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Comparative Analysis of Matrix Metalloproteinase-9 and Estrogen Receptor Expression in Intradural Extramedullary Meningioma and Their Association with Postoperative Outcomes: A 2020–2025 Study at H. Adam Malik Hospital

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ABSTRACT

Introduction: This study analyzes the association between the expression of Matrix Metalloproteinase-9 (MMP-9) and Estrogen Receptor (ER) biomarkers in intradural extramedullary (IDEM) spinal meningioma tissue and neurological deficit recovery, clinical outcomes, and postoperative complications.

Methods: An observational analytic cross-sectional study was conducted on 20 patients following IDEM spinal meningioma resection at H. Adam Malik General Hospital Medan from 2020 to 2025. Biomarker expression was evaluated using immunohistochemistry, while clinical outcomes were assessed using the modified Rankin Scale (mRS) and statistically analyzed.

Results: The majority of patients were female (80%), with the thoracic region being the most frequent tumor location (75%). MMP-9 and ER expression showed a very strong negative correlation with neurological deficit recovery ($r = -0.815$ and $r = -0.806$; $p < 0.001$). The improved patient group exhibited significantly lower median MMP-9 and ER scores ($p < 0.001$). High MMP-9 expression and positive ER status were also significantly associated with an increased incidence of postoperative complications (OR = 6.00; $p < 0.001$).

Conclusion: High MMP-9 expression and positive ER status in IDEM spinal meningioma tissue are associated with minimal neurological recovery, poorer clinical outcomes, and a higher risk of postoperative complications. Both biomarkers hold potential as prognostic predictors for patient risk stratification.

Keyword: spinal meningioma, intradural extramedullary, MMP-9, Estrogen Receptor, immunohistochemistry.

1. Introduction

Meningioma is one of the most common benign central nervous system tumors, occurring both intracranially and spinally [1]. In the spinal region, the majority of meningiomas are located in the intradural extramedullary (IDEM) compartment, with a predilection for the thoracic region and a higher incidence in females [2]. Clinical symptoms typically arise from the tumor's mass effect (space-occupying lesion/SOL) on the spinal cord or nerve roots, which can cause progressive neurological deficits [3]. The primary treatment is surgical resection, which generally yields favorable outcomes, although variations exist in the degree of recovery and the risk of recurrence [4].

Variations in postoperative clinical outcomes of IDEM meningiomas cannot always be explained solely by tumor size or anatomical location. Biological and molecular tumor factors are also believed to play a role in determining clinical behavior [5]. One molecule that has drawn significant attention is matrix metalloproteinase-9 (MMP-9), a proteolytic enzyme involved in extracellular matrix degradation, tumor invasion, angiogenesis, and tissue remodeling. High MMP-9 expression has been linked to more aggressive tumor behavior and potential recurrence in several tumor types, including meningiomas [6]. Meanwhile, Estrogen Receptor (ER) expression has been found to be elevated in meningioma cases in general, although a definitive causative relationship between ER and meningiomas has not yet been established [7]. However, most of this evidence still originates from intracranial meningioma studies or overseas population-based research.

In Indonesia, particularly at tertiary care centers such as H. Adam Malik General Hospital, research examining the relationship between the expression of molecular biomarkers like MMP-9 and ER and the clinical outcomes of IDEM spinal meningiomas remains limited. Yet, an understanding of these molecular characteristics could potentially assist in risk stratification, prediction of postoperative response, and the development of future adjuvant therapies. The scarcity of local data also complicates determining the relevance of international findings to the Indonesian population context, which may possess distinct genetic, epidemiological, and clinical variations. This study aims to compare MMP-9 and ER receptor expression in IDEM meningioma tissue with postoperative space-occupying lesion clinical outcomes. By filling this local data gap, this study is expected to serve as an initial step toward strengthening the biological understanding of spinal meningiomas in Indonesia and providing a foundation for future personalized management.

2. Method

2.1. Study design and setting

This study employed an observational analytic design with a cross-sectional approach to evaluate the association between Matrix Metalloproteinase-9 (MMP-9) and Estrogen Receptor (ER) expression in intradural extramedullary (IDEM) meningioma tissue and postoperative outcomes in patients with IDEM Space-Occupying Lesions (SOL). The study was conducted at H. Adam Malik General Hospital, Medan, Indonesia, covering a 5-year period from 2020 to 2025. Data collection and tumor tissue examinations were performed at a single time point utilizing post-surgical tissue specimens and corresponding patient medical records.

2.2. Participants

The target population comprised all patients diagnosed with intradural extramedullary (IDEM) meningioma undergoing surgical intervention. The accessible population included IDEM meningioma patients who underwent surgical resection and histopathological evaluation at H. Adam Malik General Hospital, Medan, during the 2020–2025 period.

1. Inclusion Criteria:
   a. Diagnosis of IDEM meningioma confirmed by both radiological and histopathological examinations.
   b. History of surgical tumor resection with available paraffin-embedded tumor tissue suitable for immunohistochemical (IHC) analysis of MMP-9 and ER receptor expression.
   c. Complete medical record data, including preoperative and postoperative clinical conditions (specifically neurological status and postoperative radiological evaluations).
2. Exclusion Criteria:
   a. Presence of multiple, extradural, or non-IDEM type meningiomas.
   b. Insufficient or unavailable tumor tissue for MMP-9 and ER IHC staining.
   c. Incomplete clinical or medical record documentation.
   d. Severe co-morbidities capable of significantly confounding postoperative outcomes (e.g., non-tumor neurological disorders or terminal systemic diseases).

2.3. Sample size

The minimum required sample size (n) was calculated using the formula for correlative analysis:

$$n = \left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{0.5 \text{ In } \left(\frac{1+r}{1-r} \right)} \right)^2 + 3$$

The minimum required sample size was calculated using the sample size formula for correlative analysis. Based on a significance level (α) of 10% (Z_α = 1.28), a test power of 90% (β = 10%, Z_β

= 1.28), and an anticipated minimum correlation coefficient (r) of 0.621 derived from previous literature, the minimum calculated sample size required for this study was 16 patients.

2.4. Variables and Operational Definitions

The independent variables in this study are the expression of matrix metalloproteinase-9 (MMP-9) and estrogen receptor (ER) in intradural extramedullary (IDEM) meningioma tissue, which are evaluated through immunohistochemical (IHC) staining of postoperative tissue specimens. The dependent variable is the postoperative clinical outcome of patients with IDEM space-occupying lesions (SOL), assessed based on clinical and functional recovery parameters as well as the occurrence of postoperative complications.

MMP-9 expression is defined as the level and extent of positive MMP-9 staining in IDEM meningioma tissue, assessed semi-quantitatively using an immunohistochemical scoring system based on staining intensity and the proportion of positively stained tumor cells. Estrogen receptor (ER) expression is defined as the level and extent of positive ER staining in IDEM meningioma tissue, determined semi-quantitatively through immunohistochemical examination based on staining intensity and the proportion of cells demonstrating positive nuclear and/or cytoplasmic reactivity.

Postoperative outcomes are defined as the patient's clinical and functional status assessed at hospital discharge and/or at the one-month postoperative follow-up visit, comprising symptom improvement, functional status, and postoperative complications. Symptom improvement refers to the objective and subjective recovery of pre-existing motor and/or sensory deficits, while functional status is quantitatively assessed using the modified Rankin Scale (mRS).

Postoperative complications are defined as the occurrence of surgical adverse events, including surgical-site or central nervous system infections, the need for reoperation, and/or the development of new neurological deficits.

2.5. Data Collection and Workflow

The data collection workflow commenced with the screening and selection of Spinal Intradural Extramedullary (IDEM) meningioma cases from the medical records and histopathological archives at H. Adam Malik General Hospital, Medan, according to the predefined inclusion and exclusion criteria.

For all included cases, baseline demographic and clinical data comprising age, sex, spinal lesion location, histopathological subtype, and extent of surgical resection according to the Simpson grading system were recorded. Expression data for Matrix Metalloproteinase-9 (MMP-9) and Estrogen Receptor (ER) were subsequently obtained from the Immunohistochemical (IHC) analysis of the resected tumor tissue specimens. Postoperative patient data were then traced to evaluate clinical outcomes, including motor and sensory symptom improvement, functional status

via the Modified Rankin Scale (mRS), neurological deficits, recurrence, and surgical complications at hospital discharge and during the 1-month follow-up. Finally, the compiled dataset was formatted for statistical processing.

2.6. Statistical analysis

Statistical processing and analysis were conducted using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Continuous and categorical data were processed as follows:

1. Univariate Analysis: Descriptive statistics were performed to summarize the distribution and characteristics of all study variables. Categorical data (e.g., sex, tumor location, Simpson resection grade, postoperative complication rates) were presented as frequencies and percentages, while continuous data were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate.

2. Bivariate Analysis: Pearson's correlation test was utilized to evaluate the linear relationship between independent variables (MMP-9 and ER expression levels) and dependent/clinical variables in spinal intradural extramedullary (IDEM) meningioma cases, assuming continuous data were normally distributed.

The magnitude of the correlation coefficient (r) was interpreted according to five standard categories:

- > 0.0 to ≤ 0.2**:** Very weak correlation
- > 0.2 to ≤ 0.4: Weak correlation
- > 0.4 to ≤ 0.6: Moderate correlation
- > 0.6 to ≤ 0.8: Strong correlation
- > 0.8 to ≤ 1.0: Very strong correlation

The direction of the relationship was indicated by the sign of r, where a positive value (+) signified a direct correlation and a negative value (-) indicated an inverse correlation. A p-value of < 0.05 was established as the threshold for statistical significance. Results are presented through structured tables, charts, and narrative descriptions.

2.7. Ethical considerations

The study protocol was reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara. Informed consent was obtained from all patients or their legal guardians for the utilization of archived tumor tissue specimens, medical records, and follow-up clinical data for research purposes. All collected data were anonymized using unique identification codes, and access to personal health information was strictly restricted to the research team to maintain patient confidentiality

3. Results and Discussion

3.1. Demographic and Clinical Characteristics

A total of 20 patients diagnosed with intradural extramedullary (IDEM) meningioma were included in this study. The mean age of the subjects at diagnosis was 53.45 ± 12.18 years. Females predominated significantly, accounting for 80% (n = 16) of the cohort, yielding a female-to-male ratio of 4:1.

Anatomically, the thoracic spine was the most frequent tumor location (n = 15, 75%), followed by the cervical (n = 4, 20%) and lumbar regions (n = 1, 5%). Histopathological evaluation based on the WHO 2021 classification revealed that the transitional subtype was the most prevalent (n = 7, 35%), followed by meningothelial (n = 4, 20%) and psammomatous (n = 3, 15%) subtypes. Fibrous, angiomatous, metaplastic, and clear cell subtypes each accounted for 5% (n = 1) of cases. Two cases (10%) were classified as atypical meningioma. Regarding surgical resection extent, Simpson Grade 2 resection was achieved in 10 patients (50%), Simpson Grade 1 in 6 patients (30%), and Simpson Grade 3 in 4 patients (20%).

Table 1 Demographic and Clinical Characteristics of IDEM Meningioma Patients

Variable	Categories / Metrics	n=20 (%) or Mean ± SD
Age (years)	—	53.45 ± 12.18
Sex	Male	4 (20%)
	Female	16 (80%)
Tumor Location	Cervical	4 (20%)
	Thoracic	15 (75%)
	Lumbar	1 (5%)
Histotype	Transitional	7 (35%)
	Meningothelial	4 (20%)
	Psammomatous	3 (15%)
	Fibrous	1 (5%)
	Angiomatous	1 (5%)
	Metaplastic	1 (5%)
	Clear Cell	1 (5%)
	Atypical	2 (10%)
Simpson Grade	Grade 1	6 (30%)

Grade 2	10 (50%)
Grade 3	4 (20%)

3.2. Correlation of MMP-9 and Estrogen Receptor (ER) Expression with Neurological Deficit Improvement

The median MMP-9 expression score was 2 (range: 1–6), while the median ER expression score was 5 (range: 0–20). Functional recovery, evaluated by the change in modified Rankin Scale score (ΔmRS), showed a mean improvement of 1.00 ± 0.79 points.

Spearman rank correlation analysis demonstrated a statistically significant, strong inverse correlation between MMP-9 expression scores and ΔmRS (r= -0.815, $p < 0.001$). Similarly, a strong inverse correlation was observed between ER expression scores and ΔmRS (r = -0.806, $p < 0.001$). Higher expression levels of both MMP-9 and ER were significantly associated with lower ΔmRS values, indicating diminished postoperative functional recovery.

Table 2 Correlation of MMP-9 and ER Expression Scores with Functional Improvement (ΔmRS)

Variable	Median (Min–Max)	Mean ± SD	Correlation Coefficient (r)	p-value*
MMP-9 Score	2 (1–6)	2.95 ±1.70	-0.815	<0.001
ER Score	5 (0–20)	6.00 ± 7.18	-0.806	<0.001
Δ*mRS*	1 (0–2)	1.00 ± 0.79	—	—

*Spearman rank correlation test.

3.3. Comparison of MMP-9 and ER Expression Across Clinical Outcome Groups

Patients were categorized into two clinical outcome groups based on functional recovery: Improved (n = 14) and Static (n = 6). The improved group demonstrated significantly lower median MMP-9 expression scores (2, range: 1–3) compared to the static group (5, range: 5–6; $p < 0.001$).

Substantial differences were also observed for ER expression. The improved group exhibited a median ER score of 0 (range: 0–5), indicating low or negative receptor expression, whereas the static group showed a elevated median ER score of 15 (range: 10–20; $p < 0.001$).

Table 3 Comparison of MMP-9 and ER Expression Scores Between Clinical Outcome Groups

Variable	Metric	Improved Group (n=14)	Static Group (n=6)	p-value*
MMP-9 Score	Median (Min–Max)	2 (1–3)	5 (5–6)	<0.001
	Mean ± SD	1.93 ± 0.62	5.33 ± 0.51	
ER Score	Median (Min–Max)	0 (0–5)	15 (10–20)	<0.001
	Mean ± SD	1.79 ± 2.48	15.83 ± 3.76	

*Mann-Whitney U test.

3.4. Association of MMP-9 and ER Expression with Postoperative Complications

Biomarker expressions were strongly associated with the incidence of postoperative complications. All patients with low MMP-9 expression (n = 14, 100%) experienced no complications, whereas 83.3% (n = 5) of patients with high MMP-9 expression developed complications ($p < 0.001$, OR = 6.00, 95% CI: 1.00–35.91).

An identical pattern was observed for ER expression status: all reported complications occurred within the ER-positive group (n = 5, 83.3%), while no complications occurred in the ER-negative group (n = 14, 100%; $p < 0.001$, OR = 6.00, 95% CI: 1.00–35.91). High MMP-9 expression and positive ER status were both associated with a six-fold increase in the odds of experiencing postoperative complications.

Table 4 Association of MMP-9 and ER Expression Categories with Postoperative Complications

Variable	Categories	No Complication (n=15)	Complication (n=5)	p-value*	OR (95% CI)
MMP-9 Score	Low	14 (100%)	0 (0%)	<0.001	6.00 (1.00–35.91)
	High	1 (16.7%)	5 (83.3%)		
ER Score	Negative	14 (100%)	0 (0%)	<0.001	6.00 (1.00–35.91)
	Positive	1 (16.7%)	5 (83.3%)		

*Fisher's Exact Test.

3.5. Discussion

The demographic characteristics of the subjects in this study revealed a mean age at diagnosis of 53.45 ± 12.18 years. This finding aligns with global epidemiological patterns reported in recent systematic literature. A comprehensive study by Wang et al. confirmed that the incidence of spinal meningiomas increases significantly in the fifth and sixth decades of life. This elevated incidence in middle-aged individuals is closely linked to biological aging processes that trigger the accumulation of genetic mutations in arachnoid cap cells, alongside prolonged hormonal exposure. Furthermore, female predominance in this study was remarkably prominent, reaching 80% (4:1 female-to-male ratio). This figure is consistent with literature by El-Hajj et al., which reported that spinal meningiomas exhibit a substantially higher female predilection compared to intracranial meningiomas, with female patients accounting for 72–80% across major cohort studies. This phenomenon is attributed to the high density of progesterone receptors in female spinal meninges, rendering these tumors sensitive to sex steroid hormone fluctuations [8][9].

Regarding anatomical location, the majority of tumors in this cohort were located in the thoracic region (75%), followed by the cervical (20%) and lumbar (5%) regions. This distribution closely matches data presented by Wang et al., who reported that 67–84% of spinal meningiomas occur in the thoracic segment. This anatomical predilection has a strong structural foundation, as the thoracic segment possesses the longest dural surface area and the highest density of arachnoid cap cells compared to the cervical or lumbar segments. Additionally, El-Hajj et al. noted that

hemodynamic factors within vascular watershed areas in the thoracic region may induce local hypoxia, potentially driving tumor initiation [8][9].

The histopathological profile in this study was dominated by transitional (35%) and meningothelial (20%) subtypes, with 90% of cases classified as Grade 1 (benign) and 10% as Grade 2 (atypical). This classification follows the updated 5th edition of the WHO Classification of Tumors of the Central Nervous System (2021). Under these refined guidelines, diagnostic criteria for atypical (Grade 2) meningiomas were tightened to include tissue invasion or increased mitotic activity, which is directly relevant to the 10% aggressive cases identified in this study. Although this proportion is slightly higher than classical literature estimates, it aligns with the overall trend of increased Grade 2 diagnoses following the updated WHO 2021 criteria [10].

Regarding surgical outcomes, the extent of resection was evaluated using the Simpson grading scale. Gross total resection (Simpson Grades 1 and 2) was achieved in 80% of patients, while the remaining 20% underwent Simpson Grade 3 resection. A meta-analysis by Corazzelli et al. emphasized that while Simpson Grade 1 (dural excision) remains the ideal target, Simpson Grade 2 (dural coagulation) or Grade 3 resection is frequently accepted in spinal meningiomas to avoid risks of spinal instability or cerebrospinal fluid leakage, without significantly compromising short-term recurrence rates. This validates the surgical strategy employed in this study, where surgical radicality was adapted to prioritize the safety of functional neural structures [11].

Statistical analysis demonstrated a strong inverse correlation ($r = -0.815$, $p < 0.001$) between matrix metalloproteinase-9 (MMP-9) expression and postoperative neurological improvement (ΔmRS). Patients with high MMP-9 expression scores exhibited minimal functional recovery, static conditions, or clinical deterioration. Biochemically, MMP-9 belongs to a family of zinc-dependent endopeptidases whose primary function is the degradation of extracellular matrix (ECM) components, particularly type IV collagen within the endothelial basement membrane. Overexpression of this enzyme causes disruption of the blood-spinal cord barrier (BSCB) tight junctions, leading to the extravasation of protein-rich fluid into the interstitial space and triggering peritumoral vasogenic edema. Given the restricted spatial volume within the spinal canal, massive peritumoral edema generates secondary compression, inducing microvascular ischemia that accelerates axonal degeneration. This logically explains why patients with elevated MMP-9 scores often suffer from irreversible neural damage even prior to mechanical decompression via tumor resection, ultimately leading to sub-optimal functional outcomes (ΔmRS) [12][13].

These pathophysiological findings strongly align with empirical evidence from a recent prospective cohort study by Ibrahim et al., which demonstrated that strong immunohistochemical MMP-9 expression correlates significantly ($p < 0.001$) with severe peritumoral swelling and poor clinical outcomes. Although Ibrahim et al. focused on intracranial lesions, the present study extrapolates that a similar destructive enzymatic cascade occurs within the spinal cord, albeit with sensorimotor deficits that exert a more debilitating effect on daily functionality. Furthermore, a

retrospective study by Alkhotani et al. confirmed that meningioma patients presenting with peritumoral edema secondary to vascular disruption exhibit more severe preoperative clinical manifestations and a higher susceptibility to perioperative morbidity. The high MMP-9 expression observed in this cohort provides evidence that the tumor lesion does not merely exert passive mechanical compression on the spinal cord, but actively causes tissue injury through local inflammatory processes and fluid exudation [14][15].

Beyond impairing neurological recovery, this study identified a statistically significant association between high MMP-9 expression and an increased incidence of postoperative complications ($p < 0.001$, OR = 6.00). This indicates that patients with MMP-9 overexpression face a six-fold higher risk of surgical complications, such as new iatrogenic neurological deficits or the need for reoperation. This clinical phenomenon can be comprehensively explained by molecular pathology research from Fauziah et al., who demonstrated that elevated MMP-9 levels facilitate extracellular matrix degradation, enabling tumor cells to microscopically invade healthy parenchyma even when morphologically classified as benign (Grade 1) [16].

From a microneurosurgical perspective, MMP-9-catalyzed tissue invasion obliterates the distinct arachnoid cleavage plane between the tumor capsule and the pial surface. Consequently, the tumor tissue becomes highly adherent and prone to intraoperative hemorrhage from fragile neovessels. Forced dissection of these adherent tumors significantly heightens the risk of mechanical trauma to vital vasculature (such as radiculomedullary arteries), culminating in ischemic neural injury and subsequent postoperative complications.

In conclusion, the findings of this study challenge the conventional paradigm that restricts MMP-9 enzyme overexpression to high-grade tumors. This aligns with clinical assertions by Reszec et al., who noted that MMP-9 overexpression occurs in low-grade meningiomas and accurately predicts aggressive clinical behavior. Consistent with the latest WHO oncology guidelines, which emphasize molecular profiling, evaluating MMP-9 status provides superior prognostic value compared to routine histopathological grading alone. Identifying this biomarker functions as an early warning system for neurosurgeons to anticipate surgical difficulty, implement protective surgical maneuvers, and establish realistic neurorehabilitation expectations for patients [10][12].

In addition to MMP-9, this study investigated the prognostic role of hormonal biomarkers. Bivariate analysis revealed a strong, statistically significant inverse correlation ($r = -0.806$, $p < 0.001$) between estrogen receptor (ER) expression scores and neurological improvement (ΔmRS). Furthermore, the data showed a sharp contrast between clinical outcome groups: patients with optimal functional recovery exhibited a median ER score of 0 (negative/very low), whereas those with static or deteriorating outcomes exhibited a markedly high median ER score of 15. Furthermore, elevated ER expression was observed in 100% of patients who experienced postoperative complications ($p < 0.001$, OR = 6.00). These findings demonstrate that ER

expression in spinal meningiomas is not merely a coincidental epiphenomenon, but a key determinant that actively exacerbates clinical outcomes and increases surgical morbidity.

The biological mechanism underlying the aggressiveness of ER-positive tumors involves proliferative and angiogenic signaling pathways. A comprehensive systematic review by Agopiantz et al. explained that the binding of circulating estrogen to its receptor (ER) in meningioma cells activates intracellular signaling cascades, such as the phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) pathways. Activation of these pathways not only stimulates the mitotic index of tumor cells but also upregulates vascular endothelial growth factor (VEGF) expression, inducing local hypervascularity. This hypothesis is supported by clinical findings from Prakoso and Arifin, who reported that ER-positive meningiomas exhibit more aggressive biological characteristics, higher proliferation indices, and poorer functional recovery outcomes. In the spinal cord context, estrogen-stimulated neovascularization yields highly vascularized tumors, directly compounding surgical resection difficulty [17][18].

Macroscopically during surgery, high hormone receptor expression influences tumor interaction with surrounding vital neural structures. A study by Mnango et al. highlighted that spinal meningiomas with high sex hormone receptor expression exhibit a greater tendency to derive pial blood supply and undergo pial invasion. When the tumor firmly adheres to the spinal cord's pial membrane, the safe surgical dissection plane becomes obscured. Attempts to dissect these highly adherent and vascular ER-positive tumors frequently necessitate extensive bipolar coagulation. Consequently, the risk of secondary mechanical trauma or thermal injury to spinal cord neural tracts increases dramatically, manifesting as new iatrogenic neurological deficits. This provides a clear explanation for the six-fold increase in complication risk observed in the ER-positive group [19].

Although the overall incidence of ER positivity in meningiomas is lower than that of progesterone receptor (PR) positivity, the presence of ER has proven to be a far more ominous prognostic indicator. This aligns with a systematic review by Awosusi et al., which concluded that while PR expression is commonly associated with benign tumor behavior and favorable outcomes, ER positivity correlates negatively with progression-free survival. Similar findings published by Shafat et al. demonstrated that specific immunohistochemical profiles (including PR loss alongside persistent ER expression) frequently overlap with high Ki-67 labeling indices, a marker of aggressive tumor proliferation [20][21].

Consequently, the findings of this study enrich the neuro-oncological literature by demonstrating that ER positivity in IDEM meningiomas serves as a strong predictor of intraoperative technical difficulty and impaired functional recovery. As suggested by Agopiantz et al., determining hormone receptor status in clinical practice may extend beyond epidemiological interest, proving crucial for guiding personalized medicine strategies such as adjuvant anti-estrogen therapy to

minimize recurrence risk in subtotal resection cases (Simpson Grade 3) with confirmed ER positivity [22].

This study has several limitations that should be considered when interpreting the clinical findings. First, the relatively small sample size and single-center study design conducted at a referral hospital in North Sumatra limit statistical power and the generalizability of these findings to broader neuro-oncological populations. Second, the brief postoperative follow-up duration of one month is insufficient to evaluate long-term tumor recurrence rates or maximal neurological recovery, which often requires months to years of rehabilitation. Third, although this study evaluated key biomarkers (MMP-9 and ER) and surgical radicality (Simpson Grade), it did not comprehensively explore the influence of other genetic alterations (such as NF2 mutations or DNA methylation profiles) or intraoperative hemodynamic variations, which may act as potential confounding factors for postoperative morbidity.

4. Conclusion and Future Research

IDEM meningioma patients in this cohort were predominantly female (80%) with a mean age of 53.45 ± 12.18 years, demonstrating a predilection for the thoracic segment, transitional histotype, and WHO Grade 1 classification, with gross total resection achieved in 80% of cases. Elevated expression levels of both MMP-9 ($r = -0.815$, $p < 0.001$) and ER ($r = -0.806$, $p < 0.001$) exhibited strong, statistically significant inverse correlations with functional neurological improvement (ΔmRS), where patients achieving favorable clinical recovery demonstrated markedly lower biomarker scores than those with static or deteriorating outcomes. Furthermore, high MMP-9 expression and ER positivity were significantly associated with an increased incidence of postoperative complications, imparting a six-fold increase in the odds of adverse surgical outcomes (OR = 6.00).

Future prospective, multicenter studies with larger patient cohorts are warranted to validate specific diagnostic cutoff values for MMP-9 and ER expression scores across broader populations. Additionally, extended longitudinal follow-up exceeding 12 months is recommended to evaluate the definitive impact of these biomarkers on long-term tumor recurrence rates and progression-free survival.

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Conflict of Interest

The authors declare that they have no conflict of interest. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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