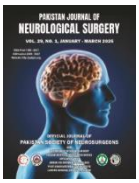

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Original Research

Micro-bleedings of Cerebrum and Leukoaraiosis: Magnetic Resonance Imaging-Based Correlation Analysis by Micro-Bleed Anatomical Rating and Fazekas

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ABSTRACT

Objectives: Using Fazekas and Micro-bleed Anatomical Rating Scales (MARS) to assess the inter-relationship of MB(C) and leukoaraiosis based on magnetic resonance imaging (MRI).

Materials and Methods: Cross-sectional observational research was carried out at the radiology department of RYK Hospital Rahim Yar Khan, Pakistan. The study involved 70 participants who had MRI brain scans and were discovered to have micro-bleeds. The Micro-bleed Anatomical Rating scale (MARS) was used to grade micro-bleeds and Fazeka's scale was implied for grading leukoaraiosis. The relationship between MARS and Fazeka's scale was ascertained by Spearman's correlation.

Results: The patient's mean age was 65 years and 2 months, with male to female gender ratio of 1.8:1. A significant correlation ($p<0.001$) was observed between micro-bleeds grading of MARS and Fazekas grades, with a significant correlation coefficient of 1. Cerebral micro-bleeds also correlated with coexisting diseases, notably hypertension (84.28%), diabetes (60.00%), and smoking (55.71%). MRI analysis showed micro-bleeds were most frequently in variable locations (44.6%), followed by lobar regions (27.7%), deeper areas (18.5%), and basal nuclei (9.2%).

Conclusion: Leukoaraiosis (LA) and MB(C) have a strong correlation that suggests micro-blood vessel ischemia and hemorrhage as ultimate outcomes.

Keywords: Leukoaraiosis, Fazekas, Intracerebral bleeds, Micro-Bleeds Anatomical Ratings, Stroke.

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INTRODUCTION

Tiny haemosiderin accumulations in the cerebrum signifying hemorrhagic episodes are called micro-bleeds of the cerebrum or MB(C). Understanding the site of hemorrhage can help understand the etiology of micro-bleeds. Whereas MB(C) found in deeper areas of the cerebrum are prone to be linked to angio-pathies of uncontrolled blood pressure, others present in distant lobar sites are frequently linked to angio-pathies caused by cerebral amyloid. Leukoaraiosis shares risk factors with micro-bleeds and hypertension and also has been connected to detrimental cognitive functions and is correlated with the severity of MB(C).

Small, clearly defined low signal patches in the lobar or deep cerebral areas that are seen on Magnetic Resonance Imaging (MRI)cerebral investigations are known as micro-bleeds of cerebrum MB(C). These bleeding episodes are linked to Small Vessel Disease (SVD) of the cerebrum and manifest like tiny haemosiderin accumulations around blood vessels in the cerebrum, typically contained within macrophages.[1,2]

Bleeding disorders, uncontrolled high blood pressure, vascular malformations, a history of stroke (ischemic and hemorrhagic), white matter abnormalities/leukoaraiosis (LA), and lacunar-shaped infarctions are risk factors linked to MB(C).[3] It has also been suggested that alcohol consumption, cigarette, and respiratory diseases of chronic duration like (COPD) are linked with MB(C)significantly. Chronic kidney diseases (CKD) and impaired kidney function are linked to MB(C).[4] Parkinson's, Alzheimer's, and multiple sclerosis as well as a few autoimmune diseases are a few more recently identified correlations.[5] Genetics also to some extent play an important role in the development of micro-bleeds of the cerebrum, it has been proved by many studies of the past that blood-associated genetic abnormalities that lead to bleeding disorders are also a risk factor for cerebral microbleeds.[6]The underlying etiology of MB(C) may be revealed by their location; MB(C) in deep cerebral locations are connected to pathologies of blood vessels associated with hypertension, while those in distant lobar areas are more closely linked with pathologies of cerebral amyloid.[7]

FLAIR and T2WI sequences identified locations of high signal, which are observed around ventricles and in white matter, are referred to as Ton magnetic resonance imaging (MRI), changes of white matter, or LA. They may be brought on by ischemia, decreased blood flow, or perivascular space dilatation around healthy arterioles.[8] Previous research has linked the presence of LA to poor cognitive functioning and has been linked to risk factors for both micro-bleeds and hypertension. It is also connected to how severe micro-bleeds of cerebrum MB(C)) are.[9] If there is a relationship between the MARS scale of MB(C) and the Fazekas grading, it has only been established through a small number of studies. There haven't been any attempts to quantitatively correlate white matter changes with the intensity of micro-bleeds in these studies. The aims and objective of the study were to quantitatively correlate white matter changes (Fazekas grading) with the intensity of cerebral micro-bleeds (MARS scale) and explore their shared risk factors, etiologies, and potential cognitive implications.

MATERIALS AND METHODS

Study design and setting

Between December 2021 and July 2023, observational cross-sectional research was carried out in the Radiology and Anatomy Disciplines of the RYK Hospital& Medical College, Rahim Yar Khan, Pakistan. The Ethics Committee approved the study (IERC RYKMC/H-2021/06219) and participants informed consent was obtained from all before the commencement of the study. Subjects diagnosed with MB(C) based on

magnetic resonance imaging (MRI) made up the sample population.

Sample Size

Based on the prior work of Yamada S et al, found a 0.48 correlation between MB(C) and periventricular hyperintensities, the sample size was determined.[10] Given an alpha error of 1% and the power of the study was 90% in the current investigation, a minimum sample size of 48 subjects was established.

Inclusion Criteria

Among the patients were those who had magnetic resonance imaging (MRI) and displayed signs of MB(C). There was no age limit or gender restrictions.

Exclusion Criteria

Patients with cerebral vasculitis, vascular anomalies, hematologic disorders, intracranial space-occupying lesions, neo-plastic diseases history of head trauma, and a history of cerebral parenchymal surgery or imaging evidence of such surgery are all considered excluded.

Study Procedure

There were 70 patients in the study. A thorough clinical history was acquired, which included information about the patient's admission, signs and symptoms, drug treatment regimen, results of different hematologic tests, and additional radiographic data. 1.5 Tesla, Matrix Coil Magnetic Resonance (MR) scanner, 18 channels (German made) were utilized to obtain the MRI images. All patients underwent Diffusion-Weighted Imaging (DWI), T1, and T2as well as Fluid Attenuation Inversion Recovery (FLAIR) and Susceptibility Weighted Imaging (SWI) sequences; a subset of patients also underwent MR Time of Flight (TOF) venography and angiography. The diagnosis of MB(C) was confirmed by SWI and for grading three observers independently implied the Micro-bleed Anatomical Rating Scale (MARS), while the Fazekas scale was used to grade the white matter pathologies based on Fluid Attenuation Inversion Recovery (FLAIR) images. The Fazekas scale and MARS severity correlation were performed afterward. Patient's signs and symptoms, co-morbidities, and lab investigations were all correlated with the outcomes.

Statistical Analysis

For the categorical data, proportions, and frequencies were displayed. The correlation between the two variables was ascertained using Spearman's correlation. Assuming compliance with all statistical test regulations, a p-value of 0.05 or less than 0.05 was considered statistically significant. Data analysis was performed by Microsoft Excel (2007) and Statistical Package for Social Sciences (SPSS) version-20 by (IBM).[11]

RESULTS

Patient's Demographics

The largest age group was 56 to 65 years with 34 (48.75%) subjects. There was a total of 45 (64.28%) men and 25 (35.71%) women and a gender distribution of 1.8:1 respectively. The mean age of the patients was 61 years and 2 months (Table 1).

Coexisting diseases and cerebral micro-bleeds (locations)

Most of the patients had coexisting diseases such as, 59 (84.28%) were confirmed patients of uncontrolled blood pressure or known hypertensive, 42 (60.00%) were Diabetes Mellitus (DM) positive, 39 (55.71%) were smokers, 20 (28.57%) were having positive history of previous myocardial infarction, 11 (15.71%) were being treated for chronic liver diseases (CLD) and 09 (12.85%) had positive history of stroke/Transient

ischemic Attack. (Table 2 & Figure 1).

Table 1: Age groups and gender distribution

Patient's age	Count	Percentage %
35 to 44 years	5	7.14%
45 to 55 years	7	10.00%
56 to 65 years	34	48.57%
66 to 75 years	18	25.71%
76to 85years	6	8.57%
Total	70	100%
Patient's gender	**Count**	**Percentage %**
Male	45	64.28%
Female	25	35.71%
Total	70	100.0%

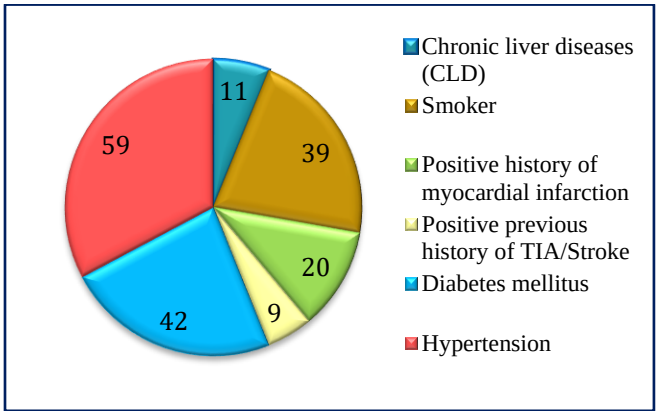

Figure 1: Association of comorbidities/systemic disease and microbleeds of the cerebrum (showing number of patients).

The Magnetic resonance imaging (MRI) based study of micro-bleeds revealed 6 (9.2%) were found in basal nuclei, 12 (18.5%) were in further deeper areas, 18 (27.7%) were located in the lobar area and 29 (44.6%) were of variable locations (Table -2).

MARS and Fazekas Consensuses

According to our findings, the majority of patients having MARS Grade1 were ranked grade 2 at

Table 2: systemic diseases/co-morbidities, location of micro-bleeds in the cerebrum

Co-morbidities or Systemic diseases	No of Patients	Percentage %
Chronic liver disease (CLD)	11	15.71%
Smoker	39	55.71%
Positive history of myocardial infarction	20	28.57%
Positive previous history of TIA/Stroke	09	12.85%
Diabetes mellitus	42	60.00%
Hypertension	59	84.28%
Cerebral locations of micro-bleeds		
Location	**No of Patients**	**Percentage**
Mixed	36	51.42%
Lobar	13	18.57%
Deep	11	15.71%
Basal Ganglia	10	14.28%
Total	70	100.0%

Table 3: Grading of patients according to Fazekas grades (1-6).

Fazekas Grades	Count	Percentage %
1	5	7.14%
2	20	28.57%
3	5	7.14%
4	18	25.71%
5	8	11.42%
6	14	20.00%
Sum up	70	100.0%

Fazekas grading 13 (50.00%); while grade -2 of MARS were classified as grade 4 of Fazekas 10 (55.55%) and graded as 3 on MARS scale were graded as 6th grade on Fazekas grading scale 12 (46.15%) (Table 4).

Statistical analysis (Spearman's correlation & Kappa)

A Spearman's correlation statistical test was conducted to evaluate the relationship between MARS and Fazekas, significant direct relationship between MARS and Fazekas was observed with a $p = < 0.001$, i.e., a rise in MARS grading resulted in an increase to Fazekas and a decline in MARS

grading resulted in a decrease in Fazekas grading. Inter-rater reliability was evaluated and was found acceptable with a (Kappa value=0.84) among all three observers.

Table 4: MARS and Fazekas consensuses.

Fazekas Grade	MARS Grade-1		MARS Grade-2		MARS Grade-3	
	Count	%	Count	%	Count	%
Fazekas 1	2	7.69%	2	11.11%	1	3.84%
Fazekas 2	13	50.00%	2	11.11%	5	19.23%
Fazekas 3	1	3.84%	1	5.55%	3	11.53%
Fazekas 4	6	23.07%	10	55.55%	2	7.69%
Fazekas 5	3	11.53%	2	11.11%	3	11.53%
Fazekas 6	1	3.84%	1	5.55%	12	46.15%
Total	26	100.0%	18	100.0%	26	100.0%

Table 5: MARS and Fazekas correlation.

Spearman's RHO		MARS	Fazekas
MARS	Correlation coefficient	1.000	0.398
	S (2-tailed)	-	<0.001*
	N	70	70

*significant value.

DISCUSSION

The sample was male dominant with 45 (64.82%)out of a total of 70 patients and the mean age of the patients was 61 years 2 months. 1289 consecutive patients were screened in previous research by Yang et al, on stroke outpatients. These patients were 60.49 years old on average; with 53.7% of them being male. This implies that cerebral micro-bleeds have age and gender as risk factors. In this study, 09 (12.85%) had previously experienced a transient ischemic attack (TIA)/stroke, mostly of the ischemic variety. Similar findings were reported previously in a study by Yang et al, research who reported that 14.6% of stroke outpatients who were screened had micro-bleeds.[12]

A previous study by Samanvitha et al, while describing the locations of micro-bleeds in the cerebrum reported that 44.6% were mixed types of cerebral micro-bleeds and were found on variable locations, 27.7 were located at lobar, 18.5% were infra-tentorial and 9.2% were present in basal ganglia. Our study demonstrated that mixed was 51.42%, the lobar location was second most affected with 18.57% of cases, deep/infratentorial were 15.71% and those of basal ganglia were 14.28%. Both the studies revealed results in agreement majority of micro-bleeds locations which was of mixed type as well as found a correlation between micro-bleeds and leukoariosis.[13]

Hypertension is a major risk factor for micro-bleeds of cerebrum MB(C). According to earlier research findings by Haller S et al, 59 participants (84.28%) in the current study had hypertension.[14] Work of Liu W et al, found that systolic hypertension has a direct link with infra-tentorial and deeper MB(C) intensity, on the other hand, the changes in diastolic hypertension were found to be exclusively related to deeper MB(C).[15] Pinping et al, the study also reported similar results Among 196 young and middle-aged patients with hypertension, 84 (42.9%) patients had CMBs. CMBs were more likely to occur in the deep brain tissue regions (41.8%), followed by the lobar or infratentorial region.[16] Micro-bleeds are more common in patients with lacunar infarction than in those with other subtypes of ischemic stroke. MB(C) rates are higher in patients with recurrent ICH. The importance of MB(C) for cognition has drawn more attention in recent years. According to the Rotterdam research, cerebral amyloid angiopathy has long been associated with lobar intra-cerebral hemorrhage

(ICH) and MB(C).[17]

Thirteen (18.57%) of the 19 patients in the current study who had strictly lobar cerebral micro-bleeds MB(C) had cognitive dysfunction, according to the analysis of cognitive dysfunction. The research work of Valenti R et al documented a relationship between the sum of MB(C) with the awareness/administrative and rhythm territories. Additionally, based on the sites, it was discovered that lobar MB(C) demonstrated a remarkable association with rhythm territories, while deep MB(C) and the attention/executive domain had a significant correlation.[18]

Research by Charidimou et al, revealed that micro-bleeds are more commonly linked to intra-cerebral hemorrhage.[19] Liu et al, in their study which had 982 MB(C) participants examined by Diffusion Tensor Imaging (DTI) reported that the internal capsule along with the corpus callosum of the patients showed increased mean diffusivity, reduced anisotropy (fractional) and increased diffusiveness (radial), suggesting that presence of MB(C) affected the degradation of micro-structural integrity of white matter, a finding similar to our study.[20]

Limitations

A relationship between anticoagulants and anti-platelets as a risk factor for the occurrence of micro-bleeds in cerebrum MB(C) could not be demonstrated because the temporal evolution of the MB(C) was not assessed in this study. Minor variations in scoring among the observers may have resulted from inconsistent counting-based grading on the MARS scale. Since many acute stroke patients failed to accomplish extensive brain study based on MRI in compliance with the protocol of SWI, so those patients were expelled from the study. Therefore, the sample size does not represent all individuals with unintentional micro-bleeds of the cerebrum.

CONCLUSION

The outcomes of small vessel ischemia and bleeding are reflected in the strong correlation between leukoaraiosis (LA) and micro-bleeds of cerebrum MB(C). When the severity of cerebral micro-bleeds increases, so do the pathological anomalies in white matter. Again, a sign of SVD, lacunar infarction is most frequently linked to MB(C). The correlation between MB(C) and stroke, hypertension, and advanced age emphasizes how crucial it is to detect and report MB(C) as soon as possible. Diagnostic hints are provided by the correlation between deep, infratentorial MB(C) and uncontrolled blood pressure and the preponderance of MB(C)in the lobar territory with analytical disorder.

Future studies should focus on developing predictive models, refining diagnostic tools, and exploring targeted therapies for early detection and management of MB(C) and associated white matter anomalies. Additionally, longitudinal research on the progression of SVD and its impact on cognitive decline, along with population-specific studies, could provide deeper insights into its prevention and treatment.

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REFERENCES

1. Jiang M, Wu S, Zhang Y, Li Y, Lin B, Pan Q, Tian S, Ni R, Liu Q, Zhu Y. Impact of White Matter Hyperintensity and Age on Gait Parameters in Patients with Cerebral Small Vessel Disease. J Am Med Dir Assoc. 2023;24(5):672-678. DOI: 10.1016/j.jamda.2022.12.001
2. Oussoren FK, Van Leeuwen RB, Schermer TR, Poulsen LNF, Kardux JJ, Bruintjes TD. Cerebral Small Vessel Disease in Elderly Patients with Sudden Sensorineural Hearing Loss. Otol Neurotol. 2023 1;44(3):e171-e177.

DOI: 10.1097/MAO.0000000000003813.
3. Aman M, Alam MS, Khan FU, Anwar SS, Ahmad A, Khan U, Bazai UK. High-altitude cerebral edema manifesting as T2/FLAIR hyperintensity and microbleeds in the white matter on MRI brain. Radiol Case Rep. 2023;18(5):1705-1709. DOI: 10.1016/J.RADCR.2023.01.071
4. Jin P, Ye S, Ye H, Tong Q, Zhang Q. Urinary microalbumin/creatinine ratio is a predictor of the occurrence and severity of leukoaraiosis. Neuro Endocrinol Lett. 202312;44(8):528-536. PMID: 38131176. https://pubmed.ncbi.nlm.nih.gov/38131176/
5. Chen TY, Chan PC, Tsai CF, Wei CY, Chiu PY. White matter hyperintensities in dementia with Lewy bodies are associated with poorer cognitive function and higher dementia stages. Front Aging Neurosci. 2022 26;14:935652. DOI: 10.3389/fnagi.2022.935652.
6. Khan S, Siddiqui M, Kamal AK. My patient's brain MRI has cerebral microbleeds—what does this finding mean? J Pak Med Assoc. 2011;61(10):1029-1030.
7. Wu B, Huang D, Yi Z, Yu F, Liu L, Tang X, Jing K, Fan J, Pan C. Correlation between body composition and white matter hyperintensity in patients with acute ischemic stroke. Medicine (Baltimore). 2023;15;102(50):e36497. DOI: 10.1097/MD.0000000000036497.
8. Cedres N, Ferreira D, Machado A, Shams S, Sacuiu S, Waern M et al. Predicting Fazekas scores from automatic segmentations of white matter signal abnormalities. Aging (Albany NY). 2020;12;12(1):894-901. DOI: 10.18632/aging.102662.
9. Evlice A, Sanli ZS, Boz PB. The importance of Vitamin-D and Neutrophil-Lymphocyte Ratio for Alzheimer's Disease. Pak J Med Sci. 2023;39(3):799-803. DOI: 10.12669/pjms.39.3.7024.
10. Yamada S, Saiki M, Satow T, Fukuda A, Ito M, Minami S, et al. Periventricular and deep white matter leukoaraiosis have a closer association with cerebral micro-bleeds than age. Eur J Neurol. 2012;19(1):98-104. Doi: 10.1111/j.1468-1331.2011.03451.x.
11. Masuadi E, Mohamud M, Almutairi M, Alsunaidi A, Alswayed AK, Aldhafeeri OF. Trends in the Usage of Statistical Software and Their Associated Study Designs in Health Sciences Research: A Bibliometric Analysis. Cureus. 2021;11;13(1):e12639. DOI: 10.7759/cureus.12639.
12. Yang Q, Yang Y, Li C, Li J, Liu X, Wang A, et al. Quantitative assessment and correlation analysis of cerebral microbleed distribution and leukoaraiosis in stroke outpatients. Neurological Research. 2015;37(5):403-09. DOI: 10.1179/1743132815Y.0000000027
13. Samanvitha G and Ananad K. Correlation between Cerebral Microbleeds and White Matter Changes on MRI using Microbleed Anatomical Rating and Fazekas Scales: A Cross-sectional Study. International Journal of Anatomy, Radiology and Surgery. 2024;13(1): 01-05. DOI: 10.7860/IJARS/2024/66333.2962.
14. Haller S, Vernooij MW, Kuijer JPA, Larsson EM, Jäger HR, Barkhof F. Cerebral micro-bleeds: Imaging and clinical significance. Radiology. 2018;287(1):11-28. DOI: 10.1148/radiol.2018170803.
15. Liu W, Liu R, Sun W, Peng Q, Zhang W, Xu E, et al. CASISP Study Group. Different impacts of blood pressure variability on the progression of cerebral micro-bleeds and white matter lesions. Stroke. 2012;43(11):2916-22. DOI: 10.1161/STROKEAHA.112.658369.
16. Pingping H, Rui J, Jianhao L, Peng W, Feizhou D. Risk factors of cerebral microbleeds in young and middle-aged hypertensive patients. Neurol Asia. 2021;26(4):688-94. Doi: 10.54029/2021yny.
17. Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, et al. Cerebral micro-bleeds are associated with worse cognitive function: The Rotterdam Scan Study. Neurology. 2012;78(5):326-33. DOI: 10.1212/WNL.0b013e3182452928.
18. Valenti R, Del Bene A, Poggesi A, Ginestroni A, Salvadori E, Pracucci G, et al. VMCI-Tuscany Study Group. Cerebral micro-bleeds in patients with mild cognitive impairment and small vessel disease: The Vascular Mild Cognitive Impairment (VMCI)-Tuscany study. J Neurol Sci. 2016;368:195-202. DOI: 10.1016/j.jns.2016.07.018.
19. Charidimou A, Kakar P, Fox Z, et al. Cerebral microbleeds and the risk of intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: systematic review and meta-

analysis. Journal of Neurology, Neurosurgery & Psychiatry 2013;84:277-280. DOI: 10.1136/jnnp-2012-303379

20. Liu JY, Zhou YJ, Zhai FF, Han F, Zhou LX, Ni J, et al. Cerebral Micro-bleeds Are associated with Loss of White Matter Integrity. AJNR Am J Neuroradiol. 2020;41(8): 1397-404. DOI: 10.3174/ajnr.A6622

Additional Information

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Human Subjects: Waiver of consent was obtained from the ethical review committee.

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AUTHORS CONTRIBUTION

Sr.#	Author's full name	Intellectual Contribution to Paper in Terms of
1	Amanullah Khokhar	1. Study design and methodology.
2	Shahid Maqbool Korai	2. Paper writing.
3	Raja Faisal Zulfiqar & Sadia Javaid	3. Data collection and calculations.
4	Shahid Kamran	4. Analysis of data and interpretation of results.
5	Sadia Sundus	5. Literature review and referencing.
6	Raja Faisal Zulfiqar	6. Editing and quality insurer.