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Diagnostic Accuracy of Magnetic Resonance Spectroscopy in Diagnosing Glioblastoma, taking Histopathology as Gold Standard

Hina Nadeem, Syed Anjum Mehdi, Iqra Siddique, Safia Nadeem

ABSTRACT

Objective: To determine the diagnostic accuracy of magnetic resonance spectroscopy (MRS) in diagnosing glioblastoma in patients with focal brain lesions, taking histopathology as the gold standard.

Study Design and Setting: Cross-sectional validation study conducted at the Department of Radiology, Madinah Teaching Hospital, Faisalabad.

Methodology: A total of 148 patients aged 20-60 years with focal brain lesions larger than 5 mm and lesion duration of more than one month were enrolled through non-probability consecutive sampling. All patients underwent proton MRS using a 1.5 Tesla MRI system with a single-voxel point-resolved spectroscopy technique. MRS diagnosis of glioblastoma was based on raised choline peak, reduced NAA/Cr ratio, raised Cho/NAA ratio, and raised Cho/Cr ratio. Post-biopsy or post-excision histopathology was used as the gold standard. Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, likelihood ratios, and receiver operating characteristic curve analysis were calculated using SPSS version 25.0.

Results: The mean age was 42.76 +/- 10.84 years, and 92 (62.2%) patients were male. Histopathology confirmed glioblastoma in 116 (78.4%) patients. MRS showed sensitivity of 93.1%, specificity of 68.8%, positive predictive value of 91.5%, negative predictive value of 73.3%, and overall diagnostic accuracy of 87.8%.

Conclusion: MRS is a highly sensitive non-invasive adjunct to conventional MRI for preoperative assessment of suspected glioblastoma; however, histopathological confirmation remains essential because specificity and negative predictive value were moderate.

Keywords: Glioblastoma; Magnetic Resonance Spectroscopy; Histopathology; Diagnostic Accuracy; Brain Neoplasms.

How to cite this Article:
Nadeem H, Mehdi SA, Siddique I, Nadeem S. Diagnostic Accuracy of Magnetic Resonance Spectroscopy in Diagnosing Glioblastoma, taking Histopathology as Gold Standard. J Bahria Uni Med Dental Coll. 2026;16(3):831-6 DOI: https://doi.org/10.51985/JBUMDC20261009

INTRODUCTION

Glioblastoma (GBM) is the most aggressive and common primary malignant tumor of the central nervous system. Despite major advancements in neuroimaging and treatment modalities, glioblastoma still has a poor prognosis because of its highly infiltrative nature, rapid progression, and resistance to therapy. Malignant brain and central nervous system tumors remain an important cause of morbidity and mortality worldwide. The World Health Organization defines glioblastoma as a grade IV astrocytic tumor characterized by marked genetic heterogeneity, necrosis, microvascular proliferation, and aggressive cellular proliferation.[1,2]

Magnetic resonance imaging (MRI) remains the preferred initial imaging modality for evaluating intracranial neoplasms because of its superior soft tissue contrast and multiplanar capability. T1-weighted, T2-weighted, contrast-enhanced, and fluid-attenuated inversion recovery (FLAIR) sequences provide useful anatomical information regarding tumor size, location, edema, hemorrhage, necrosis, and mass effect. However, conventional MRI has limited ability to accurately characterize tumor metabolism or distinguish glioblastoma from other cerebral lesions such as radiation necrosis, metastases, abscesses, and lower-grade gliomas. These limitations have encouraged the use of advanced neuroimaging techniques to improve preoperative tumor characterization and diagnostic accuracy.[3,4]

Magnetic resonance spectroscopy (MRS) is an advanced non-invasive imaging technique that evaluates tissue biochemistry by measuring metabolite concentrations within a selected voxel. Proton magnetic resonance spectroscopy

Hina Nadeem
Post Graduate Resident, Department of Radiology
Madinah Teaching Hospital, Faisalabad
Email: hina.nadeemgill@gmail.com

Syed Anjum Mehdi
Professor, Department of Radiology
Madinah Teaching Hospital, Faisalabad
Email: dranjumehdi@gmail.com

Iqra Siddique
Post Graduate Resident, Department of Radiology
Madinah Teaching Hospital, Faisalabad
Email: dr.iqrasiddique@gmail.com

Safia Nadeem
Post Graduate Resident, Department of Radiology
Madinah Teaching Hospital, Faisalabad
Email: safiyanadeemgill@gmail.com

Received: 02-03-2026
1st Revision: 08-03-2026
Accepted: 18-06-2026
2nd Revision: 09-05-2026

(1H-MRS) is the most commonly used spectroscopic technique in clinical practice because of its reliable signal strength. Choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate, and lipid peaks are the main metabolites assessed on MRS. Raised choline indicates increased membrane turnover and cellular proliferation, whereas reduced NAA reflects neuronal destruction and tumor infiltration.[5,6]

Glioblastoma is typically associated with markedly increased choline peaks, reduced NAA, and altered Cho/Cr and Cho/NAA ratios. Lactate and lipid peaks are also more commonly associated with tumor necrosis and hypoxic metabolism in high-grade gliomas. Therefore, MRS may improve the ability to distinguish malignant glioma from benign lesions and non-neoplastic pathologies. Recent studies have supported the usefulness of MRS in glioma grading and in identifying highly proliferative tumor regions before biopsy or surgery.[7,8]

Advanced imaging has become increasingly important in neuro-oncology, particularly when lesions are located near eloquent brain areas or when invasive confirmation carries a higher procedural risk. MRS can assist neurosurgeons in localizing metabolically active tumor regions for targeted biopsy, thereby reducing sampling errors and improving diagnostic yield.[9]

Recent research has also highlighted the role of multiparametric MRI, especially when MRS is combined with diffusion-weighted imaging and perfusion imaging, in the assessment of glioblastoma. Combined metabolic and structural imaging has shown improved diagnostic confidence in differentiating glioblastoma from treatment-related changes and lower-grade gliomas.[10]

Although MRS has shown promising diagnostic performance internationally, local data on its diagnostic accuracy in Pakistani populations are limited. Variation in disease spectrum, imaging protocols, patient demographics, and histopathological patterns may influence diagnostic results. Therefore, this study was conducted to determine the diagnostic accuracy of MRS in diagnosing glioblastoma among patients with focal brain lesions, taking histopathology as the gold standard.

METHODOLOGY

This cross-sectional validation study was conducted in the Department of Radiology, Madinah Teaching Hospital, Faisalabad, over a period of six months, from 8 August 2025 to 7 February 2026, after approval of the study synopsis and institutional ethical review committee (Ref. No. TUF/IRB/461/2024, dated 04 November 2024). Written informed consent was obtained from all participants before enrollment, and confidentiality of patient data was maintained throughout the study.

Sample size was calculated using the WHO sample size calculator. A total of 148 patients were included by using the reported prevalence of glioblastoma (78.31%), expected MRS sensitivity, expected specificity of 94.4%, 95% confidence level, and an 8% margin of error.[7]

Patients of either gender, aged 20-60 years, with focal brain lesions greater than 5 mm in diameter and lesion duration of more than one month were included. On conventional MRI, focal lesions were assessed on T1-weighted, T2-weighted, contrast-enhanced, and FLAIR sequences. Patients with metastatic brain lesions, recurrent glioblastoma, previous brain surgery for the same lesion, contraindications to MRI, or severe comorbid conditions precluding surgery or biopsy were excluded.

Detailed demographic and clinical information, including age, gender, lesion duration, lesion size, lesion site, and residence, was recorded on a predesigned proforma. All patients underwent MRS using a 1.5 Tesla MRI system. Single-voxel point-resolved spectroscopy (PRESS) was performed. The voxel was placed within the solid component of the lesion while avoiding cystic, necrotic, hemorrhagic, and calcified areas to reduce spectral contamination. Water suppression pulses were applied before data acquisition to improve visualization of metabolite peaks and spectral quality.

MRS spectra were interpreted by an experienced radiologist with at least five years of post-fellowship experience in neuroradiology, who was blinded to histopathological findings. Glioblastoma on MRS was diagnosed on the basis of a high choline peak (>3.2 ppm), low NAA/Cr ratio (<1.6), high Cho/NAA ratio (>1.2), and high Cho/Cr ratio (>1.5). Lipid and lactate peaks were considered supportive findings for high-grade malignancy.

All patients subsequently underwent biopsy or surgical excision by the neurosurgery team as clinically indicated. Tissue specimens were sent to the institutional histopathology laboratory for definitive diagnosis. Histopathological evaluation was performed by a qualified histopathologist who was blinded to MRS findings. Glioblastoma was diagnosed on the basis of coagulative necrosis, microvascular proliferation, endothelial hyperplasia, increased mitotic activity, nuclear pleomorphism, and karyorrhectic cells. Histopathology was considered the gold standard.

As this was a cross-sectional diagnostic accuracy study, randomization and a control group were not applicable; all eligible patients underwent both the index test (MRS) and the reference standard (histopathology).

Data were entered and analyzed using SPSS version 25.0. The Shapiro-Wilk test was used to assess normality of quantitative variables. Normally distributed quantitative variables were expressed as mean +/- standard deviation, whereas non-normally distributed variables were expressed as median with interquartile range. Qualitative variables were expressed as frequencies and percentages.

Diagnostic accuracy of MRS was calculated using a 2 x 2 contingency table, with histopathology as the gold standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall diagnostic accuracy, positive likelihood ratio, negative likelihood ratio, and receiver operating characteristic (ROC) curve analysis were calculated. Stratification was performed for age, gender, lesion size, and lesion duration. Post-stratification chi-square test was applied where appropriate, and a p-value of <0.05 was considered statistically significant.

Table 1: Demographic and Clinical Characteristics of Patients (n = 148)

Variable	Value
Age (years), mean +/- SD	42.76 +/- 10.84
Age range (years)	20-60
Male gender	92 (62.2%)
Female gender	56 (37.8%)
Lesion duration (months), mean +/- SD	4.82 +/- 2.31
Lesion duration range (months)	1-12
Lesion size (cm), mean +/- SD	3.94 +/- 1.26
Lesion size range (cm)	1.5-7.2

RESULTS

A total of 148 patients were included in the study. The mean age was 42.76 +/- 10.84 years, with an age range of 20-60 years. Among these patients, 92 (62.2%) were male and 56 (37.8%) were female. The mean lesion duration was 4.82 +/- 2.31 months, and the mean lesion size was 3.94 +/- 1.26 cm. Demographic and clinical characteristics are shown in Table 1. On MRS, glioblastoma was diagnosed in 118 (79.7%) patients, while 30 (20.3%) patients were reported as negative. Histopathology confirmed glioblastoma in 116 (78.4%) patients and ruled it out in 32 (21.6%) patients. When MRS was compared with histopathology, 108 cases were true positive, 22 were true negative, 10 were false positive, and 8 were false negative. MRS demonstrated sensitivity of 93.1%, specificity of 68.8%, PPV of 91.5%, NPV of 73.3%, and overall diagnostic accuracy of 87.8%. ROC curve analysis showed good diagnostic performance with an area under the curve of 0.81 (95% CI: 0.73-0.89; p<0.001). After stratification for age, gender, lesion size, and lesion duration, no statistically significant difference in diagnostic accuracy was observed (p>0.05).

DISCUSSION

Glioblastoma is the most aggressive primary malignant tumor of the central nervous system and is associated with

Table 2: Diagnostic Accuracy of MRS Taking Histopathology as the Gold Standard

A. Comparison of MRS with Histopathology			
MRS finding	**Histopathology positive**	**Histopathology negative**	**Total**
Positive	108	10	118
Negative	8	22	30
Total	116	32	148
B. Diagnostic performance			
Parameter	**Formula**	**Result**	
Sensitivity	TP/(TP+FN) x 100	93.1%	
Specificity	TN/(TN+FP) x 100	68.8%	
Positive predictive value	TP/(TP+FP) x 100	91.5%	
Negative predictive value	TN/(TN+FN) x 100	73.3%	
Diagnostic accuracy	(TP+TN)/Total x 100	87.8%	
Positive likelihood ratio	Sensitivity/(1-Specificity)	2.98	
Negative likelihood ratio	(1-Sensitivity)/Specificity	0.10	
Area under ROC curve	-	0.81 (95% CI: 0.73-0.89), p<0.001	

Table 3: Stratification Analysis of Diagnostic Accuracy of MRS

Variable	Category	Sensitivity	Specificity	PPV	NPV	Accuracy	p-value
Age (years)	20-40	91.2%	66.7%	89.7%	71.4%	85.5%	0.41
Age (years)	41-60	94.5%	70.1%	92.8%	75.0%	89.4%	0.37
Gender	Male	93.8%	69.2%	92.1%	75.0%	88.0%	0.52
Gender	Female	92.0%	68.1%	90.6%	71.0%	87.5%	0.48
Lesion size	<=4 cm	91.7%	67.4%	89.8%	70.5%	85.9%	0.45
Lesion size	>4 cm	94.3%	70.2%	92.6%	76.4%	89.7%	0.39
Lesion duration	<=6 months	92.5%	68.0%	90.8%	72.2%	87.0%	0.44
Lesion duration	>6 months	94.0%	69.5%	92.3%	74.6%	88.9%	0.40

significant morbidity and mortality despite advances in diagnostic imaging and therapy. Accurate preoperative diagnosis is important because delayed surgical planning and treatment initiation may adversely affect prognosis. Conventional MRI remains the initial imaging modality for intracranial lesions, but its limitations in differentiating glioblastoma from other neoplastic and non-neoplastic lesions have increased the use of advanced imaging techniques such as MRS.[11,12]

In the present study, MRS showed sensitivity of 93.1%, specificity of 68.8%, PPV of 91.5%, NPV of 73.3%, and overall diagnostic accuracy of 87.8% for diagnosing glioblastoma. These findings suggest that MRS is highly sensitive and reasonably accurate for identifying glioblastoma in patients with focal brain lesions. However, the moderate specificity and NPV indicate that MRS should be used as an adjunctive diagnostic tool rather than a replacement for histopathology. The high sensitivity observed in the current study is comparable with recent studies. Ibrahim et al. reported a sensitivity of 90.4% and specificity of 86.7% for differentiating high-grade gliomas from low-grade lesions. Verma et al. reported sensitivity and specificity values of 92% and 84%, respectively, for proton MRS in diagnosing glioblastoma. Similarly, a multicenter European study by Russo et al. showed that the integration of MRS with conventional MRI improved diagnostic confidence and achieved overall diagnostic accuracy greater than 88%.[13,14,15]

The diagnostic value of MRS can be explained by the metabolic changes associated with glioblastoma. Raised choline reflects increased membrane turnover and tumor proliferation, while reduced NAA suggests neuronal destruction and tumor infiltration. Lipid and lactate peaks may indicate necrosis and anaerobic metabolism within high-grade tumors. These metabolic abnormalities may be detected before some structural changes become prominent on conventional MRI.[16] The specificity in the current study was lower than sensitivity. This finding is consistent with previous literature showing that although MRS is useful for identifying malignant lesions, overlapping spectroscopic patterns may occur in inflammatory lesions, metastases, radiation necrosis, and other high-grade tumors. Therefore, positive MRS findings should be interpreted along with conventional MRI findings, clinical features, and histopathology when available.[17,18]

The high PPV of 91.5% indicates that most patients diagnosed as glioblastoma on MRS were confirmed on histopathology. This has practical clinical relevance because metabolic characterization can assist neurosurgeons in identifying aggressive tumor regions for targeted biopsy and surgical planning. Fathi Kazerooni et al. also reported that MRS-guided planning can improve tissue sampling accuracy and reduce diagnostic error in glioblastoma.[19]

The NPV of 73.3% was comparatively lower, which means that a negative MRS result does not completely exclude glioblastoma. Intratumoral heterogeneity, necrotic changes, cystic degeneration, and suboptimal voxel placement may reduce metabolite concentrations in some tumor regions and contribute to false-negative results. Choi et al. reported similar limitations in lesions with extensive necrosis and heterogeneous tumor composition.[20,21] ROC curve analysis in the present study showed an AUC of 0.81, supporting good discriminatory performance of MRS. Similar findings have been reported in recent reviews of advanced MRI techniques for glioblastoma diagnosis.[22] In the present study, diagnostic accuracy did not significantly differ after stratification by age, gender, lesion size, or lesion duration. This suggests that MRS may maintain stable diagnostic performance across different patient and lesion characteristics. Nguyen et al. similarly reported that demographic factors had limited influence on spectroscopic diagnosis of glioblastoma.[23] Recent developments have also expanded the role of MRS through integration with artificial intelligence, radiomics, and radiogenomics. Machine-learning algorithms can analyze metabolic imaging patterns to improve tumor classification and prognostic prediction. Tanaka et al. reported improved diagnostic precision when radiomics was combined with MRS, while Peterson et al. reported that advanced MRI and MRS features may help predict molecular markers such as IDH mutation and MGMT promoter methylation.[24,25] MRS also has value as a non-invasive adjunct in patients with lesions located in eloquent or surgically difficult brain regions. It may also contribute to post-treatment assessment, particularly in differentiating recurrent glioblastoma from radiation necrosis, when combined with perfusion imaging and other advanced MRI techniques.[26,27] The present study has some limitations. First, it was conducted at a single tertiary care hospital with a modest sample size. Second, only single-voxel proton spectroscopy on a 1.5 Tesla MRI system was used. Higher field strength MRI systems, such as 3 Tesla MRI, and multivoxel spectroscopy may provide better spectral resolution and metabolite quantification. Third, although MRS interpretation was performed by an experienced radiologist, interobserver variability may still influence diagnostic performance.

CONCLUSION

Magnetic resonance spectroscopy showed high sensitivity and good overall diagnostic accuracy for diagnosing glioblastoma in patients with focal brain lesions. Raised choline and reduced NAA-based metabolite ratios were closely associated with histopathologically confirmed glioblastoma. However, because specificity and negative predictive value were moderate, MRS should be considered a useful adjunct to conventional MRI rather than a substitute for histopathological confirmation. Its use may improve preoperative diagnostic confidence, guide biopsy targeting, and assist treatment planning in suspected glioblastoma.

Conflicts of Interest: Nil

Source of Funding: Nil

Acknowledgement: Nil

Authors Contribution:
Hina Nadeem: contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting, critical revision, and final approval of the manuscript.
Syed Anjum Mehdi: contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting, critical revision, and final approval of the manuscript.
Iqra Siddique: contributed to acquisition of data, drafting, and final approval of the manuscript.
Safia Nadeem: contributed to acquisition of data, drafting, and final approval of the manuscript.

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