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Cut-Off Point Values for the Number and Average Size of T2 Hyperintense Focies in the Brain White Matter

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Abstract

Objective: The aim of this study is to determine the cut-off values for the increase in the number and average size of T2 hyperintense focies in the brain white matter in patients with arterial hypertension (AH), type 2 diabetes mellitus (T2DM), both conditions combined, and in healthy individuals.

Methods: A total of 275 patients aged between 35 and 70 years were included in the study. The imaging was performed using a Siemens Magnetom Aera 1.5 Tesla magnetic resonance imaging device. T2 hyperintense foci were assessed using the turbo inversion recovery magnitude sequence with a slice thickness of 3.5 mm and a 10% interslice gap. Quantitative and qualitative data obtained during the study were analyzed using variation, discriminant, dispersion, correlation, Receiver Operating Characteristic (ROC) analysis, and evidence-based medicine methods with MS Excel 2019 and IBM SPSS Statistics 26 software.

Results: In healthy individuals, the cut-off point for the number of focies was determined to be 12, and the average focus size was 2.9 mm. In patients with AH, the cut-off value was 14 foci with a mean size of 1.9 mm. For those with T2DM, the corresponding values were 14 foci and 2.9 mm in average size. In individuals with both AH and T2DM, the cut-off point was 23 for foci, while the average foci size was 2.9 mm.

Conclusion: By establishing group-specific cut-off values, this study provides clinicians with a useful reference point to support differential diagnosis in routine practice.

Keywords: Cut-off point, hypertension, magnetic resonance tomography (MRT), T2 hyperintense foci, type 2 diabetes mellitus

INTRODUCTION

Strong clinical evidence from tomographic and physical examinations indicates that white matter hyperintensities increase the risk of stroke, cognitive decline, mortality, depression, gait disturbances, and motor dysfunctions.[1,2] These foci are associated with brain atrophy, complications of small vessel disease, focal progressive brain damage, and underlying silent brain injuries, which contribute to infarct expansion and deterioration of major arterial stroke regions. They serve as neuroradiological markers of brain impairment.[3]

Age-related enlargement of perivascular spaces, increased interstitial fluid concentration, heightened blood-brain barrier permeability, and plasma pooling result in combined foci with periventricular localization observable on magnetic resonance imaging (MRI) scans. Histopathologically, these areas correspond to mild demyelination.[4,5] However, since autopsy is inaccessible for living patients, it is crucial to differentiate these foci using diagnostic MRI. Literature reports that T2 hyperintense foci are more frequently observed in elderly patients, although not all of them demonstrate histopathological demyelination.[4,6] Nevertheless, in contemporary practice, it remains challenging to distinguish which portion of these foci in older adults is related to aging and which is associated with underlying diseases. Recent studies employing functional MRI have examined that even in healthy adults, the localization of T2 hyperintense foci may contribute to specific cognitive impairments.[7]

Researchers have emphasized that in migraine patients, the presence of aura and the severity of headaches increase the number of T2 hyperintense foci; however, the specific brain regions where these foci predominantly develop remain under investigation.[8]

Additionally, the relationship between T2 hyperintense foci and gender has been studied, revealing a slightly higher prevalence in females. Nevertheless, over 80% of the variance in these gender differences remains unexplained. The study of T2 hyperintense foci in white matter should advance beyond cerebrovascular diseases to broader neurological contexts.[9]

Furthermore, investigators have explored the association between diabetes mellitus and T2 hyperintense focies.[10,11] Notably, type 2 diabetes mellitus is linked with an increased number of these foci. The localization of T2 hyperintense foci in periventricular and deep white matter reflects their differing pathological characteristics. Clinically, periventricular foci are associated with brain atrophy, while deep white matter foci correlate with cerebrovascular events.

Considering the issues highlighted above, it was deemed essential to investigate clinically relevant problems that will enhance the diagnostic accuracy of T2 hyperintense focies.

MATERIAL AND METHODS

The study included MRI results of the brain conducted between 2020 and 2023 from 275 patients in ..... Hospital and ..... University. The control group consisted of 86 healthy individuals, and results were compared across all groups. Among the patients, 77 had arterial hypertension (AH), 51 had type 2 diabetes mellitus (T2DM), and 61 had both AH and T2DM. This is a non-invasive method; that is why there is no informed consent. Ethics committee of University of Azerbaijan Medical University (Approval No 22, Date 09.07.2022). The age range of the participants was between 35 and 70 years. To exclude age-related T2 hyperintense foci associated with advanced aging, patients over 70 years old were not included in the study. Individuals with a history of oncological diseases, brain trauma, brain surgery, demyelinating disorders, granulomatous diseases, alcohol abuse, or diagnosed with migraine were excluded from the research. Due to these factors, the presence of white matter hyperintensities formed by such causes could potentially lead to inaccurate results in the study. Patients with AH included in the research had elevated systolic blood pressure ranging from 140 to 200 mmHg. The duration of disease in AH patients ranged from 10 to 15 years, while in patients with T2DM, it ranged between 5 and 10 years. Only patients diagnosed with T2DM who had blood glucose levels above 7 mmol/L were included. Patients selected for this study were those referred to the clinic for brain MRI examinations due to various complaints such as headache, dizziness, head pressure, nausea, hemiparesis-hemiplegia, gait and behavioral disturbances, facial drooping, facial numbness, among others.

This study utilized high-resolution T2 turbo inversion recovery magnitude (TIRM) images acquired using a 1.5 Tesla Siemens Magnetom Aera MRI scanner. During the brain MRI examinations, all patients underwent imaging in the following sequences: axial, coronal, and sagittal T2; axial TIRM; sagittal isometric T1; and susceptibility-weighted imaging, which is more sensitive to hemosiderin and calcium deposits. For this study, the axial TIRM sequence was specifically employed. The T2 TIRM images were obtained with parameters TR = 9200 ms, TI = 2450 ms, TE = 84 ms, slice thickness of 3.5 mm, and an interslice gap of 10% of the slice thickness.

Regarding the study design, it is classified as analytical; by methodology, clinical; by scale, selective; by type, scientific; by material, prospective; by duration, cross-sectional; and by location, clinical.

MAIN POINTS

- Arterial hypertension (AH), type 2 diabetes mellitus, and their combination significantly influence the increase in both the number and size of T2 hyperintense focies detected during brain magnetic resonance imaging (MRI) examinations.
- The cut-off values for the number and average size of T2 hyperintense foci identified by brain MRI in patients without a history of AH or type 2 diabetes can serve as predictive markers for these conditions.
- There is a statistically significant positive correlation between the number and average size of T2 hyperintense foci in patients with AH, type 2 diabetes mellitus, or both. As the number of foci increases, their size also grows, indicating greater damage to the brain parenchyma.

Quantitative and qualitative data collected during the study were analyzed using variation, discriminant, dispersion, correlation, ROC analysis, and evidence-based medicine methods via MS Excel 2019 and IBM SPSS Statistics 26 (IBM SPSS Corp.; Armonk, NY, USA) software.

Quantitative data are expressed in tables as mean ± standard error (M, ±m) and median with interquartile ranges (Me, Q1, Q3). For group comparisons, the Mann–Whitney *U*-test, Student's *t*-test with Bonferroni correction, and Kruskal-Wallis tests were applied.

ROC analysis was performed using a binary classification model, constructing the integral value of sensitivity and specificity (ROC curve) across the entire range of the studied parameters. The area under the ROC curve was calculated and statistically evaluated. Identification of cut-off points, which represent the farthest point from the reference line on the ROC curve, allows the test to be used as a selection criterion in future studies.[12]

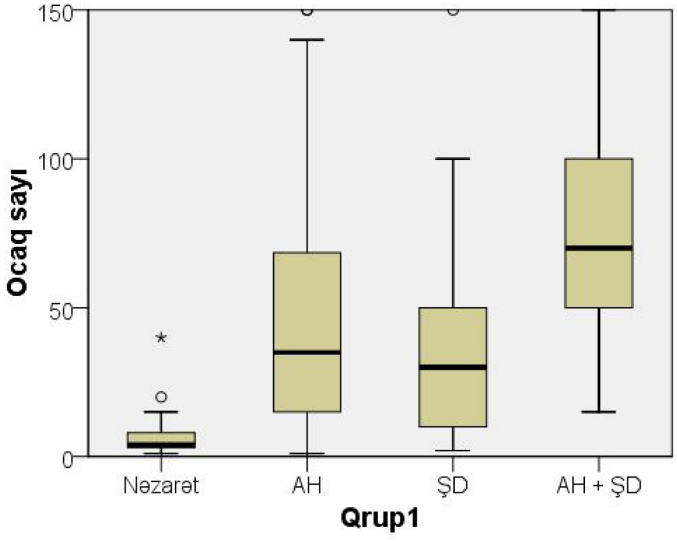
RESULTS

T2 hyperintense foci were detected in 51 patients in the control group, 68 patients with AH, 46 patients with T2DM, and 56 patients with both AH and T2DM. The presence of AH, T2DM, and their combination significantly increased both the number and size of T2 hyperintense focies in the brain compared to the control group ($p_F < 0.001$, $p_H < 0.001$) (Graph 1).

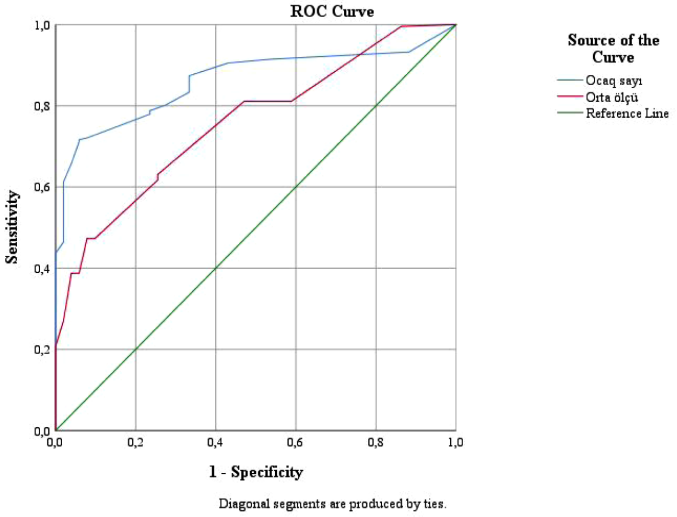
As shown in the Graph 2 below, the area under the ROC curve representing the integral sensitivity and specificity for the number of foci in the practically healthy control group was 0.862 ± 0.023. For the average foci size, it was 0.758 ± 0.033. Comparison between the control group and all other groups demonstrated statistically significant lower foci numbers and sizes in the control group ($P < .001$).

The cut-off point for the number of foci in the healthy control group was established at 12 (sensitivity 71.6 ± 3.0%, specificity 94.1 ± 3.3%, accuracy 75.8 ± 2.6%). For the average foci size, the cut-off was 2.9 mm (sensitivity 47.3 ± 3.4%, specificity 92.2 ± 3.8%, accuracy 55.7 ± 3.0%).

Therefore, having fewer than 12 foci and an average foci size smaller than 2.9 mm serves as an informative indicator for identifying healthy individuals.



Graph 1. Comparative evaluation number of foci among main gGroups.



Graph 2. Area under the ROC curve for foci number and average size in the control group.

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% CI Lower Bound	Asymptotic 95% CI Upper Bound
Number of foci	0.862	0.023	0.000	0.817	0.906
Average size	0.758	0.033	0.000	0.693	0.822

As illustrated in the Graph 3 below, the area under the ROC curve representing the combined sensitivity and specificity for the diagnosis of AH is 0.901 ± 0.029. For the average foci size, this value is 0.760 ± 0.043.

The cut-off point for the number of foci in patients with AH is 14 (sensitivity 77.9 ± 5.0%, specificity 94.1 ± 3.3%, accuracy 84.9 ± 3.3%). For the average foci size, the cut-off is 1.9 mm (sensitivity 83.8 ± 4.5%, specificity 52.9 ± 7.0%, accuracy 70.6 ± 4.2%).

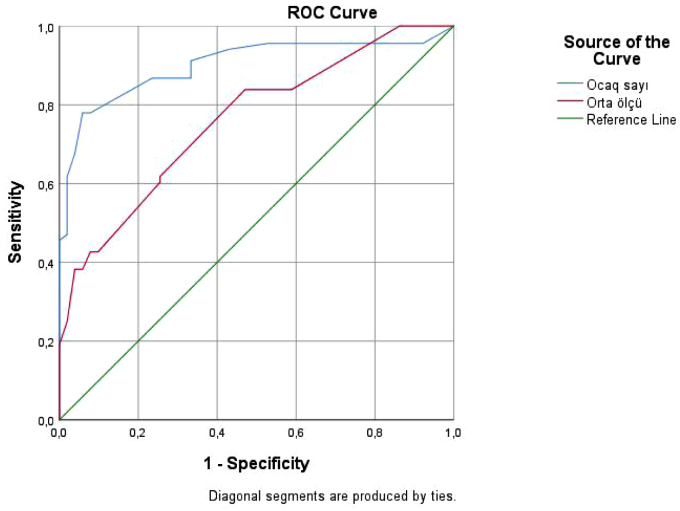
Thus, having more than 14 foci and an average foci size greater than 1.9 mm serves as an informative marker for the presence of AH.

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% CI Lower Bound	Asymptotic 95% CI Upper Bound
Number of foci	0.901	0.029	0.000	0.843	0.959
Average size	0.760	0.043	0.000	0.676	0.845

In patients with T2DM, the cut-off point for the number of focies was determined to be 14. Thus, having more than 14 foci serves as an informative indicator for the presence of T2DM. Among 46 T2DM patients, 33 had foci counts exceeding this threshold. For this cut-off value, sensitivity was calculated as 71.7 ± 6.6%. Among 51 practically healthy individuals, 48 had fewer than 14 foci, resulting in a specificity of 94.1 ± 3.3%. The overall diagnostic accuracy of the test was 83.5 ± 3.8%.

The positive predictive value (PPV) for detecting more than 14 foci was 91.7 ± 4.6%, while the negative predictive value (NPV) was 78.7 ± 5.2%.

In patients with T2DM, the cut-off point for the average foci size was determined to be 2.9 mm. Thus, an average foci size greater than 2.9 mm serves as an informative indicator for the presence of T2DM. Among the 46 patients with T2DM, 21 had an average foci size exceeding this threshold. For this cut-off point, sensitivity was calculated as 45.7 ± 7.3%. Among 51 healthy individuals, 47 had average foci sizes smaller than 2.9 mm, yielding a specificity of 92.2 ± 3.8%. The overall diagnostic accuracy of the test was 70.1 ± 4.6%. The PPV for identifying average foci sizes greater than 2.9 mm was 84.0 ± 7.3%, and the NPV was 65.3 ± 5.6%.



Graph 3. Area under the ROC curve for foci number and average size in the arterial hypertension group.

In patients with both AH and T2DM, the cut-off point for the number of focies was determined to be 23. Thus, having more than 23 foci serves as an informative marker for the presence of concurrent AH and T2DM. Among the 56 patients with AH+T2DM, 54 had foci counts exceeding this threshold. For this cut-off value, sensitivity was calculated as 96.4 ± 2.5%. Among 51 healthy individuals, 47 had fewer than 23 foci, resulting in a specificity of 98.0 ± 1.9%. The overall diagnostic accuracy of the test was 97.2 ± 1.6%.

The PPV for foci counts greater than 23 was 98.2 ± 1.8%, while the NPV was 96.2 ± 2.7%.

In patients with both AH and T2DM, the cut-off point for the average foci size was identified as 2.9 mm. Thus, an average foci size greater than 2.9 mm serves as an informative indicator for the presence of AH+T2DM. Among the 56 patients with AH+T2DM, 41 had average foci sizes exceeding this threshold. For this cut-off value, the sensitivity was 73.2 ± 5.9%. Among 51 practically healthy individuals, 47 had average foci sizes smaller than 2.9 mm, yielding a specificity of 92.2 ± 3.8%. The overall diagnostic accuracy of the test was 82.2 ± 3.7%.

The PPV for average foci sizes greater than 2.9 mm was 91.1 ± 4.2%, while the NPV was 75.8 ± 5.4%.

DISCUSSION

T2 hyperintense focies—particularly those with a tendency to merge—have been shown to impair cognitive functions such as memory, executive functioning, and response speed.[13] In light of such findings, investigating the underlying causes of T2 hyperintense foci is of great

importance in order to implement preventive measures. Magnetic resonance imaging remains the most suitable non-invasive method for detecting T2 hyperintense foci, and it also allows for follow-up imaging to monitor changes over time.

Not only the number, but also the progression rate of these foci has been associated with the development of dementia.[14] Larger foci, especially those prone to confluence, may lead to disability within 1 year.[14] This study similarly found that as the number of foci increased, their average size also grew, resulting in more extensive damage to the brain parenchyma. This supports the hypothesis that a higher foci number increases the likelihood of foci merging. This finding demonstrated a statistically significant positive correlation ($P < .001$).

T2 hyperintense foci can be evaluated using visual-manual assessment, as well as semi-automated or fully automated methods. However, automated techniques are often costly.[14] Therefore, the visual-manual method remains practical and accessible for most clinical settings. The findings obtained in this study can be effectively utilized by radiologists in routine diagnostic practice.

Alzheimer's disease manifests with dementia symptoms in 40%-80% of cases, with vascular factors cited as the primary etiology. T2 hyperintense focies detected on brain MRI serve as independent risk factors for dementia and cognitive decline, even in the absence of concurrent brain injury.[15]

There is strong evidence that hypertension independently contributes to the development and progression of T2 hyperintense foci. Studies indicate that individuals with hypertension and a high burden of T2 hyperintense foci exhibit these foci predominantly in areas of cerebral hypoperfusion. Hypertension leads to microstructural white matter damage that persists despite adequate treatment.[16] Preventing or treating hypertension is therefore a vital step in slowing the progression of T2 hyperintense foci and preserving brain health with advancing age. The presence of T2 hyperintense foci doubles the risk of dementia and triples the risk of stroke.[16]

The number of patients with T2DM continues to rise, posing a significant global health concern. The likelihood of microvascular complications is closely linked to T2DM. There is substantial evidence that T2DM causes structural brain anomalies such as T2 hyperintense foci, lacunar infarcts, and brain atrophy. Sun et al[17] investigated these changes in their compatriots, the Chinese population. T2 hyperintense foci represent silent brain injuries located in the periventricular and deep white matter. Although hypertension is a risk factor for T2 hyperintense foci, studies indicate that diabetes contributes to the formation of more numerous and larger T2 hyperintense focies.[17]

Over the past decades, both AH and T2DM have reached epidemic proportions.[18] When coexisting, T2DM and AH exhibit a synergistic effect, increasing the risk of both microvascular and macrovascular complications.[19,20] According to global assessments, over 50% of individuals with diabetes are diagnosed with AH. Epidemiological data show that the risk of dementia in diabetic patients without hypertension is 19%, whereas this risk rises to 23% in patients with both diabetes and hypertension.[21,22]

Globally, approximately 45.8% of adults with diabetes remain undiagnosed, which leads to untreated conditions and increased risk of complications.[23,24] According to the World Health Organization, about half (46%) of patients with AH are unaware of their condition.[25]

During this study, several limitations were noted. Firstly, the authors were unable to evaluate and compare the findings using fully automated systems. Secondly, they did not establish a direct clinical correlation between the detected foci and dementia.

In conclusion, based on the values obtained (along with appropriate specificity and sensitivity percentages), a subset of patients with detected T2 hyperintense foci are considered as healthy without suspected pathology. Additionally, in patients unaware of their AH or T2DM, the number and size of T2 hyperintense focies detected during brain MRI—performed due to headaches or other reasons—can guide radiologists in advising treating physicians and clinicians by utilizing the identified cut-off point values. Therefore, these findings are regarded as highly valuable.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics committee of University of Azerbaijan Medical University (Approval No 22, Date 09.07.2022).

Informed Consent: Informed consent was not obtained from the patients as the study method is non-invasive.

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Author Contributions: Concept – M.S.; Design – H.I.; Supervision – M.S.; Resources – L.G.; Materials – L.G.; Data Collection and/or Processing – L.G.; Analysis and/or Interpretation – M.S.; Literature Search – L.G.; Writing Manuscript – L.G.; Critical Review – M.S.

Declaration of Interests: The authors have no conflict of interest to declare.

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