

# Diagnostic yield of the combined Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy to predict malignant brain tumor



Rahmad Mulyadi,<sup>1\*</sup> Andi Asadul Islam,<sup>2</sup> Bachtiar Murtala,<sup>2</sup> Jumraini Tammase,<sup>2</sup> Mochammad Hatta,<sup>2</sup> Muhammad Firdaus<sup>3</sup>

## ABSTRACT

**Introduction:** Brain tumor is a neoplasm originating from various type of intracranial tissue. Histopathology is the gold standard to diagnose brain tumor. However, due to its invasive nature, the biopsy procedure poses a substantial risk. Therefore, advanced imaging, such as conventional Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS), has been widely developed to determine brain tumor type. Conventional MRI has been a routine examination for a suspected brain tumor in Indonesia, and with the utilization of MRS, could theoretically improve the diagnostic yield. This study aims to find diagnostic properties of conventional MRI, Choline/Creatine and Choline/NAA ratio extracted from MRS, and as a combined parameter to differentiate brain tumor type.

**Methods:** This cross-sectional study involved 52 patients who underwent conventional MRI, MRS, and histopathology examination

for a suspected brain tumor. The cut-off from Dean Criteria of conventional MRI, Choline/Creatine and Choline/NAA ratio to classify tumor type was determined from the ROC curve and then the diagnostic parameters were calculated from cross-tabulation. Also, a novel approach was made with logical-mathematical equation (disjunction/ /"or" and conjunction/ /"and") to combined parameter obtained from MRI and MRS to predict histopathological brain tumor type.

**Results:** Conventional MRI combined with MRS improve diagnostic yield compared to a single parameter with a sensitivity of 87.5%, a specificity of 88.6%, accuracy of 88.5%, PPV of 58.3%, NPV of 97.5%, LR+ of 7.68, dan LR- of 0.1.

**Conclusion:** Combination of conventional MRI and MRS parameter could improve the diagnostic yield in differentiating the type of brain tumor.

**Keywords:** Brain tumor, Dean Criteria, Choline/Creatine, Choline/NAA

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<sup>1</sup>Medical Faculty, Universitas Indonesia/Cipto Mangunkusumo National General Hospital, Jakarta Indonesia.

<sup>2</sup>Medical Faculty, Universitas Hasanuddin, Makassar, Indonesia.

<sup>3</sup>Dharmais Cancer Hospital, Jakarta, Indonesia.

## INTRODUCTION

Management strategy and prognosis of the brain tumor depend on several factors, such as type, stage, location, size, and development of the tumor itself. Intracranial tumor not necessarily includes only tumor originating from cerebral tissue, but also lymphatic, vascular, meningeal, and glandular, and metastatic tissue throughout the body.<sup>1,2</sup> Histopathology was known as the gold standard in diagnosing brain tumor, but the procedure to obtain specimens through biopsy is invasive.<sup>3</sup> Conventional Magnetic Resonance Imaging (MRI) is an important modality and has been a routine examination for a brain tumor to confirm the diagnosis and also to evaluate tumor extension, type, classification, and grading.<sup>4</sup> Dean L. Bruce et al. used scoring system for glioma diagnosis using conventional MRI.<sup>5</sup> Due to the nature of on non-contrast imaging, this criterion is beneficial in a particular situation with contrast injection was a contraindication.<sup>6</sup> However, conventional MRI has a wide range variation of sensitivity in identifying high-grade glioma, ranging from 55.1-83.3%.

Therefore, some advanced imaging techniques have been implemented to complement anatomical information provided by the conventional MRI.

Magnetic Resonance Spectroscopy (MRS) is one of advanced imaging technique that provides important metabolite information that complements conventional MRI.<sup>7</sup> MRS metabolite, such as Choline, Creatine, and N-acetyl aspartate (NAA), has been found useful in characterizing brain tumor. Choline reflects cell turnover, and it increased in brain tumor. Creatine reflects energy metabolism, and it is reduced in tumors due to increased energy consumption. NAA indicate neuronal density and viability. It was found decreased in the absence of healthy functioning neurons.<sup>7,8</sup> These surrogate marker has been implemented in several literatures as a ratio, i.e. Choline/Creatine ratio and Choline/NAA ratio in brain tumor grading.<sup>9-11</sup> This study used Dean criteria derived from conventional MRI, Choline/Creatine and Choline/NAA ratio determined by MRS to differentiate the histopathology type of brain tumor. Conventional MRI and MRS

\*Correspondence to: Rahmad Mulyadi. Radiology Department, Universitas Indonesia/Cipto Mangunkusumo National General Hospital;  
[dr\\_rahmad\\_radiologi@yahoo.com](mailto:dr_rahmad_radiologi@yahoo.com)

hopefully can sharpen brain tumor diagnosis and aid clinician to determine the appropriate management preoperatively.

## METHODS

This is a cross-sectional analytic study involved 52 subjects that had proven brain tumor diagnosis during October 2017 - September 2018. Initially, 84 patients who had clinical symptoms of brain tumor and underwent management in Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital during October 2017-September 2018 were followed up. Among them, 63 patients who underwent conventional MRI, MRS, and histopathology examination were included. Eleven patients were then excluded due to negative results of a brain tumor after the complete examination. Informed consent was obtained from a total of 52 subjects who were admitted in this study. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia - dr. Cipto Mangunkusumo National General Hospital (No. 950/UN2.F1/ETIK/2017 and (No. LB.02.01/X.2/984/2017), The Ethics Committee of the Dharmais Cancer Hospital (No. LB.02.02/XXII.2/14690/2017), and the Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (No. 863/H4.8.4.5.31/PP36-KOMETIK/2017).

Conventional MRI was conducted with MRI Siemens 1.5 Tesla Avanto. MRI sequences included were T2WI (TR/TE 5160/112 ms, section thickness 5 mm; inter-section gap 1 mm; matrix 269 × 384 ; FOV 20.1 × 23.0 mm), T1WI (TR/TE 500/9.4 ms, section thickness 5 mm; inter-section gap 1 mm; matrix 256 × 256 ; FOV 23.0 × 23.0 mm), T1WI with contrast was done in all patients, T2 FLAIR (TR/TE 7000/92 ms; inversion time 2214.1 ms, section thickness 5 mm, inter-section gap 1 mm, matrix 230 × 256, FOV 23.0 × 23.0 mm). Multi-voxel MRS was done with TR/TE 1690/135 ms, FOV 160.0 × 160.0 mm, VOI 80 × 80 mm (adjusted with the size of the tumor), slice thickness 25 mm, voxel 10 × 10 × 25, matrix 160 × 160 mm.

The data used in this study was the score from Dean criteria, Choline/Creatine, Choline/NAA and the histopathological result of brain tumor biopsy as the gold standard. Dean criteria determined by conventional MRI according to the original study by Dean et al.<sup>5</sup> Conventional MRI using Dean criteria which include assessment of midline shift, edema, tumor signal heterogeneity, tumor hemorrhage, tumor margin, cyst/necrotic tumor tissue, and mass effect. Each of the points consist score from 0 to 2, and the range of the total score is 0-14. Choline/Creatine and Choline/NAA ratio derived

from the calculated spectrum graph of MRS by comparing each of the respective metabolites of the lesion tissue and contralateral normal tissue.

Brain tumor defined as neoplasm in brain tissue originating from various type of tissue, including tumor of brain tissue, cranial nerve tissue, meningeal tissue, and metastatic tissue. The grade of brain tumor was further classified into benign and malignant type of tumor using WHO Classification of Central Nervous System Tumor (2016) by histopathology examination.<sup>12</sup> Grade I and II tumor were classified into the benign tumor while grade III and IV tumor were classified into malignant tumor group.

Analysis of the data conducted by generating receiver operating characteristic (ROC) curve with SPSS 20 software to determine cut-off value to classify the type of brain tumor. Then cross-tabulation to determine its diagnostic properties conducted with Microsoft Excel.

## RESULTS

This study involved 52 patients with confirmed brain tumor diagnosis in dr. Cipto Mangunkusumo National General Hospital and Dharmais Cancer Hospital. The flow diagram of the study subject selection shown in [Figure 1](#) and the description of the subject characteristics shown in [Table 1](#). Based on gender, the majority of the patients were female (78.8%, n=41). The mean age at diagnosis was 42.04 years old. According to age group, 69.2% of patients (n=36) belonged to 35-55 years of age group. Based on the Fisher-exact test and Mann-Whitney test, there were significant differences between the gender and age group compared to the type of brain tumor, respectively (p=0.007 and p=0.001).

[Table 2](#) showed that meningioma (40.4%, n=41) contributes the majority of all the benign tumor and diffuse astrocytoma (3.8%, n=2) as the most common type of malignant tumors. Patients with Meningothelial meningioma (n=11, WHO grade I) had lower Dean scores, Choline/Creatine and Choline/NAA ratio compared to the patient with rhabdoid meningioma (n=1, WHO grade III). There was no benign glioma patient admitted in this study. All of the glioma patients were malignant type glioma, which are diffuse astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, and oligoastrocytoma with Dean scores of 11±1.4, 7, 12, and 8, respectively.

However, this study found that Choline/NAA yield a wide range of value from minimum 1,37 ppm to the maximum of 134.95 ppm for the malignant group ([Figure 2](#)) and Choline/Creatine also has a

**Table 1** Gender and age distribution of the study subject

	Histopathology Result		Total	p-value
	Benign (%)	Malignant (%)		
<b>Gender</b>				
Female	38 (73.1)	3 (5.8)	41 (78.8)	0.007*
Male	6 (11.5)	5 (9.6)	11 (21.2)	
<b>Total</b>	44 (84.6)	8 (15.4)	52 (100)	
<b>Age Group (years)</b>				
0-4	0 (0)	1 (1.9)	1 (1.9)	0.001**
5-9	0 (0)	1 (1.9)	1 (1.9)	
10-14	1 (1.9)	1 (1.9)	2 (3.8)	
20-34	2 (3.8)	3 (5.8)	5 (9.6)	
35-44	17 (32.7)	1 (1.9)	18 (34.6)	
45-54	17 (32.7)	1 (1.9)	18 (34.6)	
55-64	6 (11.5)	0 (0)	6 (11.5)	
65-74	1 (1.9)	0 (0)	1 (1.9)	
<b>Total</b>	44 (84.6)	8 (15.4)	52 (100)	

\*Fisher test, \*\*Mann-Whitney test

**Table 2** Characteristic of brain tumor classification

Histology (n)	n (%)	Mean ± SD		
		Conventional MRI (Dean Score)	MRS	
			Choline/ Creatine	Choline/NAA
<b>Benign</b>				
Meningioma	21 (40.4)	3.62 ± 2.35	4.29±6.8	8.25±20
Meningotelial meningioma	11 (21.2)	2.27 ± 1.7	3.27±5.7	1.6±1.6
Pituitary adenoma	5 (9.6)	4±1.2	1.35±1.01	2.5±3.3
Scwhannoma	4 (7.7)	6±2.9	2.17±1.1	1.45±0.8
Epidermoid cyst	1 (1.9)	2	0.83	0.7
Craniopharyngioma	1 (1.9)	9	1.81	0.9
Atypical meningioma	1 (1.9)	5	0.84	1.78
<b>Malignant</b>				
Diffuse astrocytoma	2 (3.8)	11±1.4	1.62±0.7	69.3±92.8
Anaplastic oligodendroglioma	1 (1.9)	12	9.26	5.95
Oligodendroglioma	1 (1.9)	7	1.44	1.95
Oligoastrocytoma	1 (1.9)	8	9.17	1.95
Germinoma	1 (1.9)	9	1.31	1.37
Medulloblastoma	1 (1.9)	6	0.52	2.03
Rhabdoid meningioma	1 (1.9)	14	4.76	3.45

wide range of value from minimum 0,11 ppm to maximum value of 25.63 ppm which is originated from a benign group (Table 3). This was probably due to the data collection error. Despite these findings, there was a significant difference between the median of conventional MRI score and Choline/

NAA ratio between benign and malignant brain tumor with  $p < 0.0001$  and  $p = 0.019$ , respectively.

Figure 3 showed the ROC curve and AUC analysis of the Dean score and MRS parameter to predict malignant brain tumor. Based on this curve, AUC of conventional MRI score approached nearly 100%

**Table 3** Descriptive Findings

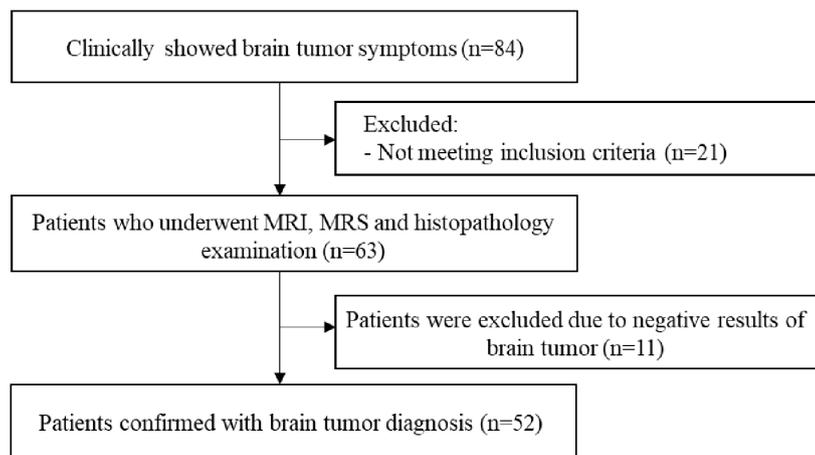
Variable		Mean	SD	Median	Minimum	Maximum	p-value*
Conventional MRI	Total	4.6	3.30	4	1	14	<0.0001
	Benign	3.6	2.41	3	1	10	
	Malignant	9.75	2.76	9.5	6	14	
Choline/Creatine	Total	3.36	5.24	1.37	0.11	25.63	0.304
	Benign	3.29	5.51	1.325	0.11	25.63	
	Malignant	3.17	3.62	1.775	0.52	9.26	
Choline/NAA	Total	7.08	22.26	1.55	0.09	134.95	0.019
	Benign	4.39	14.11	1.395	0.09	76.21	
	Malignant	19.41	46.71	2.74	1.37	134.95	

\*Mann-Whitney test

**Table 4** Diagnostic properties of single and combined parameter

Parameter	AUC	Cut-off	Sen	Spe	Accuracy	PPV	NPV	LR+	LR-
<b>Single Parameter</b>									
cMRI (p<0.0001; 95% CI 89.1%-100%)	95%	6.5	87.5%	88.6%	88.5%	58.3%	97.5%	7.68	0.14
Cho/Cr (p=0.304; 95% CI 41.6%-81.4%)	61%	1425	62.5%	56.8%	57.7%	20.8%	89.3%	1.45	0.66
Cho/NAA (p=0.019; 95% CI 62%-90.6%)	76%	1865	75%	38.6%	44.2%	18.2%	89.5%	1.22	0.65
<b>Combined Parameter</b>									
Cho/Cr $\wedge$ Cho/NAA	-	-	37.5%	68.2%	63.5%	14.3%	85.7%	1.18	0.92
Cho/Cr $\vee$ Cho/NAA	-	-	100%	27.3%	38.5%	20%	100%	1.38	0.1
(Cho/Cr $\wedge$ Cho/NAA) $\wedge$ cMRI	-	-	37.5%	90.9%	82.7%	42.8%	88.9%	4.12	0.69
(Cho/Cr $\wedge$ Cho/NAA) $\vee$ cMRI	-	-	87.5%	34.1%	69.2%	31.8%	96.7%	1.33	0.37
(Cho/Cr $\vee$ Cho/NAA) $\vee$ cMRI	-	-	100%	27.3%	38.5%	20%	100%	1.38	0.1
(Cho/Cr $\vee$ Cho/NAA) $\wedge$ cMRI	-	-	87.5%	88.6%	88.5%	58.3%	97.5%	7.68	0.14

Abbreviations: AUC, area under curve; Cho/Cr, Choline/Creatine; Cho/NAA; Choline/NAA; cMRI, conventional MRI; LR+, Positive likelihood ratio; LR-, negative likelihood ratio; Sen, Sensitivity; Spe, Specificity; PPV, positive predictive value; NPV, negative predictive value;  $\wedge$ , conjunction/and;  $\vee$ , disjunction/or.

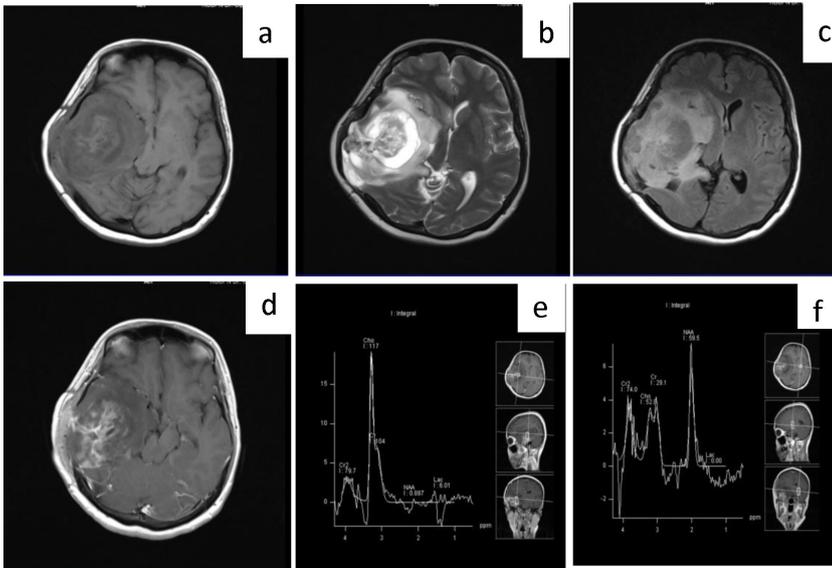


**Figure 1** Flow diagram of the subject selection

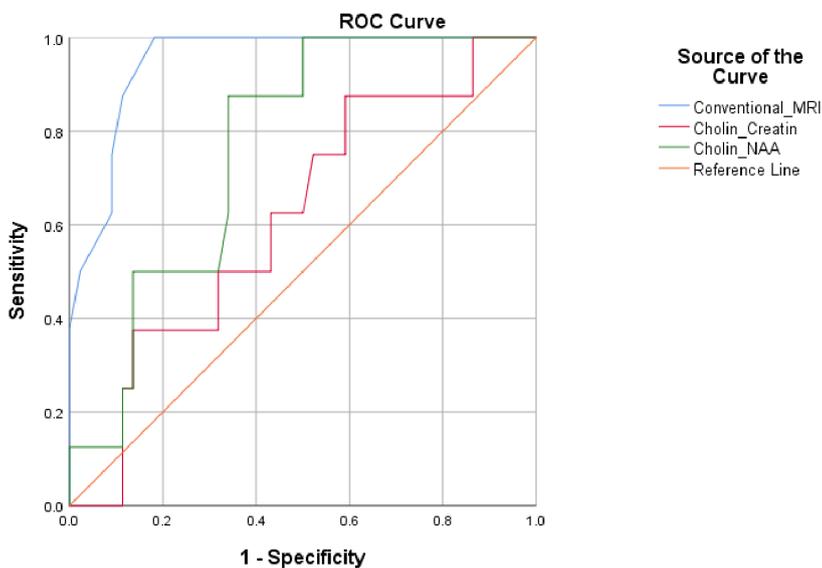
with AUC 94.9% (p<0.0001; 95% CI 89.1%-100%) and also Choline/NAA ratio showed a substantial diagnostic property with AUC 76.3% (p=0.019; 95% CI 62%-90.6%). However, Choline/Creatine had AUC close to reference line (50%) (AUC 61%; 0.304; 95% CI 41.6%-81.4%).

Bivariate analysis showed that only Choline/NAA and conventional MRI score that had p<0.05. Further analysis includes the use of logical-mathematical equation such as disjunction ( $\vee$ : "or") and conjunction ( $\wedge$ : "and") to predict whether the characteristic of brain tumor was malignant or benign with a combination of the Dean score and metabolite ratio derived from MRS.

Table 4 showed the diagnostic properties of single parameter and combined parameter. Disjunction combination [(Choline/Creatine  $\vee$



**Figure 2** Conventional MRI and MR spectroscopy of patient with diffuse astrocytoma. (a) T1WI, (b) T2WI, (c) FLAIR, (d) Post-contrast, (e) MRS graph of the lesion, (f) MRS graph of normal contralateral tissue. Dean score with conventional MRI was 10, Choline/Creatine ratio was 1.13, and Choline/NAA ratio is 134.95. Based on the disjunction-conjunction combination (Choline/Creatine  $\vee$  Choline/NAA)  $\wedge$  conventional MRI, the malignant type was concluded and consistent with the histopathology result



**Figure 3** ROC Curve of Dean Score and MRS Parameter to predict malignant brain tumor

Choline/NAA)  $\vee$  conventional MRI] and [Choline/Creatine  $\vee$  Choline/NAA] were the combinations with the highest sensitivity (100%), but low specificity (27.3%). [Choline/Creatine  $\vee$  Choline/NAA] means if at least one of the parameters tend to fall in the malignant range of value, then the brain tumor will be concluded as malignant. Thus, the combination of Choline/Creatine and Choline/NAA was

sufficient to achieve the highest sensitivity and was more sensitive compared to conventional MRI as a single parameter. In contrast to disjunction combination, conjunction combination [(Choline/Creatine  $\wedge$  Choline/NAA)  $\wedge$  conventional MRI], had the highest specificity (90.9%) with low sensitivity (37.5%). This means the combined parameter was able to detect 90.9% non-malignant tumor accurately based on the gold standard but had a tendency to detect malignant tumor as non-malignant tumor due to its low sensitivity.

The highest accuracy (88.5%) on the other hand, was achieved by the [(Choline/Creatine  $\vee$  Choline/NAA)  $\wedge$  conventional MRI] parameter. Based on this combination, if a brain tumor were interpreted as malignant in conventional MRI and at least one of Choline/Creatine or Choline/NAA ratio, a brain tumor concluded as malignant. Even so, none of the combinations had PPV higher than 60%. From overall parameter, [Choline/Creatine  $\vee$  Choline/NAA]  $\wedge$  conventional MRI had the most balanced diagnostic properties with sensitivity 87.5%, specificity 88.6%, accuracy 88.5%, PPV 58.3%, NPV 97.5%, positive likelihood ratio (LR+) 7.68 and negative likelihood ratio (LR-) 0.14. This combination had diagnostic properties almost 100%, LR+ close to 10, and LR- the close to 0.1, which means combined parameter had high diagnostic values to predict malignant brain tumor from imaging.

## DISCUSSION

Majority of the subjects in this study was female (78.8%, n=41). This may be associated with the predominant of meningioma (40.4%, n=41) and pituitary adenoma (9.6%, n=5). Some study found that up to 80% of patients with meningioma were female.<sup>13,14</sup> This finding was consistent with the analysis of CBTRUS data in 2008-2011 that meningioma was the majority of brain tumor (36.4%) followed by the pituitary tumor (15.5%).<sup>15</sup> Gender-related brain tumor may stem from genetic factors and sexual hormones of each individual.<sup>16</sup> The result of CBTRUS data showed that the incidence of brain tumor in the age group of 15-39 years was 10.94 per 100.000 population and above 40 years was 40.82 per 100.000 population.<sup>17</sup> This study showed that the mean onset was 42.04 years, thus compatible with the previous finding. The age-related tumor may be caused by the length of risk factor exposure, genetic changes, and worsening of immune surveillance along with advancing age.<sup>14</sup>

Conventional MRI is accurate for preoperative diagnosis, assess primary intra-axial tumor, and very accurate to assess the extent of malignancy in glioma. Besides, it was stated that no significant difference was found between preoperative tumor

grading with conventional MRI and histopathology in the intra-axial tumor. Conventional MRI has sensitivity of 93%, specificity of 77%, PPV of 80%, and NPV of 90% in assessing tumor necrosis, and sensitivity of 57%, specificity of 93%, PPV of 57%, and NPV 93% for evaluating tumor hemorrhage.<sup>6</sup> Similarly, Guzman et al. found that conventional MRI had significant AUC (0.89) to evaluate contrast enhancement and necrosis in glioma ( $p < 0.001$  and  $p = 0.001$ , respectively).<sup>18</sup>

Previous literatures also used Choline/Creatine and Choline/NAA ratio to determine brain tumor grade.<sup>19-22</sup> Mean ratio of Choline/NAA and Choline/Creatine increased along with the grade of the tumor ( $p < 0.001$ ).<sup>19</sup> Choline/Creatine and Choline/NAA ratio  $< 1.5$  indicate normal tissue or else necrotic tissue, ratio 1.5-2 indicates low-grade glioma, and the ratio of  $> 2$  indicates high-grade glioma or metastatic tumor.<sup>19,20</sup> In this study, we obtained the cut-off value of the Choline/Creatine ratio more than 1.425 and Choline/NAA above 1.825 indicates a malignant type of brain tumor. However, Choline/Creatine as the single parameter has AUC of 61% and statistically not significant ( $p = 0.304$ ) that might result from the disproportionate ratio of the histopathological type of the brain tumor included in this study. Previous study also showed that there is no significant difference between Choline/Creatine ratio of  $2.98 \pm 2.7$  in grade II tumor and  $3.24 \pm 3.47$  in grade III tumor ( $p = 0.847$ ).<sup>11</sup> Fawzy et al. found that Choline/Creatine ratio and Choline/NAA ratio were not statistically significant to differentiate anaplastic astrocytoma and glioblastoma multiforme. Still, these ratios can distinguish low-grade glioma and high-grade glioma (anaplastic astrocytoma and glioblastoma multiforme). In this case, both MRS metabolite ratio has a sensitivity of 100%, a specificity of 95.5%, PPV of 88.9%, NPV of 100%, and accuracy of 96.7% in glioma grading.<sup>23</sup>

Few caveats should be mentioned. There were limitations to this study. First, only a few subjects were enrolled. Second, there was low variability of cases. Further research regarding the combination of MRI and MRS in differentiating brain tumor types, specifically with larger sample size and more variability of cases is needed. Other essential things to mention were meningioma might not show NAA resonance in spectroscopy due to its extra-axial origin. Nevertheless, in some doubtful cases, meningioma shows resonance in NAA location, which is typical in astrocytoma. Hence, in this situation, biopsy might be mandatory to reach confidence diagnosis.<sup>19</sup> In other cases, high-grade glioma can be unintentionally missed by biopsy. In this case, spectroscopy can aid in locating these

high-grade areas.<sup>24</sup> Nevertheless, biopsy and imaging technique complements each other in brain tumor diagnosis and evaluation.

## CONCLUSION

Combination of MRI and MRS parameter improves the diagnostic yield in differentiate type of brain tumor compared to any single parameter. Therefore, with careful consideration, a combination of MRI and MRS can improve the overall diagnostic and support its usage in differentiating brain tumor preoperatively.

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## AUTHOR CONTRIBUTION

RM, AAI, BM, JT, MH contribute equally in constructing the concepts and design, literature evaluation, conducting the clinical study phase, data acquisition and analysis, manuscript preparation and approval for publication of the study. MF contributes in conducting the study and the data acquisition.

## CONFLICT OF INTEREST

All authors declare there is no conflict of interest regarding the publication of this manuscript.

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