RESEARCH ARTICLE

Editorial Process: Submission:01/07/2024 Acceptance:08/18/2024

The Prognostic Role of *Fibulin-2* and *Ki-67* Index in Patients with Meningioma: A Study among Minangkabau Ethnicity

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Abstract

Objective: To analyze the association between *fibulin-2* and *Ki-67* index with histopathological grade and other clinicopathological factors in patients with meningioma among the Minangkabau ethnic group. **Methods:** This cross-sectional observational study uses 50 specimens comprising 25 low-risk meningioma cases and 25 high-risk meningioma cases obtained at three anatomical pathology laboratories in Padang, West Sumatra, Indonesia, between 2019 and 2022. All samples were stained using an immunohistochemistry procedure with *Ki-67* and *fibulin-2*. The chi-square test was used to assess IBM SPSS statistics version 26 for Windows was used to assess the association of *Ki-67* and *fibulin-2* with the histopathological grade. The p-value of <0.05 was considered significant. **Result:** We found a significant association between *Ki-67* (p = 0.013) or *fibulin-2* (p = 0.001) expression with histopathological grade of meningioma. High histopathological grade has high expression of *Ki-67* and *fibulin-2*, with Odds ratio (OR) of 13.500 (1.556–117.137) and 10.028 (2,738–36,722), respectively. *Fibulin-2* expression was also associated with the age of patients (p = 0.020). The low age group (<50) has high expression of *fibulin-2* (OR 0.196 (0.056–0.691). **Conclusion:** *Ki-67* and *fibulin-2* were associated with the histopathological grade of meningioma, while *fibulin-2* is also associated with age in the Minangkabau ethnic group.

Keywords: *Fibulin-2*- histopathological grade- *Ki-67*- meningioma- protein expression- Minangkabau ethnic group

Asian Pac J Cancer Prev, **25 (8)**, 2735-2742

Introduction

Meningiomas are the most prevalent primary intracranial tumors, accounting for around one-third of all central nervous system neoplasms [1, 2, 3]. They originate from the arachnoid cap cells of the leptomeninges [4]. Currently, the risk factors identified for meningioma are exposure to ionizing radiation, hormones (progesterone, estrogen, androgen), head trauma, cell phone use, breast cancer, and genetics [5].

Meningioma is common in the USA and South Korea. In the USA, the incidence rate of meningioma was 40% of all brain tumors [6]. Meanwhile, in South Korea, it was 36% [7]. Data from GLOBOCAN 2020 show that brain tumors (central nervous system) are in 15th place in Indonesia, with 5,964 new cases (1.5%); however, the incidence of meningioma remains inconclusive due to the lack of a cancer registry [8]. The World Health Organization (WHO) classification of central nervous system tumors classifies meningiomas into three degrees (WHO degrees I, II, and III) with 15 subtypes. Meningothelial, fibrous, and transitional meningiomas are the most commonly found subtypes [9]. Approximately 80% of meningiomas are classified as benign (grade I), while 18.3% and 1.3% are classified as atypical (grade II) and malignant (grade III) by the WHO, respectively [10]. Progression-free survival for WHO grade I, II, and III meningiomas was 75–90%, 23–78%, and 0%, respectively [3].

Ki-67 is a nuclear protein produced in all proliferating vertebrate cells [11]. This protein is present during the active phase of the cell cycle (during the G1, S, and G2 phases), but not in the G0 phase [12]. MKI67 mRNA and *Ki-67* protein are abundant during the mitotic G2 phase [13]. A recent genetic study showed that during mitosis, *Ki-67* helps form the perichromosomal layer, a ribonucleoprotein sheath coating the condensed chromosomes. However, *Ki-67* is unnecessary for proliferation [11, 14]. *Ki-67* gene locus on the long arm of chromosome 10; 10q25-ter [15]. Currently, besides as a marker for proliferation, *Ki-67* has become a standard in assessing the diagnosis and prognosis of malignancies [13]. *Ki-67* is a histological biomarker associated with high recurrence rates in meningiomas [16]. It is also an important biomarker in gastric carcinoma [17], triple negative breast cancer [18], and cervical neoplasm [19].

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According to studies, cases with a proliferation index above 4% had recurrence rates comparable to WHO grade II meningiomas, while those with an index above 20% had mortality rates similar to WHO grade III meningiomas [1, 9].

Fibulin-2, found at the junction of elastin cores and microfibrils, is an extracellular glycoprotein that constructs and stabilizes various extracellular matrix (ECM) components through binding and interaction. This protein is the fibulin family's second-biggest molecule [20]. The human FBLN2, the gene symbol of *fibulin-2*, is mapped to chromosome 3p24-p25 [21]. *Fibulin-2*'s function in tumorigenesis depends on its interaction with other protein ECM. The protumor manifestation of *fibulin-2* results from the interaction of *fibulin-2* with type 1 transmembrane glycoprotein mucoprotein 4 (MUC-4), disrupting the basement membrane integrity and promoting the metastatic process in pancreatic cancer. Otherwise, its interaction with ADAMT12 enhances the antitumor effect of breast cancer cell lines and subcutaneous tumors in mice [20, 22].

Currently, *Ki-67* is the gold standard for differentiating the grade of meningioma. However, additional prognostic biomarkers must still be assigned to meningioma subtypes (choroid and clear cell) as WHO grade II [9]. A study posits *fibulin-2* in plasma as a new WHO grade II meningioma biomarker. Therefore, this study aimed to analyze the association between *Ki-67* and *fibulin-2* immunoexpression with histopathological grade and other clinicopathological factors in meningioma patients, especially among the Minangkabau ethnic group.

Materials and Methods

Study design

This was an observational descriptive study with a cross-sectional design. The study population was all cases of meningioma that had been diagnosed in three Anatomic Pathology laboratories in West Sumatra, the Diagnostic Center of the Faculty of Medicine, Andalas University Padang, Dr. M, Djamil Padang Hospital and Dr. Ahmad Moechtar Bukittinggi Hospital from January 2019 to December 2022. The inclusion criteria were meningioma cases that provided complete patient status data, including age, gender, tumor location, slides, and paraffin blocks that could be resectioned for immunohistochemical examination. Meningioma cases with incomplete data and broken or missing paraffin blocks were excluded. We collected 201 cases of meningioma, where only 25 were categorized as high-risk. High-risk meningioma is defined as meningioma with WHO grades II and III. Meanwhile, low-risk meningioma is meningioma with WHO grade I. However, low-risk meningioma was selected by simple random sampling. Two pathologists assessed the study results and re-evaluated the slides.

This study was approved by the Health Research Ethics Committee RSUP Dr. M. Djamil Padang (No. LB.02.02/5.7/140/2022).

Data collection

The research sample was meningioma cases with complete data, including age, gender, tumor location, slides, and paraffin blocks. The histopathological degree of meningioma was assessed based on the 2021 WHO classification: WHO grades I, II, and III [9]. Based on the risk of recurrence and aggressive behavior, the histopathological grade was grouped into low risk (WHO grade I meningioma) and high risk (WHO grades II and III meningiomas).

Ki-67 and fibulin-2 immunohistochemistry staining protocol

The meningioma tissue in paraffin blocks was cut with 4-µm thickness using a microtome, then deparaffinization with xylol, rehydration with decreased alcohol concentration (100%, 96%, 80%, and 70% each for 5 minutes), and rinse with running water. The tissue pieces were incubated in Core Retrieval Buffer pH 9.0 (Biogear, UK) in Retrieval Generation 1 (RG1) (Biogear, UK) at 95°C for 20 minutes, followed by cooling at room temperature (30-35 °C) for 30 minutes. Washed with PBS for 10 minutes (2x5 minutes), then incubated in Block Peroxidase (Paramount Block, Biogear, UK) for 30 minutes, PBS for 10 minutes (2x5 minutes), and followed by Blocking Biotin (Paramount Ostium Blocker, Biogear, UK) for 15 minutes. Incubation in Ki67 rabbit monoclonal antibody (clone MRQ-64, Cell Marque, Burlington, USA, at 1:100 dilution) and *fibulin-2* rabbit polyclonal antibody (Bioenzy, at 1:200) for 1 hour in a humid chamber. After incubation with Ki67 and *fibulin-2*, the preparations were re-incubated with secondary antibodies (Paramount Secondary Link, Biogear, UK) for 30 minutes. Washed with PBS for 10 minutes (2x5 minutes). Incubated with Polymer HRP (Paramount HRP, Biogear, UK) for 30 minutes at room temperature. Washed with PBS for 10 minutes (2x5 minutes). Stained with DAB solution (Biogear, UK) for 2–5 minutes, then washed in running water for 5 minutes. Counterstained with Hematoxylin Meyer for 5–10 minutes, then washed in running water for 5 minutes. Dipped in Lithium Carbonate solution for 30 seconds, then washed in running water. Lastly, dehydrated with increased alcohol concentration (70%, 80%, 96%, and 100% each for 5 seconds). The slide was purified in xylol and covered with a cover glass.

Data Definition

Ki-67 expression was assessed using the Qu-path application [21]. The cut-off point was set at 4% [22]. For statistical analysis, the *Ki-67* expression was divided into low *Ki-67* expression if the calculation result was ≤ 4% and high *Ki-67* expression if the result was >4%.

Fibulin-2 expression was assessed semi-quantitatively by multiplying the score of the percentage of the number of cells by the intensity value of the brown color in the cytoplasm of meningioma cells plus one to produce a histoscore value with the formula $\sum(I+1)Pi$, where I is the intensity of immunoreactivity (0 to +3). Score 0 negative; +1 weak intensity; +2 moderate intensity; +3 strong intensity. Pi represents the percentage of stained tumor cells (0%–100%). The results will show a minimum score of 0 (negative) and a maximum of 400. The cut-off point was the median value. For statistical analysis, *fibulin-2*

expression was divided into low *fibulin-2* expression if the result is below the median h-score and high *fibulin-2* expression if the result is above or equal to the median h-score [23].

Statistical analysis

The univariate analysis of descriptive data of meningioma characteristics, such as age, gender, tumor location, histopathological subtype, histopathological grade, Ki-67, and *fibulin-2* expression. The chi-square test used IBM SPSS statistics version 26 for Windows to analyze the relationship between *fibulin-2* and *Ki-67* expression with histopathological grade and other clinicopathological features in meningioma. Test results with p-values <0.05 were considered significant.

Results

General characteristic of meningioma patients

The frequency distribution of general characteristics of meningioma patients is in Table 1.

Table 1 shows the characteristics of the study sample. The average age of patients with meningioma was 46.26 years, with the youngest and oldest ages of 12 and 67 years, respectively. The highest incidence of meningioma was found in the age group 41–50 years (23 cases (46%)). Most patients were female (40 cases (80%)). Meanwhile, the most common tumor was located intracranially (43 cases (86%)), with details of the convexity area occupying the most intracranial locations (35 cases (81.3%)). The most common subtype of meningioma was atypical meningioma (22 cases (44%)). The histology of meningioma is shown in Figure 1. The mean *fibulin-2* score was 224.30 (SD 78.044). After grouping based on the median value, the *fibulin-2* degree was found to be equal between low and high degrees (25 cases each (50%)) (Figure 2). The mean *Ki-67* count was 4.298 (SD 8.124). The highest *Ki-67* group was low grade (40 cases (80%)) (Figure 3).

Correlation between fibulin-2 expression and clinicopathologic factors of meningioma

Table 2 shows that *fibulin-2* has high expression in the group of patients under 50 years of age (20 cases (80%)), female gender (22 cases (88%)), intracranial location (22 cases (88%)), high histopathological degree (19 cases (76%)), and meningioma cases with a picture of fibrotic tumor vessels (14 cases (56%)). Meanwhile, the highest number of *fibulin-2* expressions was in low *Ki-67* expression (22 cases (88%)). Statistically, *fibulin-2* expression showed a significant relationship with age (p-value = 0.020) and histopathologic grade (p-value = 0.001).

Correlation between Ki-67 and clinicopathologic factors of meningioma

Table 3 shows that the number of low *Ki-67* expressions was the highest in the group of patients under 50 years of age (25 cases (80.6%)), female gender (31 cases (77.5%)), intraspinal location (5 cases (83.3%)), low histopathologic degree (24 cases (96%)), low *fibulin-2* expression (22

Table 1. The Clinicopathologic Characteristics of Patients with Meningioma

Variables N = 50	
Age (year)	
Average	46.3 (Median 47.5, SD 9.8)
Range	12-67
Age group (year)	
<20	1 (2%)
21-30	2 (4%)
31-40	10 (20%)
41-50	23 (46%)
51-60	10 (20%)
>60	4 (8%)
Gender	
Male	10 (20%)
Female	40 (80%)
Location	
Intracranial	43 (86%)
Convexity	35 (81.3%)
Cerebelo-pont angle	2 (4.7%)
Parasagital	2 (4.7%)
Parasellar	1 (2.3%)
Infratentorial	2 (4.7%)
Cerebellum	1 (2.3%)
Intraspinal	6 (12%)
Orbital	1 (2%)
Histopathologic subtype	
Meningothelial meningioma	5 (10%)
Fibrous meningioma	2 (4%)
Transitional meningioma	9 (18%)
Psammomatous meningioma	3 (6%)
Angiomatous meningioma	2 (4%)
Microcystic meningioma	4 (8%)
Chordoid meningioma	2 (4%)
Atypical meningioma	22 (44%)
Anaplastic meningioma	1 (2%)
WHO Degree	
WHO grade I	25 (50%)
WHO grade II	24 (48%)
WHO grade III	1 (2%)
Histopathologic grade	
Low degree	25 (50%)
High degree	25 (50%)
Fibulin-2 Histoscore	
(mean ± SD)	(224.3 ± 78)
Fibulin-2 Degree	
≤ 200 (low)	25 (50%)
>200 (high)	25 (50%)
Ki-67	
(mean ± SD)	4.3 ± 8
Ki-67 degree	
≤ 4% (low)	40 (80%)
>4% (high)	10 (20%)

Table 2. *Fibulin-2* Expression Relationship to Clinicopathologic Factors of Patients with Meningioma

Variables	Case	Fibulin-2 low expression (N = 25)	Fibulin-2 high expression (N = 25)	Odds Ratio (95% CI)	p-value
Age (year)					
	<50	11 (44%)	20 (80%)	0.196 (0.056–0.691)	0.02
	≥50	14 (56%)	5 (20%)		
Gender					
	Male	7 (28%)	3 (12%)	2.852 (0.643–12.642)	0.289
	Female	18 (72%)	22 (88%)		
Location					
	Intracranial	21 (84%)	22 (88%)	2.095 (0.346–12.671)	0.42
	Intraspinal	4 (16%)	2 (8%)		
	Orbital	0 (0%)	1 (4%)		
Histopathologic grade					
	Low	19 (76%)	6 (24%)	10.028 (2.738–36.722)	0.001
	High	6 (24%)	19 (76%)		
Ki-67 Expression					
	Low	22 (88%)	18 (72%)	2.852 (0.643–12.642)	0.289
	High	3 (12%)	7 (28%)		

cases (88%)), and meningioma cases without picture of fibrotic tumor vessels (19 cases (82.6%)). Statistically *Ki-67* expression showed a significant relationship only with histopathologic grade (p-value = 0.013).

Discussion

Based on the frequency distribution in Table 1, the average age of patients with meningioma is below 50 years old. Several meningioma cases were found in the age group of 41–50 years. The average age of meningioma patients is not much different from previous studies. Research conducted by Mulyadi et al., reported that several meningioma cases were found in the age group of 36–60 years [23]. Damayanti et al. [24] reported that the age group with several cases was 45-49 years old at Dr. Soetomo Surabaya [24, 25]. Yunnica et al. [25] reported that the average age of patients with meningioma at Hasan Sadikin Hospital in Bandung was 42 years [25]. Research by Mayasari and Fauziah [26] reported that the average age of patients with meningioma at Dr. Soetomo Surabaya is 43 (SD 15.09) years [26].

Risk factors for high-grade meningioma are age, male sex, and prior cranial ionizing radiation [27]. The risk of meningioma increases with age; the median age at diagnosis is >60 years. Females are at high risk. Meningiomas are rare in children and adolescents, with females and males having similar incidence ratios. Children frequently have a high meningioma grade, with a high chance of recurrence found in unusual locations [1, 2, 6, 7]. According to the initial site, convexity-located meningiomas showed an increased risk of a high-grade meningioma [28].

The results of research on meningioma in Indonesia differ from those of other countries. The average age of meningioma sufferers is higher in other countries than in

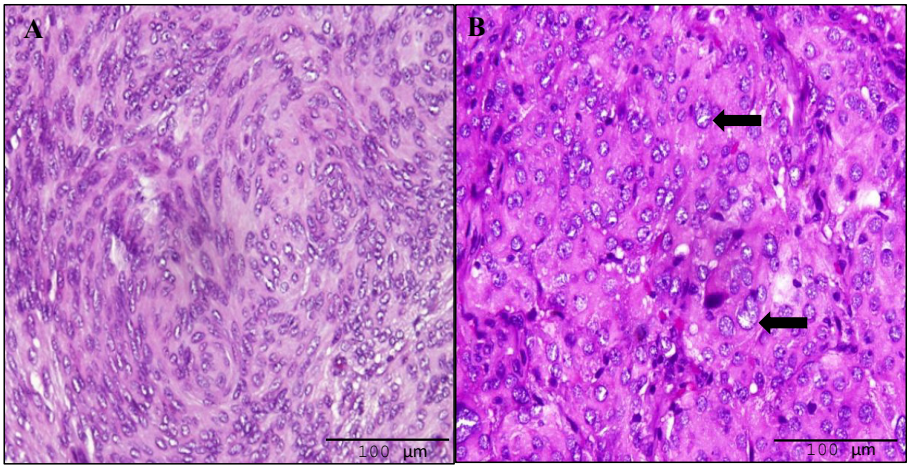

Figure 1. The Histopathological Grade of Meningioma. A. Low-risk meningioma (WHO grade I meningioma, meningothelial meningioma) B. High-risk meningioma with large nuclei and nucleolus visible (WHO grade III meningioma, anaplastic meningioma) (arrow). (A–B, HE staining, 400x).

Table 3. *Ki-67* Expression Relationship with Clinicopathologic Factors of Patients with Meningioma

Variables	Case	*Fibulin-2* low expression (N = 25)	*Fibulin-2* high expression (N = 25)	Odds Ratio (95% CI)	p-value
Age (year)					
	<50	25 (62.5%)	6 (60%)	1.111 (0.269–4.587)	1
	≥50	15 (37.5%)	4 (40%)		
Gender					
	Male	9 (22.5%)	1 (10%)	2.613 (0.291–23.469)	0.663
	Female	31 (77.5%)	9 (90%)		
Location					
	Intracranial	34 (85%)	9 (90%)	1.324 (0.137–12.802)	0.809
	Intraspinal	5 (12.5%)	1 (10%)		
	Orbital	1 (2.5%)	0 (0%)		
Histopathologic grade					
	Low	24 (60%)	1 (10%)	13.500 (1.556–117.137)	0.013
	High	16 (40%)	9 (90%)		
Fibulin-2 Expression					
	Low	22 (55%)	3 (30%)	2.852 (0.643–12.642)	0.289
	High	18 (45%)	7 (70%)		

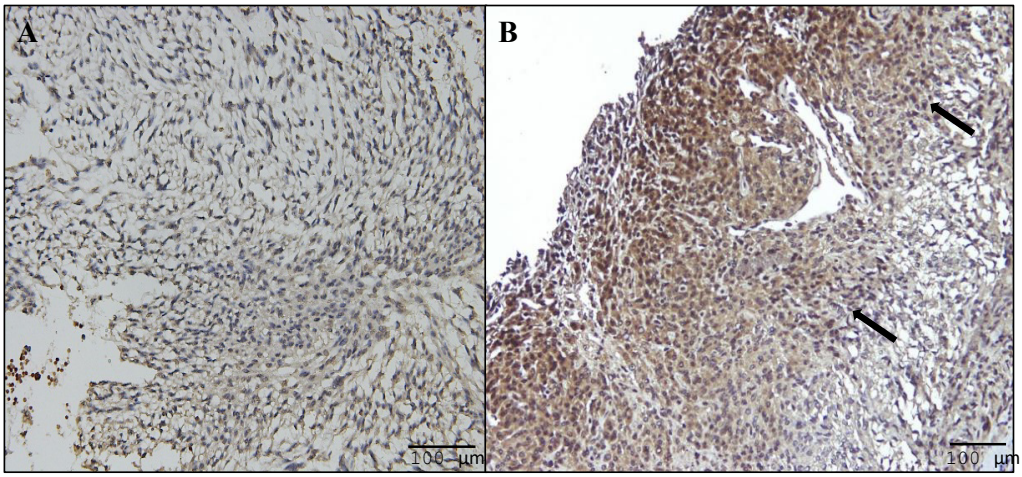

Figure 2. *Fibulin-2* Expression in Meningiomas Seen in the Cytoplasm (200x magnification). A. Low fibulin-2 expression (h-score ≤200). B. High fibulin-2 expression. Most tumors stained with high-intensity (h-score >200) (arrow).

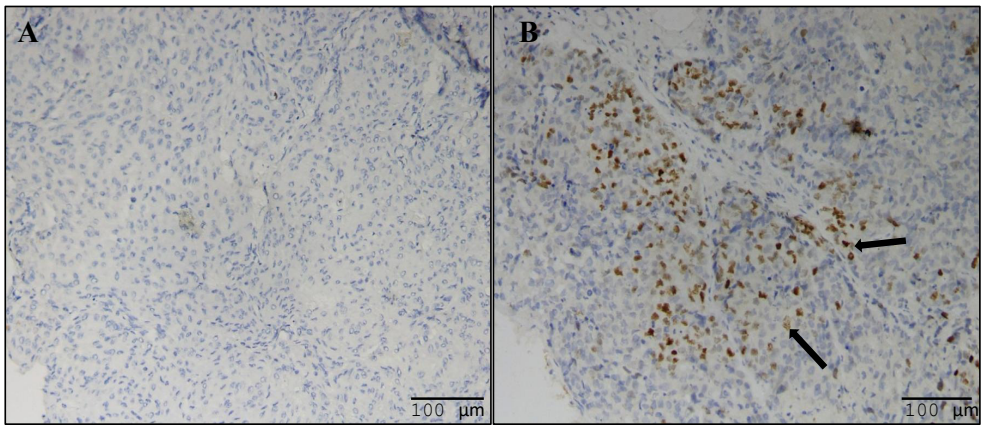

Figure 3. *Fibulin-2* Expression in Meningiomas Seen in the Cytoplasm (200x magnification). A. Low fibulin-2 expression (h-score ≤200). B. High fibulin-2 expression. Most tumors stained with high-intensity (h-score >200) (arrow).

Indonesia. Holleczek et al. [29] reported that the average age of meningioma patients was 63 years in the German population, with 55–74 years being the largest age group of patients with meningioma [29]. Lee et al. [30] reported that the average age of meningioma sufferers in Korea was 56.5 years [30]. Meanwhile, Ogasawara et al. [1] reported that the incidence of meningioma increased with age in America, with 66 years being the median age at diagnosis, and the age group with several meningioma cases was over 40 years. This indicates that sociodemographic factors influence meningioma incidence [1].

Most patients in this study are the female gender, with about 80% of cases. Mulyadi et al. [23] also found that women (91.9%) comprised most subjects in their study [23]. Women have been recognized to be at high risk for meningioma. The women-to-men ratio decreases to 1.7 in atypical or anaplastic meningiomas based on the WHO degree from three in-patients with benign meningiomas [29]. The risk of meningioma in women is particularly high at reproductive age. Research shows an association between endogenous and exogenous estrogen exposure and the incidence of meningioma [31].

In this study, *fibulin-2* expression (Figure 2 and Table 2) showed a significant association with age group ($p = 0.020$) and histopathologic grade ($p = 0.001$). A total of 80% of meningiomas (20 cases) with high *fibulin-2* expression were found in the age group below 50 years. A total of 76% (19 cases) of meningiomas with high *fibulin-2* expression were high-grade meningiomas. Sofela et al. [32] reported that the intensity of *fibulin-2* expression was stronger in WHO grade II meningioma in 64% of cases than in WHO grade I meningioma, which were only strongly positive in 40% of cases. Also, it was found that an increase in plasma *fibulin-2* levels with a cut-off value of >2.5 ng/mL could be a marker for WHO grade II meningioma, distinguishing it from WHO grade I meningioma [32]. In this study, 96% (24 cases) of meningiomas classified as high grade were grade II meningiomas. This may explain the high expression of *fibulin-2* in the group of meningiomas this study classified as high grade and further supports the possibility of *fibulin-2* as a non-invasive marker to differentiate WHO grade II meningiomas from grade I ones.

The grading standards were changed in the most recent WHO classification issued in 2021. All subtypes failing to meet WHO Grades III and III requirements are classified as WHO grade I meningioma. WHO grade II meningiomas are tumors with specialized histology features (choroid and clear cell), mitotic features of 4–19 in 10 consecutive high-power fields (HPF) (at least 2.5/mm2), unequivocal brain invasion, or three of the following criteria: increased cellularity, small cells with a high nuclear-cytoplasmic ratio, prominent nucleoli, a sheet growth pattern, and spontaneous necrosis. A WHO grade III meningioma is a meningioma with one of the following criteria: ≥ 20 mitoses in 10 consecutive HPF; obvious anaplasia (sarcoma, carcinoma, or melanoma); TERT promoter mutation; and homozygous deletion of CDKN2A and/or CDKN2B [9]. The WHO grade is the most reliable morphologic predictor for tumor recurrence [33].

The significant relationship between *fibulin-2* expression and age group in this study is attributed to meningioma cases classified as a high histopathologic grade, 72% (18 cases), at <50 years old.

Chromosome analysis of 124 samples showed that 29% of WHO grade I had gene copy number features consistent with high-grade meningiomas, and 25% of WHO grade II meningiomas had gene copy numbers consistent with less aggressive tumors [3]. However, grade reproducibility remains challenging in one study, reporting only 87.2% concordance of meningioma grade grading between different observers in a multicenter trial [10].

In this study, *Ki-67* expression (Figure 3 and Table 3) showed a significant association with histopathologic grade ($p = 0.013$). A total of 96% of meningiomas (24 cases) of low histopathologic grade had low *Ki-67* expression. Low *Ki-67* expression was more prevalent in the high-grade meningioma group than in the low-grade meningioma group at 64% (16 cases). However, almost all high *Ki-67* expressions (9 out of 10 cases) were found in the high-grade meningioma group. The cut-off value of *Ki-67* in this study was 4%. Research by Rejeki et al. [34] reported no significant difference between *Ki-67* expression and the degree of WHO meningioma ($p = 0.616$) [34]. Meanwhile, Mayasari and Fauziah (2016) found a significant relationship between histopathologic grade and *Ki-67* expression ($p = 0.001$) [26].

Based on the 2021 WHO classification, the degree of meningioma is determined by several criteria. Mitotic count and/or *Ki-67* expression are one of these criteria. Eye-balling mitotic count is no longer recommended at this time. *Ki-67* expression can determine the mitotic count precisely. This study found that samples suspected as high-risk meningioma group had low *Ki-67* expression, while some samples grouped as low-risk had high *Ki-67* expression. The assessment of *Ki-67* expression with the application shows more accuracy than without it because the presence of crush artifacts will complicate the calculation.

In addition, several studies have shown that *Ki-67* expression acts as a proliferation marker and functions as a prognosis factor. Mirian et al. (2020) reported that high *Ki-67* expression had a shorter median recurrent time of 0.6–0.75 years than *Ki-67* <4%, with that of 4.8 years. The same findings were also reported by Liu et al. [35], where the cut-off point of *Ki-67* expression >4% has a prognosis value in patients with meningioma [35]. This study has limitations in sample size and has not been correlated with therapy response or recurrence, and the standard assessment or cut-off value for *fibulin-2* expression is currently unavailable.

In Conclusions, *Ki-67* and *fibulin-2* are associated with the histopathological grade of meningioma, while *fibulin-2* is associated with age in the Minangkabau ethnic group.

Author Contribution Statement

Yessy Setiawati: Conceptualization, Methodology, Investigation, Validation, Data Analysis, Writing-

Original draft preparation and review. Tofrizal Alimuddin: Conceptualization, Methodology, Investigation, Data curation, Writing-review. Henny Mulyani: Methodology, Data analysis, Writing-edit. Muthia Kamelia: Methodology, Data analysis, Writing-edit. Furthermore, all authors approved the final version of the manuscript.

Acknowledgements

This study was funded by the Research and Development of RSUP dr. M. Djamil Padang in 2022. This study was not registered in any registering dataset.

Ethical Declaration: This study was approved by the Health Research Ethics Committee RSUP Dr. M. Djamil Padang (No. LB.02.02/5.7/140/2022).

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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