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Beyond the Surface: Delving Deeper Into Leukoaraiosis With Multivoxel Magnetic Resonance Spectroscopy

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Abstract

Objective: To investigate metabolite changes in patients with leukoaraiosis employing multivoxel magnetic resonance spectroscopy (MRS) with the focus on periventricular white matter and explicate the biochemical alterations associated with leukoaraiosis and their impact on lesion load.

Methods: This prospective study was conducted on 64 patients with a known history of leukoaraiosis (mean age, 66.40±8.96 years; 54 men and 10 women) referred for magnetic resonance imaging, wherein MRS was performed. For comparison, 128 age- and gender-matched healthy individuals (mean age, 61.98±8.18 years; 40 men and 88 women) who comprised the control group also underwent MRS. We correlated metabolite ratios (NAA/Cr, NAA/Cho, and Cho/Cr) analyzed on MRS with lesion load measured by semiautomated software.

Results: The NAA/Cr ratio was significantly lower, whereas the NAA/Cho ratio was significantly higher in the control group compared with the patients with leukoaraiosis ($P<.0001$). The Cho/Cr ratio was also significantly higher in the controls compared with the patients with leukoaraiosis ($P<.0034$). This suggests that patients with leukoaraiosis exhibit significant metabolic differences compared with healthy controls. We observed no correlation between the metabolite ratios and lesion load, which indicates that the degree of white matter hyperintensities is not related to the metabolic changes in leukoaraiosis.

Conclusions: This study explicates the understanding of leukoaraiosis and underscores the potential of MRS as a biomarker for early diagnosis of leukoaraiosis.

Keywords: leukoaraiosis, multivoxel magnetic resonance spectroscopy, NAA/Cr, NAA/Cho, Cho/Cr, biomarkers

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Что скрывается за лейкоареозом? Углубленное изучение методом мультивоксельной магнитно-резонансной спектроскопии

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Резюме

Цель: Изучить метаболические изменения у пациентов с лейкоареозом посредством мультивоксельной магнитно-резонансной спектроскопии (МРС), уделив особое внимание перивентрикулярному белому веществу, и проанализировать биохимические изменения, связанные с лейкоареозом, и их влияние на объем поражения.

Методы: В данном проспективном исследовании приняли участие 64 пациента (средний возраст: 66,40 ± 8,96 лет; 54 мужчины и 10 женщин), имевших в анамнезе лейкоареоз и направленных на МРТ, в ходе которой им проведена мультивоксельная МРС. Для сравнения мультивоксельную МРС также выполнили 128 здоровым участникам, соотносящихся по возрасту и полу (средний возраст: 61,98 ± 8,18 лет; 40 мужчин и 88 женщин) и вошедших в контрольную группу.

Соотношения метаболитов NAA/Cr, NAA/Cho и Cho/Cr, проанализированные с помощью мультивоксельной МРС, коррелировали с объемом поражения, измеренным полуавтоматической программой.

Результаты: Соотношение NAA/Cr было достоверно ниже, а соотношение NAA/Cho достоверно выше в контрольной группе по сравнению с пациентами с лейкоареозом ($p<0,0001$); кроме того, соотношение Cho/Cr было достоверно выше в контроль-

ной группе по сравнению с пациентами с лейкоареозом (p<0,0034). Это свидетельствует о том, что пациенты с лейкоареозом демонстрируют существенные метаболические различия по сравнению со здоровыми участниками. Кроме того, не наблюдалось корреляции между соотношением метаболитов и объемом поражения, что указывает на то, что выраженность гиперинтенсивности белого вещества не связана с метаболическими изменениями при лейкоареозе.

Заключение: Данное исследование расширяет понимание лейкоареоза и подчеркивает потенциал применения мультивоксельной МРС в качестве биомаркера для ранней диагностики лейкоареоза.

Ключевые слова: лейкоареоз, мультивоксельная магнитно-резонансная спектроскопия, NAA/Cr, NAA/Cho, Cho/Cr, биомаркеры

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Introduction

Leukoaraiosis (LA), also known as white matter hyperintensities (WMH), is commonly observed on magnetic resonance imaging (MRI) scans of older adults and individuals with vascular risk factors. Characterized by areas of high signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences, LA primarily affects the periventricular and subcortical white matter in the brain. These lesions are associated with a variety of neurological and cognitive impairments, including dementia, gait disturbances, and cerebral small vessel disease. Furthermore, LA is linked to adverse clinical outcomes, such as cognitive decline and increased risk of stroke.[1,2]

The LA pathophysiology involves chronic ischemic damage due to hypoperfusion, leading to demyelination, axonal loss, and gliosis within the affected white matter.[3] Despite its clinical importance, precise mechanisms underlying LA development and progression are not fully understood. This knowledge gap underscores the need for more detailed investigation into metabolic and biochemical changes associated with these lesions. Previous studies primarily focused on structural aspects of LA, using imaging modalities, eg, MRI, to quantify lesion load and distribution.[3] However, there is growing recognition of the need to explore the metabolic changes associated with these lesions to gain a more comprehensive understanding of their pathophysiology. Advanced imaging techniques, such as multivoxel magnetic resonance spectroscopy (MRS), can be crucial in this effort.

MRS offers a promising approach: noninvasive in vivo measurement of various brain metabolites, providing a window into the brain's biochemical environment. Analyzing metabolite ratios, such as N-acetyl aspartate to creatine (NAA/Cr), N-acetyl aspartate to choline (NAA/Cho), and choline to creatine (Cho/Cr), gives insights into neuronal health, membrane turnover, and cellular energy metabolism.[4] These metabolic markers are essential for understanding the pathophysiological changes occurring in LA.

Our study aims to delve deeper into the metabolic alterations in LA using multivoxel MRS, specifically focusing on the periventricular white matter, a frequently affected region. The choice of an intermediate echo time (TE) (135 milliseconds) is critical for optimizing the detection of these metabolites and minimizing the overlap of their signals.[5,6] By correlating these metabolite ratios with the lesion load, we aim to elucidate the metabolic changes that occur in the LA progression. Understanding these changes is essential for developing targeted therapeutic interventions and improving clinical outcomes.

This study leverages the capabilities of MRS to explore the metabolic landscape of LA. By examining key metabolite ratios and their relationship with lesion severity, we aim to contribute to the growing body of knowledge on the pathophysiology of white matter lesions. Our findings have the potential to inform future research and clinical practices aimed at mitigating the LA impact on the brain health and cognitive function.

Methods

Image Acquisition

Brain MRI was performed using a MAGNETOM ESSENZA – a Tim+Dot system 1.5 T scanner with a 16-channel head/neck coil (Siemens Healthineers, Germany). This setup enabled both standard MRI and MRS without repositioning. The routine brain MRI sequences included T1-weighted (repetition time [TR], 500 ms; TE, 8.9 ms; slice thickness, 5.0 mm; distance factor, 30%; number of slices, 23; voxel size, 0.7×0.7×5.0 mm; flip angle, 90°; field of view [FOV], 230×230 mm), T2-weighted (TR, 4290 ms; TE, 101 ms; slice thickness, 5.0 mm; distance factor, 30%; number of slices, 23; voxel size, 0.5×0.5×5.0 mm; flip angle, 150°; FOV, 230×230 mm), and T2 FLAIR axial images (TR, 9000 ms; TE, 92 ms; slice thickness, 5.0 mm; distance factor, 30%; number of slices, 23; voxel size, 0.4×0.4×5.0 mm; flip angle, 150°; FOV, 230×220 mm).

WMH Volume Measurement

Hyperintense signal changes, indicative of LA, were visually graded on MRI scans. Volume measurements of these regions were further validated using ITK-SNAP 4, semiautomated software supported by the Chan Zuckerberg Initiative through grant "Bridging the Gap In Medical Image Analysis and Biomechanics with ITK-SNAP" (Figure 1). During the active contour step, the low threshold mode was adjusted to automatically segment and isolate hyperintense areas. Only periventricular WMH within the 1H-MRS area were analyzed.

Multivoxel MRS (1H-MRS)

1H-MRS was employed to accurately measure metabolite concentrations in specific brain regions. Sagittal and coronal T1-weighted spin-echo and coronal T2-weighted

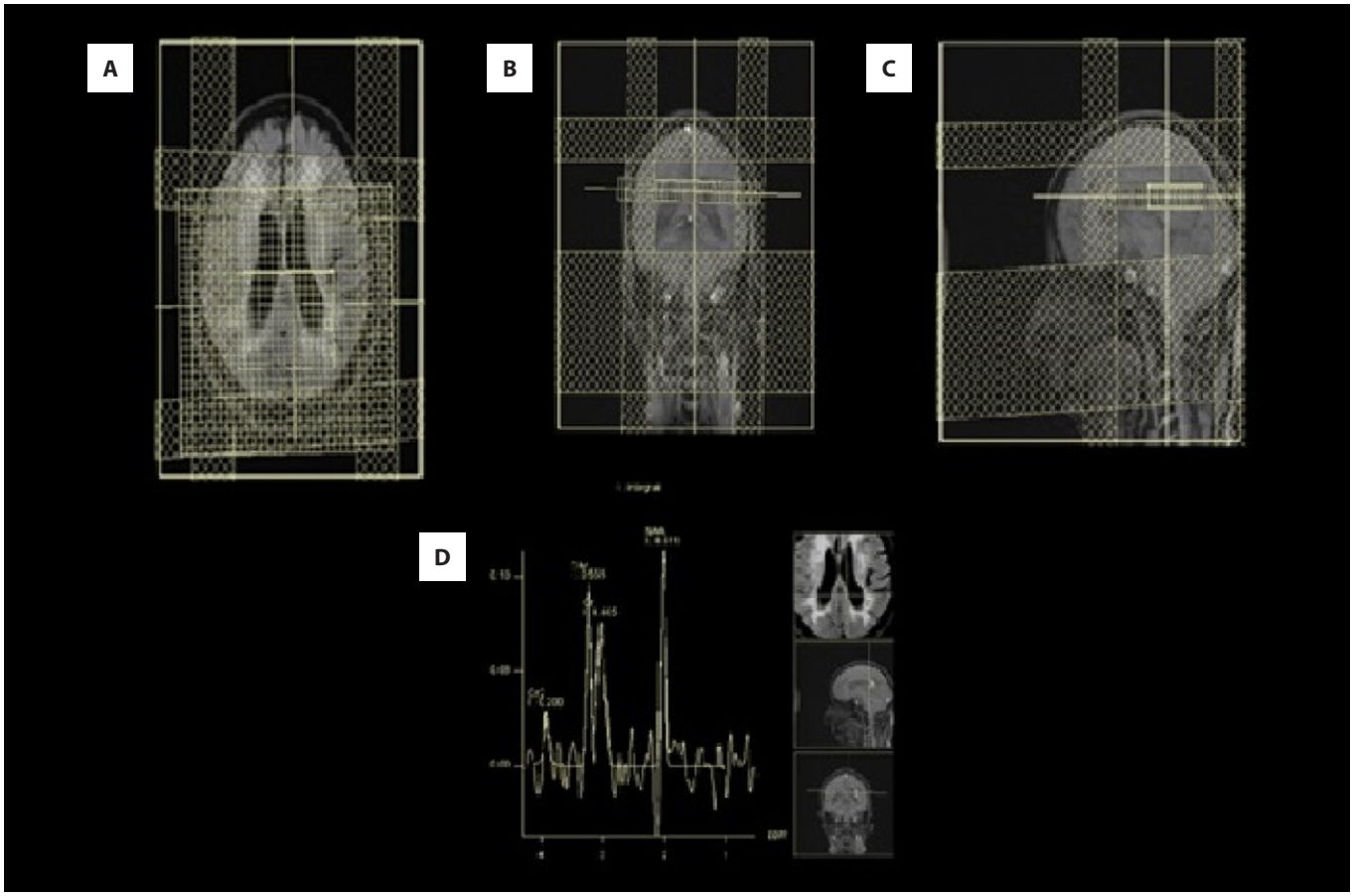

Figure 1. A-C, T2-weighted FLAIR axial, coronal, and sagittal images with the yellow box as the region of interest in 3 different plains selected for spectroscopy; D, multivoxel magnetic resonance spectra obtained from the periventricular region in a patient with a Fazekas grade 3 lesion
Рисунок 1. А–С – Т2-взвешенные изображения в режиме FLAIR в аксиальной, корональной и сагиттальной проекциях (желтая рамка – область исследования в 3-х плоскостях, выбранная для спектроскопии); D – мультивоксельные магнитно-резонансные спектры, полученные из перивентрикулярной области у пациента с поражением 3-й степени по шкале Фазекаса

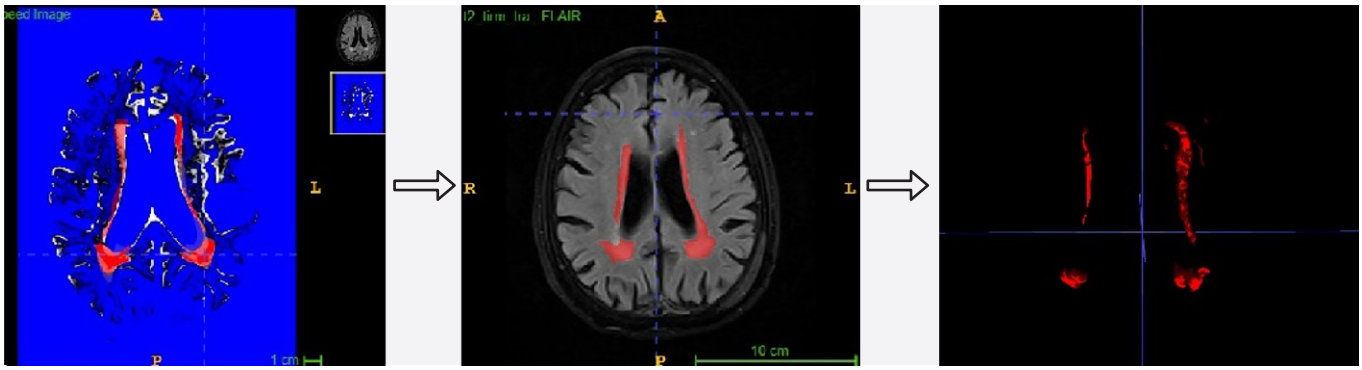

Figure 2. Steps to measure volume with semiautomatic segmentation using ITK-SNAP software
Рисунок 2. Этапы измерения объема посредством полуавтоматической сегментации с помощью программы ITK-SNAP

sequences served as references to locate the voxel of interest for MRS data acquisition. 1H-MRS was performed using a chemical shift imaging sequence, namely point-resolved spectroscopy (Figure 2).

Statistical Analysis

The data were collected and processed using Microsoft Excel (Microsoft Corp, USA), and statistical analysis was conducted with SPSS version 29.0 (IBM Corp, USA). Demographic characteristics were evaluated using the χ^2 test. The independent samples t test was applied to compare the means between the controls and the disease group, with statistical significance set at $P < .05$*. The Pearson correlation coefficient was used to assess the relationship between metabolite ratios and lesion volume in the LA patients and lesion volumes in any of the grades.

Results

Our prospective study conducted between January 2022 and July 2023 received approval from the Institutional Review Board of the SRM Institutional Ethical Committee (8474/IEC/2022) and included a total of 192 patients: 64 adult patients (median, 31.5 years; range, 50-70 years; 10 women [15.62%] and 54 men [84.37%]) with a known history of LA (disease group) and 128 adult patients (median, 63.5 years; 88 women [68.75%] and 40 men [31.25%]) without LA (control group). The age of the participants ranged from 50 to 75 years, with the mean age of 66.40 and 61.98 years, respectively, and showed statistical significance at $P<.000797$. The proportion of men in the groups had no statistically significant difference ($P<.986437$), whereas the proportion of women had statistically significant difference between the groups, with $P<.0012$ (Table 1).

Patients with intracranial tumors, lacunar infarcts, stroke, recent head injuries, space-occupying lesions, multiple sclerosis, parkinsonism, psychiatric or associated mental disorders were excluded from this study to ensure that the observed changes were primarily due to LA. For the sake of compliance and complete data acquisition, all the patients provided informed consent.

The disease group (64 patients) exhibited changes in the periventricular white matter detected on T2-weighted FLAIR axial images and graded with the Fazekas scale by a neuroradiologist. These changes were not limited by severity and ranged from mild to severe LA. The participants had no significant disabilities on assessment by instrumental activities of daily living scales.[7,8] Thus, the study focused on individuals whose daily functional abilities were relatively unaffected by other conditions.

A total of 128 healthy participants were age- and gender-matched to those in the disease group to ensure comparability between the groups. The control participants were selected based on routine MRI scans as part of regular checkups, and their scans were reviewed to confirm the absence of any brain lesions or abnormalities. They had no history of head injury, seizures, stroke, or significant disabilities, were neurologically healthy and free from conditions that could affect the brain metabolism and structure.

MRS revealed that the NAA/Cr ratio was significantly lower, whereas the NAA/Cho ratio was significantly higher in the control group compared with the LA patients ($P<.0001$); also, the Cho/Cr ratio was significantly higher in the control group compared with the LA patients ($P<.0034$) (Table 2).

Table 1

Clinical characteristics of the main and control groups

Таблица 1

Клиническая характеристика основной и контрольной групп

Groups	Age (years)	Men (%)	Women (%)
Control group (n=128)	61.98	31.25	68.75
Disease group (n=64)	66.40	84.37	15.62
P value	.000797	.986437	.001231

Discussion

This study highlights the effect of LA on the brain structure and function, using MRS to identify associated metabolic alterations. Older patients were more likely to belong to the disease group, possibly due to disease progression, comorbidities, or treatment differences, suggesting that age can be a significant factor in the disease progression and management. LA patients were generally older, emphasizing the need for age-specific management strategies.[9,10]

Gender analysis showed a higher proportion of women in the control group and more men in the disease group, indicating potential gender-related factors in the disease management. This disparity may stem from biological, behavioral, or social differences, including medication adherence, lifestyle, and healthcare access, or such factors as hormones, comorbidities, and genetics.[11-13]

The study revealed significant metabolic differences between the groups. The NAA/Cr ratio was lower in the controls compared with the LA patients, while the NAA/Cho ratio was higher in the control group compared with the disease group, indicating better neuronal health in the controls. Furthermore, the Cho/Cr ratio was higher in the control group, suggesting potential cellular turnover or inflammation. These findings underscore the complexity

Table 2

NAA/Cr, NAA/Cho, and Cho/Cr ratios in the disease and control groups

Таблица 2

Соотношения NAA/Cr, NAA/Cho, Cho/Cr в основной и в контрольной группах

Ratio	Control group Mean	Disease group Mean	*P* value	*t* value
NAA/Cr	1.04	1.28	<.0001	−5.47306
NAA/Cho	1.98	1.64	<.0001	5.91039
Cho/Cr	2.12	1.56	.003389	2.7375

of metabolic changes and highlight the need for further investigation, particularly regarding the lower NAA/Cr ratio in the controls (Table 2).

The NAA/Cr ratio is commonly used as a marker of neuronal health and integrity.[14] However, the lack of a significant correlation in this context suggests that NAA/Cr levels are not strongly associated with lesion volume in the disease group.[15] Similar to the NAA/Cr ratio, the NAA/Cho ratio does not demonstrate a significant relationship with lesion volume in the disease group, further supporting the idea that these metabolic ratios may not be reliable indicators of lesion volume in this patient population.[16]

The mean Cho/Cr ratio of 1.642, with statistical insignificance ($P < .7228$) and weak positive correlation (0.0452) to lesion volume, indicates that only 0.2% of lesion volume variability is explained by the Cho/Cr ratio. These findings suggest that metabolic ratios (NAA/Cr, NAA/Cho, and Cho/Cr) do not significantly correlate with lesion volume in LA, rendering them poor predictors. Further, it indicates that other clinical or biological markers may assess lesion volume better, reflecting the complexity of disease mechanisms in LA patients[17] (Table 3).

The NAA/Cr ratio reflects neuronal integrity, with reduced levels indicating neuronal loss or dysfunction. Lower NAA/Cr ratios correlate with increased white matter lesion burden in LA and are linked to cognitive decline and disease progression.[18-20] The NAA/Cho ratio highlights the balance between neuronal integrity (NAA) and membrane turnover (Cho).

Changes in the NAA/Cho ratio indicate alterations in neuronal health and metabolism. Studies link decreased NAA/Cho ratios to cognitive decline in LA, while elevated Cho/Cr ratios, markers of membrane turnover and cellular proliferation, are observed in WMH.[21,22]

The mean NAA/Cr and Cho/Cr ratios showed statistical insignificance and a weak correlation with grade 1 lesion load, reinforcing that metabolic ratios are not strong indicators of lesion volume in early-grade lesions.[15] Similarly, the mean NAA/Cr and NAA/Cho ratios for grade 2 and 3 lesions also demonstrated statistical insignificance and a weak correlation, suggesting that none of these ratios reliably predict lesion volume (Table 4).

The mean NAA/Cho ratio of 1.612 and the mean Cho/Cr ratio of 1.684 showed a weak positive correlation

Table 3

Correlation of NAA/Cr, NAA/Cho, and Cho/Cr ratios with lesion volume

Таблица 3

Соотношение NAA/Cr, NAA/Cho, Cho/Cr с объемом поражения

Ratio	Mean	Correlation coefficient	*P* value	R^2 value
Disease group (N = 64)				
NAA/Cr	1.28	−0.0293	.820054	0.0009
NAA/Cho	1.565	0.0073	.954346	0.0001
Cho/Cr	1.642	0.0452	.722848	0.002

Table 4

Correlation of NAA/Cr, NAA/Cho, and Cho/Cr ratios with grade 1-3 lesion volume in the leukoaraiosis patients

Таблица 4

Соотношения NAA/Cr, NAA/Cho, Cho/Cr при объеме поражения 1, 2 и 3 степени у пациентов с лейкоареозом

Ratio	Mean	Standard deviation	Correlation coefficient	*P* value	R^2 value
Grade 1 (n = 31)					
NAA/Cr	1.329	0.35	0.0522	.780334	0.0027
NAA/Cho	1.612	0.77	−0.1884	.31116	0.0355
Cho/Cr	1.684	0.47	0.0135	.942539	0.0002
Grade 2 (n = 19)					
NAA/Cr	1.18	0.29	0.1979	.41671	0.0392
NAA/Cho	1.520	0.44	0.176	.471069	0.031
Cho/Cr	1.561	0.44	0.1862	.445321	0.0347
Grade 3 (n = 14)					
NAA/Cr	1.321	0.43	0.1945	.525213	0.0378
NAA/Cho	1.514	0.40	0.1052	.720404	0.0111
Cho/Cr	1.657	0.36	−0.3471	.224166	0.1205

with age which implies that this ratio is not influenced by age and remains relatively stable across different ages in grade 1 lesions. The Cho/Cr ratio in Grade 3 patients shows a significant negative correlation with age.[23] This highlights that age might influence choline and creatine levels variably in more advanced stages of the disease and indicate alterations in membrane turnover or cellular density,[24] suggesting reduced cellular proliferation or metabolic shifts.[25] Therefore, the Cho/Cr ratio could serve as a potential biomarker for monitoring disease progression, tailoring more age-specific therapeutic approaches, and designing interventions that target metabolic pathways, potentially improving patient outcomes. Moreover, LA patients demonstrate elevated levels of choline, indicating ongoing cellular damage and repair processes within the white matter.

The metabolic changes in LA are complex, involving alterations in neuronal integrity and membrane turnover. However, no significant correlation was found between lesion load and these metabolic changes. Further research is needed to clarify the pathways underlying these alterations and their impact on disease progression and clinical outcomes.

Conclusions

The metabolic alterations observed in LA highlight the complex and multifactorial nature of this disease, particularly as it pertains to neuronal integrity and membrane turnover. It was also observed that the NAA/Cr and NAA/Cho ratios can be used as an analytical tool in the LA diagnosis. MRS provides valuable insights into the biochemical environment of the brain, offering potential biomarkers for early diagnosis and treatment strategies.

The lack of relationship between lesion volume and MRS metabolite ratios in LA suggests that the overall volume of the lesion alone is insufficient to accurately assess the biochemical environment or the extent of neuronal damage. Improved understanding of these mechanisms will be crucial in developing effective therapeutic strategies to address the metabolic components of LA, ultimately aiming to improve patient care and quality of life.

Authors contributions

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Manuscript drafting: R. Ramesh
Statistical analysis and administrative support: Aiyappan, S. Ramesh
Critical revision of the manuscript for important intellectual content: Subbiah, Aiyappan
Supervision: Subbiah

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