

Prognostic Value of Magnetic Resonance Spectroscopy in Patients With Diffuse Axonal Injury: Systematic Review Of The Literature

Ali Shamsa^{1*}

¹ Department of neurosurgery, ghaem hospital, mashhad university of medical science

ARTICLE INFO	ABSTRACT
Article type Original Article	Introduction: Magnetic resonance spectroscopy (MRS) is an imaging technique that provides spectroscopic information on the changes in biological markers. Studies suggest that MRS can be valuable in the prognosis of patients with diffuse axonal injury (DAI).
Article history Received: 02 Oct 2024 Revised: 03 Dec 2024 Accepted: 06 Jan 2024	Methods: PubMed and Scopus, two major databases, were systematically searched in June 2015 using the following search strategy: (((Magnetic resonance spectroscopy OR MRS OR MR spectroscopy)) AND (Diffuse axonal injury OR DAI)) AND Prognosis). Relevant articles were selected, and the prognostic value of MRS in patients with traumatic DAI was investigated. All necessary information was extracted for data synthesis based on the primary objective of this study.
Keywords Brain metabolite Diffuse axonal injury Prognosis Traumatic brain injury	Results: Out of 19 articles found in PubMed and 151 in Scopus, eight documents were selected for data extraction following inclusion/exclusion criteria. The total number of patients included in the selected studies was 197. All selected articles demonstrated that MRS can be used to quantitatively analyze metabolite changes in patients with DAI.
	Conclusion: Based on the results of the included studies, MRS is a sensitive tool that can help predict the prognosis of patients with DAI.

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Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide and represents a significant global health issue. Diffuse axonal injury (DAI) is one of the most common causes of deterioration in patients with TBI, affecting approximately half of those with head injuries. Traffic accidents are the most common cause of DAI (1). DAI is a brain pathology that can result in prolonged traumatic coma. It typically occurs following TBI, with extensive axonal damage caused by disorganization of cellular structures and axonal edema in various areas of the brain (2-5). In conventional imaging, there is often a weak correlation between the prognosis of patients and the primary lesion. This may be due to DAI affecting surrounding areas or regions beyond the original injury, as well as microscopic axonal damage (6, 7). DAI is a significant cause of long-term disability. Although the exact prevalence of brain injuries varies by region, the incidence of mild TBI is estimated to be between 100 and 600 cases per

100,000 people (8).

The prognosis of a disease can vary depending on the severity, location of the lesion, and access to medical care. However, severe axonal damage often leads to coma and is associated with an unfavorable outcome (8-10). Since CT scans and other macroscopic imaging techniques cannot effectively visualize these microscopic processes, diagnosing diffuse axonal injury (DAI) can be challenging. To date, no diagnostic method has been able to accurately predict the prognosis of patients with diffuse axonal brain lesions. According to the results of various studies, the levels of brain metabolites are directly correlated with the severity and prognosis of patients. Clinical findings suggest that measuring brain metabolites using magnetic resonance spectroscopy (MRS) may help predict the prognosis of the disease.

Nuclear magnetic resonance (NMR) spectroscopy, commonly known as magnetic resonance spectroscopy (MRS), is a sensitive, accurate, and non-invasive method that allows for the evaluation

***Corresponding author:** Ali Shamsa, Department of neurosurgery, ghaem hospital, mashhad university of medical science
E-mail: dr_shamsa2006@yahoo.com
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of brain metabolite changes following trauma (11). It is an imaging technique that provides spectroscopic information about changes in biological biomarkers and other metabolites during organ activation. Studies suggest that neurobiochemical findings can aid in evaluating the prognosis of patients with diffuse axonal injury (DAI) (12). This study aimed to systematically review the prognostic value of MRS imaging in diffuse brain lesions.

Methods

Search methods

We systematically searched PubMed and Scopus, two major databases, using the key terms “Magnetic resonance spectroscopy” and “Diffuse axonal injury” in the title, keywords, and abstract of papers where the prognostic value of MRS as a practical and non-invasive imaging technique had been evaluated in traumatic diffuse axonal injury. The following search strategy was used: (((Magnetic resonance spectroscopy OR MRS OR MR spectroscopy)) AND (Diffuse axonal injury OR DAI)) AND Prognosis) to find relevant documents in PubMed and Scopus. Additionally, a customized search strategy was employed for Scopus: “magnetic resonance spectroscopy” was first searched, followed by “diffuse axonal injury” within the results. The results from both databases were then limited to documents published in English and conducted on human subjects. The database search was performed in June 2015. To further minimize the possibility of data loss, after systematically searching the databases, Google Scholar and the Google search engine were also used to search for the relevant key terms. The reference lists of the collected articles were manually screened to identify other potentially relevant studies.

Study selection and inclusion/exclusion criteria

No time range was defined in the customized search strategy for selecting appropriate documents. However, only articles published in English were included in this study to minimize data loss, reduce the risk of errors, and prevent possible misinterpretation of data in the subsequent data synthesis process. The customized search method allowed the inclusion of articles with various types of clinical designs, including case-control studies, cross-sectional studies, clinical trials, comparative studies, and prospective cohort studies for further data processing. However, conference papers, abstracts, editorials, review articles, and meta-analyses were excluded from further evaluation. In the first step of article selection, publications with duplicated data and articles with irrelevant subjects

or languages were excluded based on a review of the title, keywords, and abstract. Articles with unavailable full text were also excluded from the data synthesis process. Additionally, studies conducted in vitro or on animals were excluded. Similarly, articles in which MRS was used for the clinical evaluation of metabolites in pathological conditions other than DAI were also excluded. Therefore, the inclusion criteria for article selection in this review were all English-language articles in which the prognostic value of MRS had been investigated in patients with DAI.

Data synthesis

General information was extracted and recorded, including the first author's name, country of origin, date of publication, study design, and the number of participants. Additional data, including demographic information, assessment methods, and main findings, were collected under the primary objective of this study. Data were extracted and analyzed based on studies reporting the efficacy and prognostic value of MRS in DAI. Two reviewers independently performed all data processing, including article selection and data extraction, following the recommended standard protocol outlined in the PRISMA 2009 checklist (13). Any discrepancies during the data extraction process were resolved between the authors before proceeding with further data synthesis.

Results

Study search results

A total of 19 relevant articles were found in the PubMed database and 151 in Scopus. After thoroughly reviewing the abstracts, 93 irrelevant articles were excluded in the first step. Additionally, 23 documents were excluded due to language irrelevancy. Twenty-five documents with duplicated data were then excluded during the article selection process. Eighteen articles in which MRS imaging had been used to diagnose hepatic diseases or other pathological conditions were also excluded from further assessment. Furthermore, nine studies conducted on animals were excluded. Five additional relevant documents were identified through manual reference list screening of the previously selected articles. One more paper was found and included through a Google Scholar search. Four of these papers were excluded due to the unavailability of the full text. Finally, after a rigorous article selection and comprehensive review, only eight relevant articles that met all the defined inclusion/exclusion criteria were included for data analysis. The step-by-step process of literature search and study selection is shown in Figure 1.

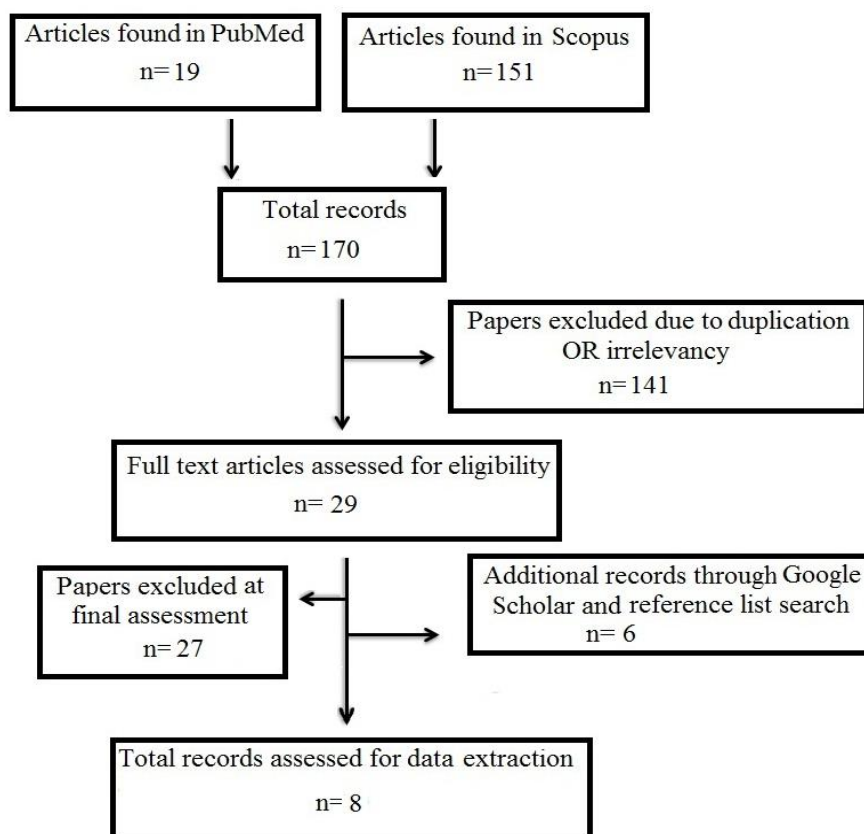


Figure 1. The literature search strategy for the selection of relevant documents.

General characteristics of the included articles

A total of 197 participants were enrolled in the selected studies, in which the prognostic value of MRS as an accurate and non-invasive imaging technique was evaluated in patients with DAI. In some studies, 55 healthy participants were included as a control group. The number of patients enrolled in the selected studies ranged from 8 to 60. According to the extracted data, participants of both genders were included in the selected studies. However, the sex ratio was not reported in 2 studies, preventing gender-based analysis. In those articles with fully described demographic data, 86 participants were male and 63 were female. The

ages of patients in the selected studies ranged from 1-year-old children to 65 years. Among the included studies in this literature review, one was a prospective cohort study, two were cross-sectional studies, and one was a comparative study. Additionally, there was one retrospective study and three evaluation studies. The most recent study included in this review was published in 2013, while the oldest was published in 2002. The general characteristics of the included studies are presented in Table 1 in chronological order of publication.

Table 1. General information about the included articles.

No	First author	Year	Country	Study design*	Study population®	Sex ratio (M/F)	Patients number
1	Kirov II (14)	2013	USA	PSC	mTBI	21/5	26
2	Babikian T (15)	2010	USA	CSS	TBI	8/2	10
3	Govind V (16)	2010	USA	ES	TBI	25/4	29
4	Gasparovic C (17)	2009	USA	RS	mTBI	4/6	10
5	Holshouser BA (12)	2005	USA	ES	TBI	-	40
6	Yoon SJ (18)	2005	Korea	CS	TBI	-	8
7	Uzan M (19)	2003	Turkey	ES	VS	9/5	14
8	De Stefano N (20)	2002	Italy	CSS	MS	19/41	60

* PCS: Prospective cohort study, RS: Retrospective study, CSS: Cross-sectional study, CS: Comparative study, ES: Evaluation study,

® Mild traumatic brain injury (mTBI), VS: Vegetative state, MS: Multiple sclerosis

Study results

The results of this review indicate that MRS is a suitable imaging technique capable of accurately

detecting even small variations in metabolite levels in clinical practice, particularly for brain pathological assessments. All of the articles

included in this study demonstrated that MRS can quantitatively detect changes in primary brain metabolites, such as N-acetyl aspartate (NAA), total choline (Cho), total creatine (Cr), myo-inositol (ml), glutamine, glutamate, and cerebrospinal fluid fractions in patients with DAI. Therefore, the

findings of this study suggest that MRS can be considered a reliable imaging method for assessing axonal injuries. The primary clinical outcomes and methods of assessment are summarized in Table 2.

Table 2. Detailed information on the included documents.

No	First author	Assessment @	Variables *	Main findings
1	Kirov II	MRI, multivoxel proton MRS, pathological analysis	NAA, Cho, Cr, ml	DAI is quantifiable with Proton MRS imaging
2	Babikian T	MRI, proton MRS, NST	NAA, Cr	MRS provides non-invasive, quantifiable metabolite measures
3	Govind V	MRI, MRS, NST	NAA, Cho, Cr, GCS	MRS provides valuable quantitative information in the diagnosis of mTBI
4	Gasparovic C	Single-voxel MRS, MRS, NST	NAA, Cr, Glu, Gln	H-MRS is more sensitive than other methods in predicting metabolite alterations.
5	Holshouser BA	MRS, SWI, HL	NAA, Cr, Cho, Lac, GCS	Proton MRSI more accurately detected metabolite changes of DAI in brain tissue that appeared normal on imaging.
6	Yoon SJ	MRS, FIM	NAA, Cho, Cr, ml	MRS has the potential to be used for detecting DAI
7	Uzan M	MRI and MRS	NAA, Cr	MRS determines the degree of severity in neuronal and axonal injury
8	De Stefano N	MRS, SWI, MTr	NAA, Cr	MRS is suitable for metabolite detection in MS patients with neuronal injury

* NAA: N-acetylaspartate, Cho: Choline, Cr: Creatine, ml: myo-inositol, Gln: Glutamine, Glu: Glutamate. GCS: Glasgow coma scale

@ MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, NST: neuropsychological test, HL: Hemorrhagic lesions, SWI: Susceptibility-weighted imaging, MTr: Magnetization transfer ratio, FIM: Functional independence measure.

The research limitations in this study were unreported data, particularly demographic information, including the sex ratio.

Discussion

Diffuse axonal injury, which is histopathologically characterized by the observation of axonal edema, is a subset of brain damage caused by trauma (21, 22). This injury occurs in nearly half of the cases of brain damage resulting from severe trauma and is a significant cause of the vegetative state in these patients (23). Conventional imaging methods like CT scans and MRI have limited diagnostic capabilities. Magnetic resonance spectroscopy (MRS) is a non-invasive and sensitive method by which post-traumatic brain metabolite changes can be evaluated. It appears that MRS may help evaluate the prognosis of patients with diffuse axonal injury by measuring brain metabolites such as creatine and choline, which serve as markers of metabolic energy and cell membrane health, respectively (12). Numerous studies have assessed the prognostic value of MRS in acute brain injury and coma, evaluating metabolite levels in different brain regions (24). The results indicate significant changes in brain metabolites following neuronal damage (3, 25, 26). Evaluation of brain metabolite levels, such as the NAA/Chol, Lip/Cr, and Lac/Cr ratios in the normal brain, internal capsule, and cerebral peduncle using MRS in patients with mild TBI, showed that these metabolite ratios significantly change in patients with DAI (5, 27, 28). Studies indicate that MRS imaging can be an

effective tool for determining the prognosis of patients with DAI. Additionally, the findings showed that metabolite indices, such as the NAA/Chol ratio, can accurately assess the severity of DAI. The results also demonstrated that NAA levels are directly associated with both the severity of the injury and the prognosis of patients, with lower levels of this metabolite suggesting more severe injury and a poorer prognosis.

Conclusion

The findings show that MRS imaging can accurately assess the levels of brain metabolites such as NAA, choline (Chol), and creatine (Cr), which may reflect the severity of DAI. According to the results of the studies included in this literature review, MRS is a sensitive, accurate, and noninvasive imaging method that holds prognostic value for patients with severe TBI and DAI.

References

1. Wolf JA, Stys PK, Lusardi T, Meaney D, Smith DH. Traumatic axonal injury induces calcium influx modulated by tetrodotoxin-sensitive sodium channels. *J Neurosci*. 2001;21(6):1923-30. <https://doi.org/10.1523/JNEUROSCI.21-06-01923.2001> PMID:11245677 PMCID:PMC6762603
2. Adams JH, Graham DI, Murray LS, Scott G. Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. *Ann Neurol*. 1982;12(6):557-63. <https://doi.org/10.1002/ana.410120610> PMID:7159059
3. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology*. 1989;15(1):49-59. <https://doi.org/10.1111/j.1365-2559.1989.tb03040.x> PMID:2767623
4. Meythaler JM, Peduzzi JD, Eleftheriou E, Novack TA. Current concepts: diffuse axonal injury-associated traumatic brain

- injury. *Arch Phys Med Rehabil.* 2001;82(10):1461-71. <https://doi.org/10.1053/apmr.2001.25137> PMID:11588754
5. Povlishock JT, Christman CW. The pathobiology of traumatically induced axonal injury in animals and humans: a review of current thoughts. *J Neurotrauma.* 1995;12(4):555-64. <https://doi.org/10.1089/neu.1995.12.555> PMID:8683606
 6. Garnett MR, Blamire AM, Rajagopalan B, Styles P, Cadoux-Hudson TA. Evidence for cellular damage in normal-appearing white matter correlates with injury severity in patients following traumatic brain injury: A magnetic resonance spectroscopy study. *Brain.* 2000;123 (Pt 7):1403-9. <https://doi.org/10.1093/brain/123.7.1403> PMID:10869052
 7. Garnett MR, Blamire AM, Corkill RG, Cadoux-Hudson TA, Rajagopalan B, Styles P. Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. *Brain.* 2000;123 (Pt 10):2046-54. <https://doi.org/10.1093/brain/123.10.2046> PMID:11004122
 8. Zink BJ. Traumatic brain injury outcome: concepts for emergency care. *Ann Emerg Med.* 2001;37(3):318-32. <https://doi.org/10.1067/mem.2001.113505> PMID:11223769
 9. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol.* 2008;7(8):728-41. [https://doi.org/10.1016/S1474-4422\(08\)70164-9](https://doi.org/10.1016/S1474-4422(08)70164-9) PMID:18635021
 10. Armin SS, Colohan AR, Zhang JH. Traumatic subarachnoid hemorrhage: our current understanding and its evolution over the past half century. *Neurol Res.* 2006;28(4):445-52. <https://doi.org/10.1179/016164106X115053> PMID:16759448
 11. Yeo RA, Phillips JP, Jung RE, Brown AJ, Campbell RC, Brooks WM. Magnetic resonance spectroscopy detects brain injury and predicts cognitive functioning in children with brain injuries. *J Neurotrauma.* 2006;23(10):1427-35. <https://doi.org/10.1089/neu.2006.23.1427> PMID:17020480
 12. Holshouser BA, Tong KA, Ashwal S. Proton MR spectroscopic imaging depicts diffuse axonal injury in children with traumatic brain injury. *AJNR Am J Neuroradiol.* 2005;26(5):1276-85.
 13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals Intern Med.* 2009;151(4):W-65-W-94. <https://doi.org/10.7326/0003-4819-151-4-200908180-00136> PMID:19622512
 14. Kirov, II, Tal A, Babb JS, Lui YW, Grossman RI, Gonen O. Diffuse axonal injury in mild traumatic brain injury: a 3D multivoxel proton MR spectroscopy study. *J Neurol.* 2013;260(1):242-52. <https://doi.org/10.1007/s00415-012-6626-z> PMID:22886061 PMID:PMC3729330
 15. Babikian T, Marion SD, Copeland S, Alger JR, O'Neill J, Cazalis F, et al. Metabolic levels in the corpus callosum and their structural and behavioral correlates after moderate to severe pediatric TBI. *J Neurotrauma.* 2010;27(3):473-81. <https://doi.org/10.1089/neu.2009.1058> PMID:19925210 PMID:PMC2867590
 16. Govind V, Gold S, Kaliannan K, Saigal G, Falcone S, Arheart KL, et al. Whole-brain proton MR spectroscopic imaging of mild-to-moderate traumatic brain injury and correlation with neuropsychological deficits. *J Neurotrauma.* 2010;27(3):483-96. <https://doi.org/10.1089/neu.2009.1159> PMID:20201668 PMID:PMC2867627
 17. Gasparovic C, Yeo R, Mannell M, Ling J, Elgie R, Phillips J, et al. Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: a 1H-magnetic resonance spectroscopy study. *J Neurotrauma.* 2009;26(10):1635-43. <https://doi.org/10.1089/neu.2009.0896> PMID:19355814 PMID:PMC2822798
 18. Yoon SJ, Lee JH, Kim ST, Chun MH. Evaluation of traumatic brain injured patients in correlation with functional status by localized 1H-MR spectroscopy. *Clin Rehabil.* 2005;19(2):209-15. <https://doi.org/10.1191/0269215505cr8130a> PMID:15759537
 19. Uzan M, Albayram S, Dashti SG, Aydin S, Hanci M, Kaday C. Thalamic proton magnetic resonance spectroscopy in vegetative state induced by traumatic brain injury. *J Neurol Neurosurg Psychiatry.* 2003;74(1):33-8. <https://doi.org/10.1136/innp.74.1.33> PMID:12486263 PMID:PMC1738168
 20. De Stefano N, Narayanan S, Francis SJ, Smith S, Mortilla M, Tartaglia MC, et al. Diffuse axonal and tissue injury in patients with multiple sclerosis with low cerebral lesion load and no disability. *Arch Neurol.* 2002;59(10):1565-71. <https://doi.org/10.1001/archneur.59.10.1565> PMID:12374493
 21. Heath DL, Vink R. Impact acceleration-induced severe diffuse axonal injury in rats: characterization of phosphate metabolism and neurologic outcome. *J Neurotrauma.* 1995;12(6):1027-34. <https://doi.org/10.1089/neu.1995.12.1027> PMID:8742131
 22. Kirov, II, Tal A, Babb JS, Reaume J, Bushnik T, Ashman TA, et al. Proton MR spectroscopy correlates diffuse axonal abnormalities with post-concussive symptoms in mild traumatic brain injury. *J Neurotrauma.* 2013;30(13):1200-4. <https://doi.org/10.1089/neu.2012.2696> PMID:23339670 PMID:PMC3700460
 23. Marmarou A, Foda MA, van den Brink W, Campbell J, Kita H, Demetriadou K. A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. *J Neurosurg.* 1994;80(2):291-300. <https://doi.org/10.3171/jns.1994.80.2.0291> PMID:8283269
 24. Conzen M, Ebel H, Swart E, Skreczek W, Dette M, Oppel F. Long-term neuropsychological outcome after severe head injury with good recovery. *Brain Inj.* 1992;6(1):45-52. <https://doi.org/10.3109/02699059209008121> PMID:1739852
 25. Sinson G, Bagley LJ, Cecil KM, Torchia M, McGowan JC, Lenkinski RE, et al. Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: correlation with clinical outcome after traumatic brain injury. *AJNR Am J Neuroradiol.* 2001;22(1):143-51.
 26. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol.* 1993;50(8):873-80. <https://doi.org/10.1001/archneur.1993.00540080076020> PMID:8352676
 27. Bayly PV, Cohen TS, Leister EP, Ajo D, Leuthardt EC, Genin GM. Deformation of the human brain induced by mild acceleration. *J Neurotrauma.* 2005;22(8):845-56. <https://doi.org/10.1089/neu.2005.22.845> PMID:16083352 PMID:PMC2377024
 28. Hardman JM, Manoukian A. Pathology of head trauma. *Neuroimaging Clin N Am.* 2002;12(2):175-87, vii. [https://doi.org/10.1016/S1052-5149\(02\)00009-6](https://doi.org/10.1016/S1052-5149(02)00009-6) PMID:12391630