being smoking.[9] To measure clinical cognitive function, the Montreal Cognitive Assessment (MoCA) is the single most used test given its efficacy at evaluating cognition through various domains including memory, visuospatial skills and executive function.[10]

Some studies have shown greater volumes of WMH and higher rates of increases in the volume of these lesions correlating with lower performances on the MoCA and other measures of cognitive ability.[11-14] However, most of the research focuses on overall volume of WMH within the brain. Only a few studies explored the significance of the location of WMH, comparing differences in effect between PV and SC WMH on cognition. Additionally, there is limited research on the association between WMH and cognition that adjusts for major vascular risk factors such as hypertension, diabetes and smoking; this is important given that these have been shown to be predictors of cognitive decline. Finally, there have not been any local studies to our knowledge conducted on this topic. This is extremely important to explore in the community given the high prevalence of WMH risk factors – such as stroke, smoking, hypertension, diabetes and older age – and the lower socioeconomic status reported around the hospitals within the local population of Hamilton, Canada.[15] Our study aims to add to the existing research by exploring the relationship between MRI FLAIR WMH and cognitive function at a single time point in the local Hamilton population, as well as evaluating the separate effects of PV and SC changes.

Methods

Participants

This study is a retrospective cross-sectional study. Hamilton Integrated Research Ethics Board (HiREB) approval was obtained for the study. Patients aged at least 18 years who presented to the Hamilton General Hospital from January 1, 2020, to December 31, 2020 and who received a head MRI as well as a cognitive assessment using MoCA within 6 months of the MRI were included. Six months was chosen due to the reported marked decline in MoCA scores over short periods of time in patients with cognitive impairment, up to an average decrease of 1.83 points over 3.5 years as reported by Krishnan et al.[16] Other studies examining the association between MRI changes and cognitive testing have also used the 6-month timeline as a cutoff to ensure better accuracy.[17] 313 patients matched our inclusion criteria. 33 patients with a known alternative diagnosis that could alter imaging characteristics, including cerebral amyloid angiopathy, tumor, post-operative changes, vasculitis or demyelination, were excluded from the study. An additional 6 patients were excluded due to inadequate FLAIR images on the MRI. A final number of 274 patients were included in the study (Figure 1). Demographic data were collected from patient charts including age, sex, hypertension diagnosis, diabetes diagnosis, smoking status and MoCA score. WMH predominance (PV or SC), PV and SC Fazekas scores and overall Fazekas scores were then assigned by examining patients' MRIs.

MRI acquisition and interpretation

All MRI brain images were acquired using a 1.5 T Siemens MAGNETOM MRI machine at the Hamilton General Hospital. Axial 2D FLAIR Images were obtained from the skull base to the vertex (TE = 114 ms, TR = 9000 ms, slice thickness 5 mm and matrix 256/187). The images were assessed by a medical student (first author of the paper) trained under a fellowship-trained neuroradiologist (principal investigator of the paper) to determine the extent and distribution of WMH using the Fazekas scale – a numerical scale ranging from 0 to 3 based on the severity of the white matter lesions, both in PV and SC locations.[18,19] A score of 0 indicates no lesions, 1 indicates PV caps and/or punctate SC foci, 2

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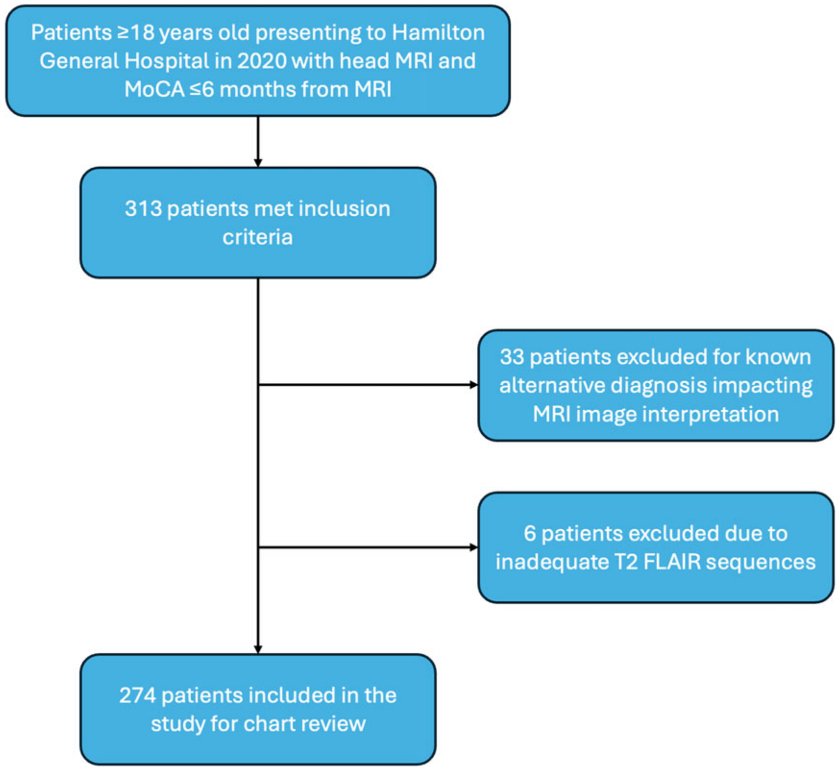

Figure 1. Inclusion flowchart highlighting number of patients included for chart review and analysis.

indicates PV halos and/or small confluent SC foci and 3 indicates the extension of PV white matter into deep white matter and/or large confluent SC foci.[18,19] This scale has been shown to provide the most valid estimate of WMH compared to quantitative assessment, hence is the most widely used tool by radiologists for qualitative assessment of WMH.[20] Cases were classified as "PV predominant," "SC predominant" or "codominant" based on subjective assessment of volume of lesions in each location. Complex cases that could not be determined by the student alone (such as complex tumors and vascular etiologies resembling WMH) were reviewed by the neuroradiologist. The assessor was blinded to the patient chart including any demographic data or MoCA scores.

Cognitive function assessment

Cognition was assessed using the MoCA test, and the result was collected directly from the patient chart, using the test result closest to the time at which the MRI was performed in the case of multiple cognitive tests. The cognitive test timelines ranged from same day up to within 6 months of the MRI. Test dates that exceeded the range of 6 months surrounding the date of the MRI were excluded. The MoCA is a robust 30-point assessment of seven different cognitive domains – visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, 5-minute delayed verbal memory and orientation – that has been validated in the literature and shown to be reliable cross-culturally.[21,22] A score cutoff of 26 or less out of 30 is a marker for cognitive decline, with 18–25 signifying mild cognitive impairment and less than 18 indicating moderate to severe impairment.[21]

Statistical analysis

We used descriptive statistics to summarize patients' demographic data. All regression analyses were conducted using GraphPad Prism software (version 10.4.1). Multiple linear regression analyses between the WMH Fazekas scores and MoCA were conducted with adjusting for confounding variables. The confounders adjusted for in this study were hypertension, diabetes and smoking history. A p-value of 0.05 was used as the cutoff for statistical significance.

Results

The total number of patients included in the study was 274, with a mean age of 69.49 years and a standard deviation (SD) of 15.14 (Table 1). The proportion of males within the population was 60.22%, and most patients had a history of hypertension, diabetes and/or smoking. Within the patient cohort, 44.16% of patients had a Fazekas score of 2, and 68.25% of patients had PV WMH predominance. Using the aforementioned MoCA thresholds, the largest portion of the patients fell into the mild cognitive impairment category.

The multiple regression analysis model between overall Fazekas and MoCA was statistically significant with an R^2 value of 0.097. A negative association was found between the overall Fazekas scores and MoCA ($p < 0.001$) (Figure 2). Further analysis of PV and SC Fazekas revealed significant negative associations for both, with a stronger effect between PV scores and MoCA ($R^2 = 0.050$; $p < 0.001$), compared to SC scores and MoCA ($R^2 = 0.036$; $p = 0.002$).

A sub analysis was conducted for age with the various Fazekas and MoCA categories to further examine the trends between age, FLAIR WMH severity and cognition. The mean ages in patients with overall Fazekas scores of 0, 1, 2 and 3, were, respectively, 43.88, 63.59, 73.79 and 75.64 (Figure 3). The mean ages in patients with MoCA scores 0 – 17, 18 – 25 and 26 – 30, were, respectively, 73.66, 69.28 and 65.31 (Figure 4).

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Table 1. Patient demographics

Patient demographics	
Variable	**Statistic**
Age (years): mean (SD)	69.49 (15.14)
Sex: *n* (%)	
Male	165 (60.22)
Female	109 (39.78)
Personal medical history: *n* (%)	
Hypertension	221 (80.66)
Diabetes	105 (38.32)
Smoking	162 (59.12)
Radiological summary: *n* (%)	
Overall Fazekas score 0	16 (5.84)
Overall Fazekas score 1	79 (28.83)
Overall Fazekas score 2	121 (44.16)
Overall Fazekas score 3	58 (21.17)
WMH PV predominance	187 (68.25)
WMH SC predominance	71 (25.91)
WMH No predominance	16 (5.84)
Cognitive test summary: *n* (%)	
MoCA score 26–30 (no cognitive impairment)	67 (24.45)
MoCA score 18–25 (mild cognitive impairment)	133 (48.54)
MoCA score 0–17 (moderate/severe cognitive impairment)	74 (27.01)

WMH = white matter hyperintensities; PV = periventricular; SC = subcortical; MoCA = Montreal Cognitive Assessment.

Discussion

To our knowledge, this is the only study examining MRI WMH and cognitive function as well as providing separate PV and SC WMH effect analysis on cognition in the local population with a high prevalence of vascular risk factors. We found that the higher severity of WMH is associated with lower cognitive function, with about 9.7% of the variability in the MoCA being attributable to the Fazekas score according to the model analysis R^2 of 0.097. PV location of WMH was more strongly associated with cognitive decline compared to SC location, demonstrating a 5.0% and 3.6% attributable effect on MoCA reduction, respectively.

Prior studies have shown that WMH visualized on FLAIR MRI are associated with cognitive decline in the aging population.[23] These findings have been replicated across healthy patients as well as those with mild cognitive impairment (MCI), Alzheimer's disease (AD) and post-stroke populations.[24] MCI is generally diagnosed through a change in function of one or more cognitive domains without any changes in memory or activities of daily living.[25] AD requires characteristics of amyloid plaques and brain MRI changes to supplement the diagnosis.[25] Finally, post-stroke populations have clinical features of vascular damage seen on imaging leading to cognitive decline.[25] In all these cases, WMH are a baseline predictor of increased rate of cognitive decline longitudinally.[24] This has also been shown in some cross-sectional studies revealing a link between WMH seen in certain regions of the brain and some cognitive deficits.[26,27] However, none of these cross-sectional studies have diverse groups of patients, with one stratifying patients into either a specific diagnosis of dementiaor non-dementia group and the other recruiting all healthy participants who volunteered for the research.[26,27]

A study investigating WMH in different regions of the brain using MRI FLAIR sequences and cognitive function concluded that white matter damage in each specific area is correlated with a

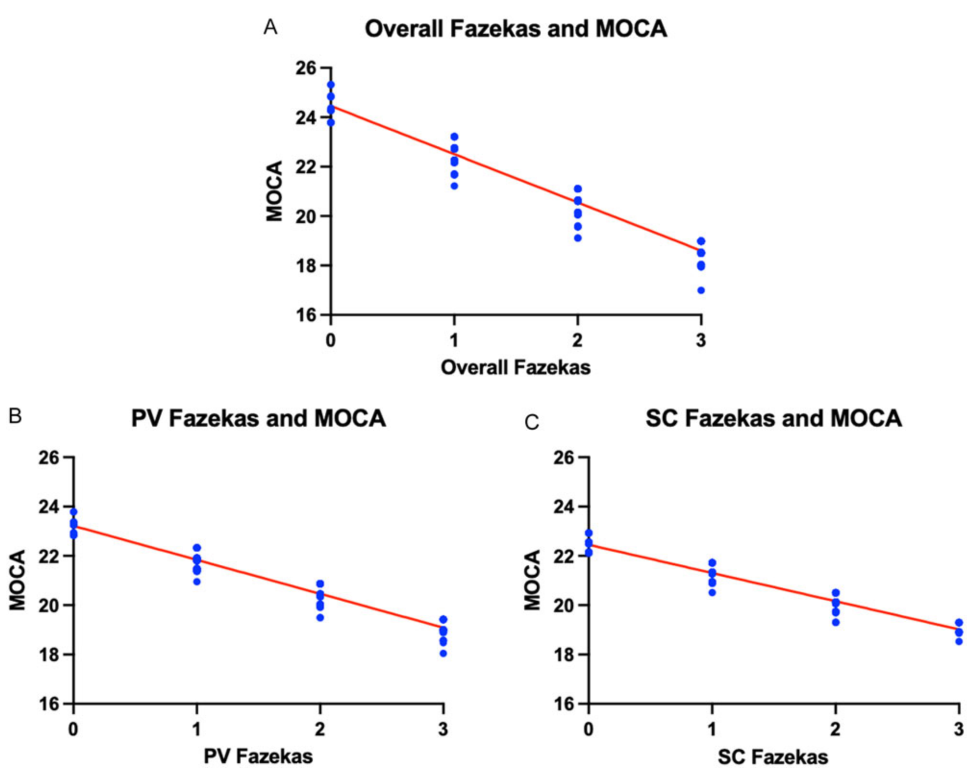

Figure 2. Graphical representation of the linear regression scatter plots between overall Fazekas score and predicted MoCA score **(Figure 2A)**; PV Fazekas and predicted MoCA score **(Figure 2B)**; and SC Fazekas and predicted MoCA score **(Figure 2C)**. The predicted MoCA scores were based on conducting multiple linear regression analyses adjusting for confounders. The model for overall Fazekas and MoCA was statistically significant with $R^2 = 0.097$, showing a negative association between overall Fazekas and MoCA (B = −2.11; 95% CI −2.89 to −1.33; $p < 0.001$). The model for PV Fazekas and MoCA was statistically significant with $R^2 = 0.050$, showing a negative association between overall Fazekas and MoCA (B = −1.46; 95% CI −2.23 to −0.68; $p <$ 0.001). The model for SC Fazekas and MoCA was statistically significant with $R^2 = 0.036$, showing a negative association between overall Fazekas and MoCA (B = −1.21; 95% CI −1.97 to −0.45; $p =$ 0.002). PV = periventricular; MoCA = Montreal Cognitive Assessment; SC = subcortical.

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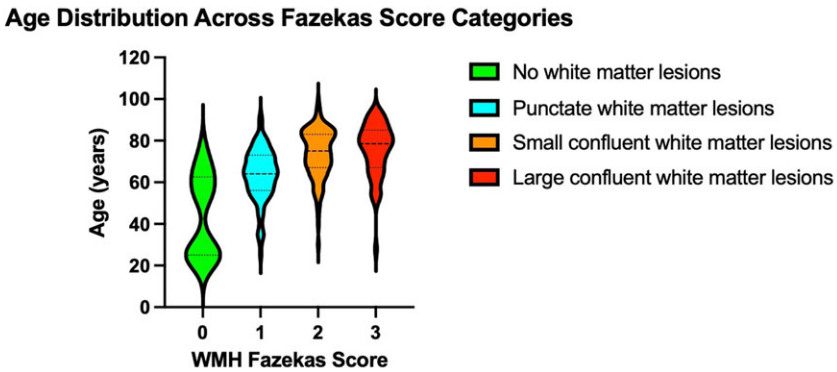

Figure 3. Violin plot demonstrating distribution of the age among different WMH Fazekas score categories based on the FLAIR MRI assessment. Within the Fazekas 0 group, 16 patients with a mean age and SD of 43.88 (19.92). Within the Fazekas 1 group, 79 patients with a mean age and SD of 63.59 (12.51). Within the Fazekas 2 group, 121 patients with a mean age and SD of 73.79 (11.99). Within the Fazekas 3 group, 58 patients with a mean age and SD of 75.64 (12.90). Note a bimodal distribution of patients with Fazekas score of 0; this could be due to the small number of patients within that group skewing the results. PV = periventricular; FLAIR = fluid-attenuated inversion recovery; SD = standard deviation.

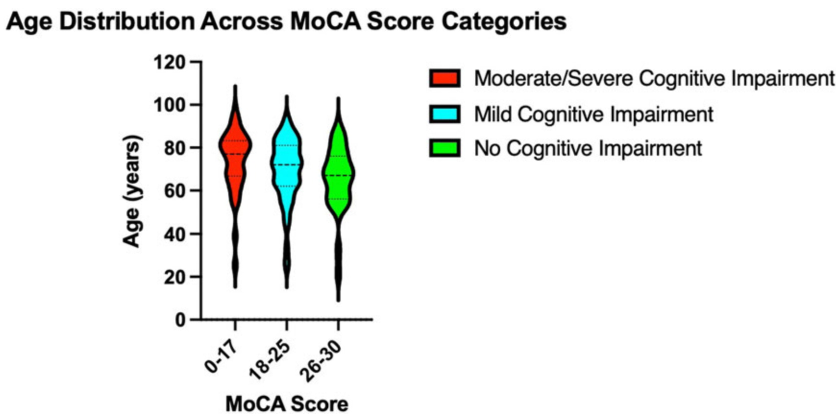

Figure 4. Violin plot demonstrating the distribution of the age among different MoCA score categories. Within the MoCA 0-17 group, 74 patients with a mean age and SD of 73.66 (14.63). Within the MoCA 18–25 group, 133 patients with a mean age and SD of 69.28 (14.93). Within the MoCA 26–30 group, 67 patients with a mean age and SD of 65.31 (15.12). MoCA = Montreal Cognitive Assessment; SD = standard deviation.

particular deficit in cognition.[28] Comparing PV and SC white matter generally, PV white matter has been shown to be more related to cognition.[29] In patients with all cause dementia, a meta-analysis reported that PV WMH were particularly shown to increase the risk of cognitive decline in dementia.[30] Another meta-analysis supported this association in patients without the diagnosis of dementia.[31] Evaluating the body of literature on PV vs SC changes, both the meta-analyses reported significant heterogeneity, and only a few of the included studies adjusted for WMH risk factors such as hypertension, diabetes and smoking.

The results of this study support prior findings, mirroring the significant association between an increased radiological quantification of WMH and decreased cognitive functioning found in the literature. Building upon this, PV lesions had a more significant effect with higher attributability to lowering cognitive performance, suggesting a stronger association between the PV white matter changes and cognitive function pathways as compared to SC white matter changes. Finally, age distributions across the Fazekas and MoCA categories within our local population demonstrate an association between older age and increased WMH severity on FLAIR MRI sequences as well as increased cognitive decline.

The association between WMH severity and worse cognitive function in this study therefore supports the prognostic use of WMH for earlier detection of cognitive decline. Given the ease of identification of these pathological features on FLAIR MRI sequences and the increasing use of MR imaging for various indications, our study suggests that the "incidental" finding of WMH should prompt risk factor evaluation and stratification. Patients with strong risk factors for cognitive decline could benefit from potentially earlier intervention, especially with new amyloid drugs on the horizon. Next steps would therefore entail the evaluation of treatment determination informed by MRI WMH severity in the local population and correlating this with patient clinical outcomes.

A standard regional WMH evaluation in patients who undergo brain MRI as a general practice in the future would possibly improve the outcomes of patients with cognitive decline. Radiologists should routinely report the extent and location of WMH even if incidentally found. Furthermore, to address the disproportionate PV white matter impact on cognition compared to SC white matter, future research may focus on developing a revised Fazekas scale weighing PV and SC changes differently. With the developing integration of artificial intelligence into the field of radiology, there is promise that evaluation of WMH will continue to improve in both efficiency and accuracy. A study by Kuwabara et al., 2024 introduced an artificial intelligence software developed to measure WMH volumes on FLAIR sequence images, which showed comparable accuracy to human reading.[32] Models could be adjusted to implement varying weighing scales depending on WMH regions with artificial intelligence software improving radiologists' efficiency and feasibility to integrate WMH evaluation in routine assessments.

One of the strengths of this study is that the analyses adjust for hypertension, diabetes and smoking, which helps attribute a more direct effect of the WMH on cognition. Moreover, examining WMH in patients who had a brain MRI at the hospital allows us to examine a wider range of patients without a specific diagnosis to improve generalizability while also maintaining relevance given the increased prevalence of risk factors in the in/outpatient setting, unlike healthy volunteers. Utilizing a validated qualitative tool such as the Fazekas scale also provides clinical relevance due to ease and efficiency of interpretation. Limitations of this study include the smaller sample size and patient selection from only one hospital. Finally, having both a qualitative and quantitative assessment of WMH severity could potentially provide more concrete results, eliminating the human error associated with qualitative MRI assessment.

Conclusion

We conducted a local study evaluating the cross-sectional relationship between severity of WMH lesions and cognitive functioning. Our findings support results seen in the literature, showing increased WMH severity to be associated with lower cognitive performance and confirming applicability to our population. We also demonstrate that WMH within the PV white matter had a greater effect on cognitive function compared to SC. The findings of this study suggest that MRI WMH evaluation should be routinely reported using Fazekas scale for early identification and perhaps intervention to address cognitive impairment.

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Authors contributions. FE drafted the protocol, collected the data, organized and processed the data, assisted with conducting statistical analysis, prepared the figures and tables and drafted the manuscript. LM conducted the statistical analysis and edited the manuscript. CF critically evaluated and edited the manuscript.

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