Research Article / Araştırma Makalesi

Evaluation of Lesion Burden in Pediatric Patients with Multiple Sclerosis by Computer Aided Algorithm and Comparison with Standard Detection Methods

Multipl Sklerozlu Pediatrik Hastalarda Lezyon Yükünün Bilgisayar Destekli Algoritma ile Değerlendirilmesi ve Standart Tespit Yöntemleriyle Karşılaştırılması

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Abstract

Background: The aim of this retrospective study was to assess the lesion burden in pediatric patients with multiple sclerosis (pMS) using a computer-assisted algorithm, specifically the VolBrain program. The study aimed to compare the performance of this automated tool with traditional detection methods performed by neuroimaging analysts, providing valuable insights into the potential of automated tools for lesion quantification in pMS.
Materials and Methods: The study cohort consisted of 20 PMS patients, aged 10-18 years, registered at Atatürk University Research Hospital. Lesion assessment was performed using the VolBrain program (by an anatomist) and standard detection methods (by a neuroradiologist) using T2 SPACE dark matter sequences. Statistical analysis included Wilcoxon and Pearson correlation tests, and the study adhered to ethical considerations and standardised magnetic resonance imaging (MRI) protocols.
Results: In this study, pMS patients aged 10-18 years, the cohort consisted of 60% females (n=12) and 40% males (n=8). The mean age for females was 15.67±1.969 and for males 14.50±2.20 years (p=0.24). Plaque count analysis showed a statistically significant difference between radiologist and VolBrain assessment in all pMS patients (p=0.021). Significant differences were also observed in female pMS patients (p=0.034) but not in males (p=0.362). Correlations between radiologist and VolBrain assessments showed significant associations in both female and male patients, with strong correlations observed for plaque number, lesion burden and Expanded Disability Status Scale (EDSS) scores (p<0.01).
Conclusions: This study demonstrates the potential of the VolBrain programme in assessing lesion burden in pMS patients. The observed correlations with traditional methods and clinical parameters support the concurrent validity of VolBrain and emphasise its potential clinical relevance. Incorporating automated tools into routine clinical practice could improve the accuracy of lesion quantification and thus contribute to improved monitoring and management of pMS.

Key Words: Pediatric MS, VolBrain, Lesion Plaque Number, Lesion Burden, EDSS

Öz

Amaç: Bu retrospektif çalışmanın amacı, bilgisayar destekli bir algoritma olan VolBrain programını kullanarak pediatrik Multiple Skleroz'lu (pMS) hastalarda lezyon yükünü değerlendirmektir. Çalışma, bu otomatik aracın performansını nörogörüntüleme analistleri tarafından gerçekleştirilen geleneksel tespit yöntemleriyle karşılaştırarak pMS'de lezyon ölçümü için otomatik araçların potansiyeline ilişkin önemli bilgiler sunmayı hedeflemiştir.
Materyal ve Metod: Çalışma grubu Atatürk Üniversitesi Araştırma Hastanesi'ne kayıtlı 10-18 yaş arası 20 pMS hastasından oluşmuştur. Lezyon değerlendirmesi VolBrain programı (anatomist tarafından) ve standart tespit yöntemleri (bir nöroradyolog tarafından) kullanılarak T2 SPACE dark matter sekansları kullanılarak yapıldı. İstatistiksel analiz Wilcoxon ve Pearson korelasyon testlerini içeriyordu ve çalışma etik hususlara ve standartlaştırılmış manyetik rezonans görüntüleme (MRI) protokollerine bağlı kaldı.
Bulgular: Bu çalışmada 10-18 yaş arası pMS hastalarının %60'ı kız (n=12) ve %40'ı erkeklerden (n=8) oluşmaktadır. Yaş ortalaması kızlarda 15,67±1,969, erkeklerde ise 14,50±2,20 yıldı (p=0,24). Plak sayımı analizi, tüm pMS hastalarında radyolog ve VolBrain değerlendirmesi arasında istatistiksel olarak anlamlı bir fark olduğunu gösterdi (p=0,021). Kız pMS hastalarında da anlamlı farklılıklar gözlenirken (p=0,034), erkeklerde ise bu fark görülmedi (p=0,362). Radyolog ve VolBrain değerlendirmeleri arasındaki korelasyonlar, hem kız hem de erkek hastalarda plak sayısı, lezyon yükü ve Genişletilmiş Engellilik Durum Ölçeği (EDSS) skorları için güçlü korelasyonlar olduğunu göstermiştir (p<0,01).
Sonuç: Bu çalışma, VolBrain programının pMS hastalarında lezyon yükünü değerlendirmedeki potansiyelini ortaya koymaktadır. Geleneksel yöntemler ve klinik parametrelerle gözlemlenen korelasyonlar VolBrain'in eşzamanlı geçerliliğini desteklemekte ve potansiyel klinik uygunluğunu vurgulamaktadır. Otomatik araçların rutin klinik uygulamaya dahil edilmesi, lezyon miktarının doğruluğunu artırabilir ve böylece pMS'nin daha iyi izlenmesine ve yönetimine katkıda bulunabilir.

Anahtar Kelimeler: Pediatrik MS, VolBrain, Lezyon Plak Sayısı, Lezyon Yükü, EDSS

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system with a wide range of neurological findings reflecting both focal and widespread damage to the brain and spinal cord (1). MS patients (diagnosed at <18 years of age) constitute 3.5-5% of all MS patients and their incidence varies between 0.2-0.64/100000 (2). The fact that some signs and symptoms are observed in these children from an early age and that these findings are not specific to MS disease are seen as precursors of uncertainties about the disease. To address these uncertainties, MRI sensitively detects lesions associated with MS. MRI serves as a crucial tool for the objective monitoring of disease progression and the evaluation of treatment effectiveness. Precise and accurate lesion measurements, including number, volume, and type, obtained from MRI are essential endpoints for assessing the impact of the disease (3). Therefore, the segmentation and quantification of MS lesions necessitate high precision and accuracy to provide reliable clinical insights. Alternatively, the detection of MS lesions is often performed by radiologists or trained neuroimaging analysts. These professionals manually annotate and measure lesions using semi-automatic annotation tools in both clinical trials and imaging studies. While manual segmentation remains a necessary practice, its broader clinical application must be improved due to its inherent time-consuming and labor-intensive nature and its susceptibility to inter/intra-observer biases and errors. Consequently, there is a growing demand for fully automated tools that facilitate rapid, accurate, and precise segmentation of MS lesions from MRI scans (4). Numerous automatic segmentation methods have been proposed, and the recent integration of deep learning techniques has expedited the development of more accurate intuitive lesion segmentation tools. Nonetheless, challenges persist, and current state-of-the-art techniques need to achieve the precision of radiologist manual segmentation (3, 4).

In light of this information, our study was aimed to retrospectively evaluate the lesion burden in patients with pMS using a computer-aided algorithm and compare its performance with standard detection methods.

Materials and Methods

Study Design

This retrospective study examined pediatric patients diagnosed with MS registered at Atatürk University Research Hospital. pMS cases were assessed using the VolBrain program, employing a computer-aided algorithm. Concurrently, the same cohort of patients with pMS underwent evaluation by neuroimaging analysts using traditional detection methods.

By the 2010 McDonald criteria, this study encompassed individuals within the age range of 10 to 18 years who received a diagnosis of MS. EDSS scores of all MS patients were evaluated. Exclusion criteria were applied to eliminate children with other neurodegenerative diseases from the study cohort.

Evaluation of Plaque Number and Lesion Burden by the Radiologist

In this study, measurements of plaque number and lesion burden in the traditional detection method were conducted by a neuroradiologist employing T2 Space dark fluid sequences. The number of lesions was determined as the total number, and lesion burdens are classified as mild-moderate and advanced by the neuroradiologist.

Evaluation of Plaque Number and Lesion Burden by VolBrain

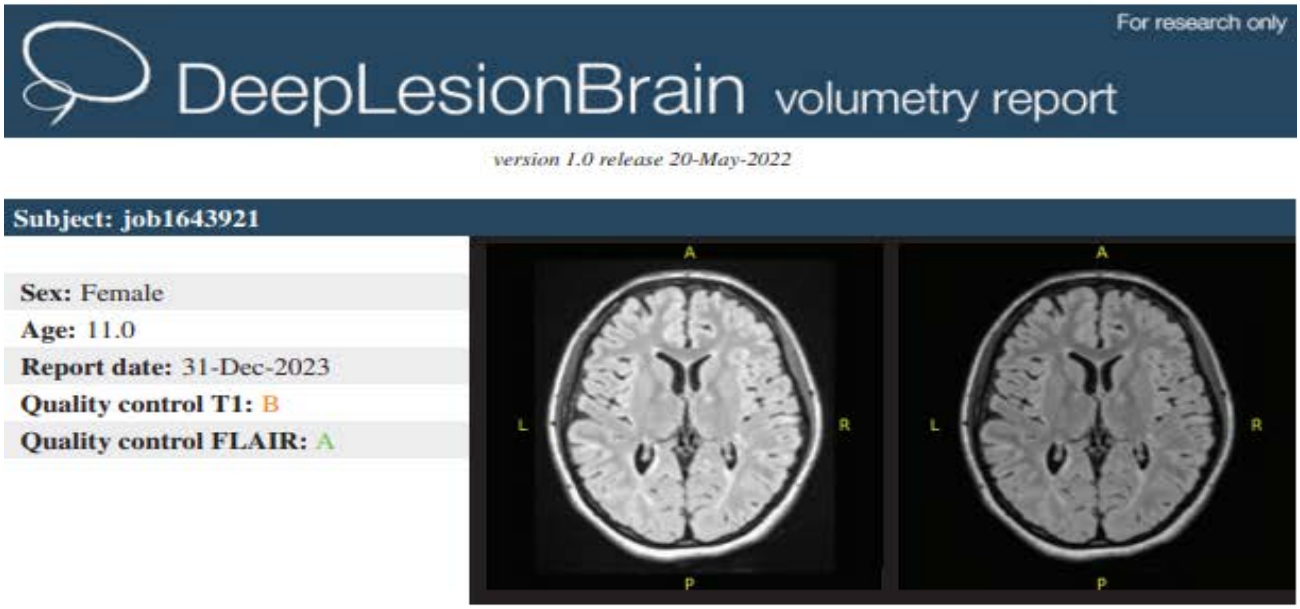
In this study, measurements of plaque number and lesion burden in the VolBrain program were conducted by an anatomist employing T2 SPACE dark fluid sequences. The VolBrain program computed lesion numbers as discrete numerical data, delineating counts for Total lesions, Periventricular, Deepwhite, Juxtacortical, and Infratentorial categories. Furthermore, the VolBrain program determined lesion burden as percentages, separately delineating proportions for Total lesions, Periventricular, Deepwhite, Juxtacortical, and Infratentorial lesions (Figure 1.).

A cohort of 28 pediatric patients diagnosed with MS and registered at Atatürk University Research Hospital, Department of Radiology, was examined. Eight patients were excluded from the study due to the unavailability of MRI scans in the specified sequence, resulting in a final evaluation of 20 pMS. A priori power analysis, conducted using the G-Power 3.1.9.4 software, determined that the sample size was adequate. The calculated effect size was 0.88, with a power of 0.95 at a 95% confidence interval and a significance level of 0.05 (5). These parameters affirm that the sample size meets the desired criteria.

The Clinical Research Ethics Committee of Ataturk University Faculty of Medicine, by the Helsinki Declaration, rendered a decision with the assigned ethics committee reference B.30.2.ATA.0.01.00/808 on October26, 2023.

MR protocol

The MRI protocol used in the study is as follows. Anatomical structures were visualized using high-resolution T2 SPACE dark fluid sequences. The imaging sequence was sagittal, with a repeat time of 1900 ms/2.84s, a flip angle of 15 degrees, an echo time of 2.67 ms, a field of view (FOV) of 256 mm^2, a matrix size of 256x256, and a total of 160 slices. The slice thickness was 1 mm, and the imaging resolution was 1x1x1 mm^3 isotropic (6).



Lesion	Count	Volume (cm^3 / %)	Lesion burden (%)
Total lesions	49	5.8973 / 0.3765	0.9647
Periventricular	17	4.6218 / 0.2951	0.7560
Deepwhite	22	0.8588 / 0.0548	0.1405
Juxtacortical	8	0.2733 / 0.0174	0.0447
Infratentorial	2	0.1434 / 0.0092	0.0235
Cerebellar	2	0.1434 / 0.0092	0.0235
Medular	0	0.0000 / 0.0000	0.0000

All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the IC volume).

The quality control evaluates the input image quality after preprocessing. A = good, B = moderate (i.e., the output requires human verification) and C = bad (i.e., the output should not be used).

The Lesion burden is calculated as the lesion volume divided by the total WM volume (in percent).

The Asymmetry Index is calculated as the difference between right and left volumes divided by their mean (in percent).

All the result images are located in the MNI space (neurological orientation).

Values between brackets show expected limits (95%) of normalized volume in function of sex and age for each measure for reference purpose. Values outside the limits are highlighted in red.

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Figure 1. Lesion brain measurement in Volbrain program

VolBrain Method

The VolBrain method, accessible at https://volbrain.net/, serves as an open-access platform for automated segmentation of diverse brain structures. In our study, Total Lession, Periventricular, Deepwhite, Juxtacortical, Infratentorial, Cerebellar and Medular lesion numbers were calculated using the VolBrain lesion-brain program. Additionally, the Mricloud method, a web-based software developed by Johns Hopkins University, was utilized for lesion calculation coupled with brain parcellation in MRI—the initial step in the calculation process involved converting MR images to "gz or rar" format. Subsequently, a file with the "DICOMDIR" extension was opened through a DICOM viewer software program. High-resolution T2 SPACE dark fluid sequences were accessed using Mricron to exhibit anatomical structures, and a gz extension file in compressed FSL format was generated. The ensuing stage comprised uploading the converted images in "gz" format to the VolBrain webpage and registering and submitting gz extension files to the system. After an approximate duration of 5-10 minutes, volumetric and lesion datas for all brain regions were acquired, with the outcomes being saved as PDF files. The images were further documented in native and MNI formats, facilitating a three-dimensional visual evaluation using itksnap (6, 7).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows was used to analyze all study parameters. The normality of data was verified using Skewness and Kurtosis values, which should fall between −2 and +2 for normally distributed data (1). However, it was determined that the data did not adhere to a normal distribution. The Wilcoxon test was employed to evaluate the significance of binary parameters relative to each other. The median of the 25–75 percentile was used to present continuous variables, while frequencies (n) and percentages (%) were used for categorical variables (8). Pearson Correlation test was used to examine the relationships between parameters. Statistical values with $p<0.05$ were considered significant.

Results

In this study, an investigation was conducted on pediatric patients diagnosed with multiple sclerosis within the age range of 10 to 18 years. The cohort comprised 12 female individuals, constituting 60% of the sample, and 8 male individuals, representing 40% of the cohort. The mean age of pMS females was determined to be 15.67±1.969. Similarly, the mean age of pMS males was calculated as 14.50±2.20 (p=0.24).

In the analysis of plaque counts among all pMS patients, a statistically significant disparity was observed between assessments conducted by radiologists and those performed by the VolBrain (p=0.021). In scrutinizing the plaque counts among female pMS patients, a statistically significant disparity emerged between assessments conducted by radiologist and those undertaken by VolBrain (p=0.034). Conversely, in the analysis of plaque counts among male pMS patients, no statistically significant difference was discerned between evaluations carried out by radiologist and those facilitated by VolBrain (p=0.362). Table 1 displays the means of plaque numbers and lesion burdens assessed by the radiologist, the averages of plaque numbers and lesion burdens evaluated by VolBrain, and the average EDSS scores across all patients.

The relationship between the plaque numbers, lesion burden and expanded disability status scale in volbrain and radiologist evaluations of pMS Patients was evaluated separately in the total patient (Table 2.), female patients and male patients.

Significant correlations were observed in female patients with pMS between the number of lesions assessed by the radiologist, the number of lesions evaluated by the VolBrain program, and the EDSS scores (r=0.647, p=0.023; r=0.850, p=0.001, respectively). Also significant correlations were observed in female patients with pMS between the number of lesions assessed by the VolBrain program with the number of lesions evaluated by the radiologist, VolBrain assessed lesion burden, and the EDSS scores (r=0.647, p=0.023; r=0.665, p=0.018; r=0.871, p=0.001, respectively). Significant correlations were observed in female patients with pMS between the lesion burden assessed by the VolBrain program with the lesion burden evaluated by the radiologist and the number of lesions evaluated by the VolBrain program (r=0.822, p=0.001; r=0.665, p=0.018, respectively).

Significant correlations were observed in male patients with pMS between the number of lesions assessed by the VolBrain program with the EDSS scores (r=0.945, p=0.001). Significant correlations were observed in male patients with pMS between the lesion burden assessed by the VolBrain program with the lesion burden evaluated by the radiologist (r=0.877, p=0.004).

Table 1. Mdian and Percentage Values of Expanded Disability Status Scale Scores, Plaque Counts, and Lesion Burdens

	Female pMS			Male pMS			Total pMS		
	Median	**%25**	**%75**	**Median**	**%25**	**%75**	**Median**	**%25**	**%75**
Number of Plaques Assessed by the Radiologist	36	17.25	45	22.50	12.75	30.25	28	16.50	44
Number of Plaques Assessed by VolBrain	44	38	48.50	28	11.50	38.25	39	27	46.75
Lesion Burden Assessed by the Radiologist	1.5	1	2	1.5	1	2	1.5	1	2
Lesion Burden Assessed by VolBrain	0.62	0.35	1.06	0,53	0,42	1,80	0.55	0.40	1.15
Expanded Disability Status Scale	3	2	3,87	2	1.5	2,75	2.5	2	3

pMS: pediatric multiple sclerosis

Table 2. Relationship Between Plaque Numbers, Lesion Burden, and Expanded Disability Status Scale in Volbrain and Radiologist Assessments of pMS Patients.

		Number of Plaques Assessed by the Radiologist	Number of Plaques Assessed by VolBrain	Lesion Burden Assessed by the Radiologist	Lesion Burden Assessed by VolBrain	Expanded Disability Status Scale
Number of Plaques Assessed by the Radiologist	**r**	1	0.663	0.108	-0.002	0.832
	p		0.001**	0.651	0.994	0.001**
Number of Plaques Assessed by VolBrain	**r**	0.663	1	0.108	-.0155	0.899
	p	0.001**		0.651	0.515	0.001**
Lesion Burden Assessed by the Radiologist	**r**	0.108	0.108	1	0.766	0.166
	p	0.651	0.651		0.001**	0.484
Lesion Burden Assessed by VolBrain	**r**	-0.002	-0.155	0.766	1	-0.028
	p	0.994	0.515	0.001**		0.905
Expanded Disability Status Scale	**r**	0.832	0.899	0.166	-0.028	1
	p	0.001**	0.001**	0.484	0.905	

**:p<0.05, **:p<0.01*

Discussion

This study sought to retrospectively assess the lesion burden and number in pediatric patients with MS using a computer-aided algorithm and to compare its performance with standard detection methods. The findings from this investigation offer valuable insights into the potential of automated tools, such as the VolBrain program, for accurately quantifying MS lesions and assessing disease burden in the pediatric population and as far as we know, it is among the first studies in the literature on patients with pMS.

MRI has an important role in the diagnosis of MS, as it shows the spread in time and space and reveals the findings of other demyelinating diseases in the differential diagnosis (9). pMS presents distinctive challenges attributable to the heterogeneous nature of symptoms and the intricacies involved in diagnosing children. MRI emerges as a pivotal modality for discerning lesions associated with MS in this pediatric cohort, offering indispensable data for ongoing disease monitoring and treatment assessment (10). Nonetheless, the manual segmentation of these lesions, conventionally executed by radiologists, is riddled with challenges, primarily stemming from the dual burdens of labor-intensive temporal demands and vulnerability to inherent biases. In response to these challenges, the integration of automated tools propelled by deep learning methodologies stands as a promising avenue (11). Nevertheless, the judicious consideration of the precision of such automated tools remains paramount in ensuring their clinical utility and reliability in the pMS context (12).

The quantitative evaluation of plaque numbers assumes paramount importance in the realm of MS as it functions as a pivotal metric for assessing the severity and progression of the disease. Plaques, indicative of demyelination and axonal damage within the central nervous system, stand as distinctive pathological hallmarks of MS. The vigilant monitoring of the dynamic evolution of plaque numbers through imaging modalities, such as MRI, offers critical insights into the trajectory of the disease. A heightened plaque burden frequently correlates with augmented disability and a more aggressive clinical course (13, 14).

In this study, the number of plaques was measured by both radiologists and the Volbrain program. The observed disparities in plaque counts among pMS patients, as assessed by both radiologists and VolBrain, give rise to crucial considerations regarding the reliability and consistency of evaluation methods in clinical settings. The statistically significant difference noted in the total pMS patient group suggests potential variations in the interpretation of plaque counts between traditional radiological assessments and those conducted using VolBrain. Notably, when specifically scrutinizing female pMS patients, a similar statistically significant disparity was observed, reinforcing the notion that the evaluation methods might have a differential impact based on gender. On the contrary, in the analysis of plaque counts among male pMS patients, no statistically significant difference was discerned between assessments conducted by radiologists and those facilitated by VolBrain. This finding underscores the importance of considering gender-specific factors in the assessment of multiple sclerosis lesions, as the disease may manifest differently in male and female patients (15).

Lesion burden assumes paramount significance in the comprehensive comprehension and management of MS. Lesions, characterized by areas of demyelination and inflammation in the central nervous system, serve as crucial indicators of the disease's progression and its impact on neurological function. The extent and distribution of these lesions contribute directly to the clinical manifestations and levels of disability experienced by individuals with MS. Assessing lesion burden and lession plaque numbers not only facilitates the diagnosis and monitoring of the disease but also informs treatment decisions and aids in prognosis estimation. A high lesion burden often correlates with increased neurological impairment and a heightened likelihood of disability progression (16). Monitoring changes in lesion burden over time

through advanced imaging techniques provides valuable insights into disease activity and the response to therapeutic interventions. Consequently, understanding and quantifying lesion burden in MS patients play a pivotal role in tailoring personalized treatment plans, optimizing patient care, and advancing research efforts aimed at developing more effective therapies for this intricate neurological disorder (17).

The findings of this study highlight a significant correlation between lesion burden measurements obtained by radiologists and those generated by VolBrain, reinforcing the reliability of both methods in assessing lesion burden. The overall strong correlation in the total patient cohort (r=0.766, p=0.001) suggests a consistent and robust relationship between the two measurement techniques. This alignment is particularly noteworthy as the lesion burden was quantified using different units–percentage for VolBrain and a qualitative scale (mild-moderate-severe) for radiologists.

The observed high correlation within specific patient subgroups, such as female and male patients with pMS, further strengthens the validity of the lesion burden assessments. In female pMS patients, the correlation coefficient was notably strong (r=0.822, p=0.001), indicating a reliable association between the two measurement methods. Similarly, male pMS patients exhibited a remarkably high correlation (r=0.877, p=0.004), emphasizing the consistency of lesion burden measurements across diverse patient demographics. These findings have important implications for clinical practice and research, as they suggest that VolBrain, a tool that employs percentage-based measurements, aligns closely with the assessments made by experienced radiologists using a different scale. The high correlation coefficients not only support the concurrent validity of VolBrain in measuring lesion burden but also underscore its potential as a valuable and efficient tool for lesion quantification, offering a quantitative perspective that complements traditional qualitative assessments. In conclusion, the strong correlation observed between lesion burden measurements by VolBrain and radiologists across the total patient cohort, as well as within gender-specific subgroups, supports the concurrent validity of VolBrain in assessing lesion burden in pMS. These findings contribute to the growing body of literature on automated image analysis tools, showcasing their potential to enhance and streamline the diagnostic process in neuroimaging studies (18).

Similar outcomes to the present study have been reported in existing literature. Koc et al (11). documented a noteworthy correlation between VolBrain and radiologists in quantifying lesion numbers. In a related investigation, Yamamoto et al (19). posited that a computer-aided algorithm, such as VolBrain, holds utility in the determination of lesion burden. Their study emphasized the potential benefits of employing computational tools for lesion burden assessment. The findings from these studies above align with the results presented in our investigation, collectively underscoring the robustness and reliability of automated methods, particularly VolBrain, in the realm of lesion quantification. These consistent observations across various studies contribute to the growing body of evidence supporting the effectiveness of computer-aided algorithms in enhancing the precision and efficiency of lesion assessments, thereby offering valuable insights into neuroimaging research and clinical applications (18, 19).

The observed significant correlations among various parameters in female patients with pMS provide valuable insights into the relationship between lesion assessment, burden, and clinical disability. The study reveals compelling connections between the number of lesions assessed by both the radiologist and the VolBrain program, emphasizing the consistency in lesion identification between traditional imaging analysis and automated software.

The robust correlation between the number of lesions evaluated by VolBrain and the EDSS scores underscores the clinical relevance of these imaging findings. This suggests that the extent of lesions, as identified by the automated program, is closely linked to the overall disability level in female patients with pMS. The strong correlation coefficients (r=0.850 and r=0.871) highlight the potential of automated lesion assessment in predicting and understanding the severity of clinical manifestations. Furthermore, the interplay between different assessment methods is highlighted by the significant correlations observed between the number of lesions assessed by VolBrain and the lesion burden evaluated by the radiologist. This emphasizes the consistency in lesion burden determination, whether through manual or automated processes. The positive correlation with the number of lesions evaluated by VolBrain further supports the reliability of this software in capturing the comprehensive lesion profile in pMS (19). The significant correlations observed in this study provide a strong foundation for the integration of automated lesion assessment tools, such as VolBrain, in the comprehensive evaluation of female patients with pMS. These findings not only validate the reliability of such tools in lesion detection and burden assessment but also emphasize their potential clinical utility in predicting and understanding the severity of disability in pMS. Further research and validation studies may be warranted to solidify the role of automated tools in enhancing the precision and efficiency of clinical decision-making in the management of pMS (11, 18).

Limitations and Future Directions

While promising, our study has limitations, including a relatively small sample size and a single-center setting, which may impact the generalizability of the findings. Future studies with larger, more diverse cohorts and multi-center collaborations are needed to ensure we validate our results' external validity. Additionally, the study focuses on a specific automated tool, and comparisons with other existing algorithms could provide a more comprehensive understanding of their relative merits.

Conclusion

In conclusion, our study contributes valuable insights into the evaluation of lesion burden in pediatric MS patients using the VolBrain program. The observed correlations with traditional methods and clinical parameters support the potential clinical relevance of this automated algorithm. As technology advances, incorporating such tools into routine clinical practice could enhance the efficiency and precision of lesion parameters, contributing to improved monitoring and management of pediatric multiple sclerosis.

Ethical Approval: *The Clinical Research Ethics Committee of Ataturk University Faculty of Medicine, by the Helsinki Declaration, rendered a decision with the assigned ethics committee reference B.30.2.ATA.0.01.00/808 on October26, 2023.*

Author Contributions:
Concept: G.D., A.Y.
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