Immunohistochemical Markers Associated with Meningioma Recurrence: A Systematic Review

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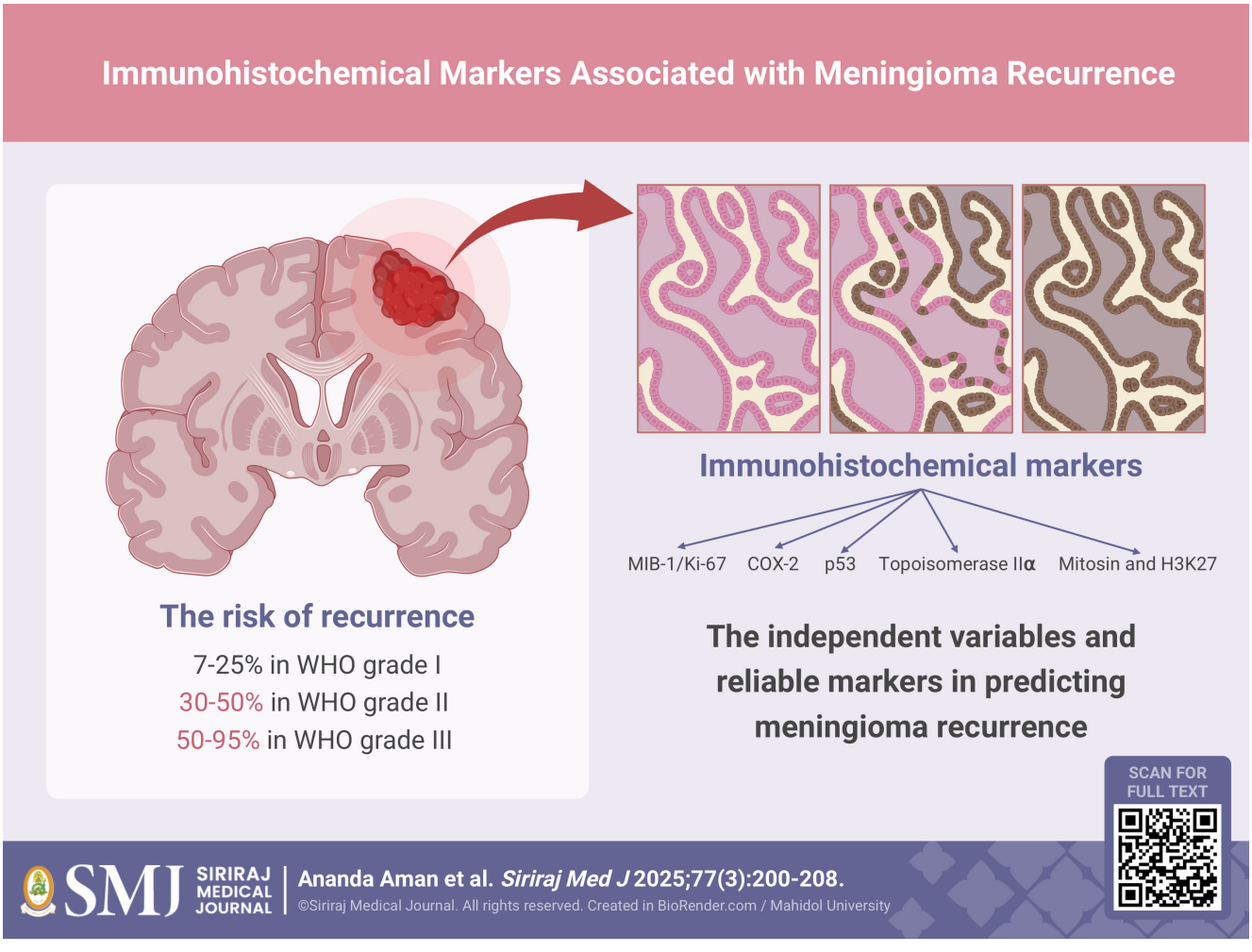

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ABSTRACT

Objective: This study aims to know the role of immunohistochemical markers in the recurrence of surgically treated meningiomas.

Material and Methods: We conducted a comprehensive search of the PubMed, ScienceDirect, Cochrane Library, and Google Scholar databases to locate studies published within the past decade. The inclusion criteria for this study were patients aged 18 years or older who had undergone surgical treatment for meningioma. Studies that were not written in English, case report studies, case series studies, literature review studies, and studies involving patients who received treatment other than surgery or multimodal therapy were excluded. All studies that met the inclusion criteria were subjected to critical appraisal.

Results: Four studies comprising 3176 cases of meningioma cases were included in the analysis. Multivariate analysis showed that two immunohistochemical markers (COX-2 and MIB-1/Ki-67) were independent variables for meningioma recurrence. This study also found no statistical differences between grade I and grade II meningiomas with respect to the overexpression of COX-2 and MIB-1/Ki-67. The second study compared the nonrecurrence/relapse (non-R/R) and recurrence/relapse (R/R) groups and found a significant correlation with MIB-1 percentage, intensity, histoscore, and p53 percentage, regardless of tumor grade. The third study found that mitosin and topoisomerase IIα were significant predictors of recurrence but not MIB-1. The fourth study demonstrated that H3K27me3 loss is significantly associated with more aggressive meningiomas.

Conclusion: Our study concluded that MIB-1/Ki-67, COX-2, p53, topoisomerase IIa, mitosin and H3K27 were independent variables and reliable markers in predicting meningioma recurrence.

Keywords: Immunohistochemical marker; meningioma; recurrence (Siriraj Med J 2025; 77: 200-208)

INTRODUCTION

Meningioma accounts for 20-30% of all primary brain tumors; it is considered the most common central nervous system tumor with benign characteristics and an excellent prognosis if resected utterly.[1] Meningiomas are stratified into three groups, according to the 2016 World Health Organization (WHO) classification scheme: grade I (benign), grade II (atypical), and grade III (anaplastic).[2] The risk of recurrence is 7-25% in WHO grade I, 30-50% in WHO grade II and 50-95% in WHO grade III.[3] Gross total microsurgical resection is the initial choice of treatment, and mostly the outcomes improved post-surgery.[4] The completeness of removal is classified according to the Simpson Grading System on a 5-tier scale. Grade I is the complete removal of the tumor with resection of the dura and bone that are involved; Grade II is the resection of the tumor entirely with coagulation of the dural attachment; Grade III is total removal of the intradural tumor without resection or coagulation of the dura or extradural component; Grade IV is subtotally tumor removal; and Grade V is simple decompression. The recurrence rates increased by Simpson Grades; they were 9, 19, 29, and 40% at ten years in Grade I to IV.[5] Recently, one study showed Simpson Grade IV was significantly correlated with a high risk of recurrence compared to Simpson Grade I, II, and III in meningioma WHO Grade I.[6] Another paper concluded that patients who underwent Simpson Grade I and II surgery gained improvement in recurrence-free survival (RFS) significantly compared to patients with Simpson Grade III and IV.[7]

Despite the removal of the entire tumor (Simpson Grade I-III), the recurrence of benign meningioma remains a concern. A study revealed that recurrence in completely resected Grade I meningiomas accounted for 15% of the 10-year follow-up. In addition to histopathological findings and Simpson grade, immunohistochemical markers are increasingly being recognized as contributing factors to meningioma recurrence. We conducted a systematic review to assess the role of immunohistochemical markers in the recurrence of surgically treated meningiomas.

MATERIALS AND METHODS

Search strategy

We thoroughly searched for available literature from the last ten years in the electronic databases PubMed, ScienceDirect, Cochrane Library, and Google Scholar through December 31, 2023. The inclusion criteria were surgically treated meningioma patients and age > 18 years. Non-English articles, case report studies, case series studies, literature review studies, and studies on patients who received non-surgical treatment or multimodality therapy were excluded. Keywords used to find relevant literature: "meningioma" AND "recurrence OR free-recurrence

survival" AND "biomarkers OR immunohistochemical markers OR markers". An initial search identified 105 articles from PubMed, ScienceDirect, the Cochrane Library, and Google Scholar. Two reviewers (DRS and SAHP) independently screened the titles and abstracts of all the initially identified studies and read the full text to determine whether the studies were relevant to the research question. Any inconsistencies were resolved through a discussion with the first author (RAA). We did not review ongoing relevant studies.

Quality assessment

The reviewers critically appraised the selected articles using a critical appraisal tool for prognostic studies. Cohort and case control studies assessed using Newcastle and Ottawa Quality Assessment Scale. Systematic review and meta-analysis appraised using Oxford Critical Appraisal Worksheet. Any disagreements were resolved through discussion between the two reviewers or by consulting with other authors.

RESULTS

Searching result

The detailed literature selection process is presented in Fig 1. Six journals relevant to our research question were retrieved after the titles and abstracts were screened, full-text read, and double-excluded. Three articles were excluded after being critically appraised, resulting in four studies being included in this systematic review. Quality assessment reported in Table 3 and Table 4.

Study characteristics

Four studies, comprising 3176 cases of meningioma cases were selected. Three studies were conducted in Europe and one in the USA, and all were single-center studies. All four studies were retrospective observational cohort studies conducted between 2012-2022. The sample size ranged from 70 to 292 patients, all surgically treated between 1980 and 2022. Two papers contained meningioma WHO Grades I and II without WHO Grade III, and the other two studies constituted samples of meningioma WHO Grades I, II, and III. Tumors of 1448 patients from two studies underwent total removal (Simpson Grade I-III), whereas the tumors of 660 patients from two other studies underwent total or subtotal resection. All patients in each study were followed up; the duration of follow-up in one study was 0-96 months with a median of 96 months, the second study did not mention the duration of the follow-up but evaluated the recurrence of meningioma in 5 years, the third study followed up patients within a range of 1.5 – 25 years with a mean of eight years and two months, and the fourth study followed up patients within the range of 3 – 17.5 years. Radiological workup in all studies evaluated tumor recurrence, and one study used post-mortem studies to assess recurrence.

TABLE 1. Research question.

Study Component	
Patient	Meningioma
Intervention/Exposure	Immunohistochemical marker
Comparison	-
Outcome	Recurrence/Free-Recurrence Survival

TABLE 2. Inclusion and exclusion criteria.

Inclusion	Exclusion
Surgically treated meningioma patients	Case report study
Age ≥ 18 years old	Case series study
Last ten years of study	Literature review study
English language articles	Received treatment other than surgery of multimodality therapy

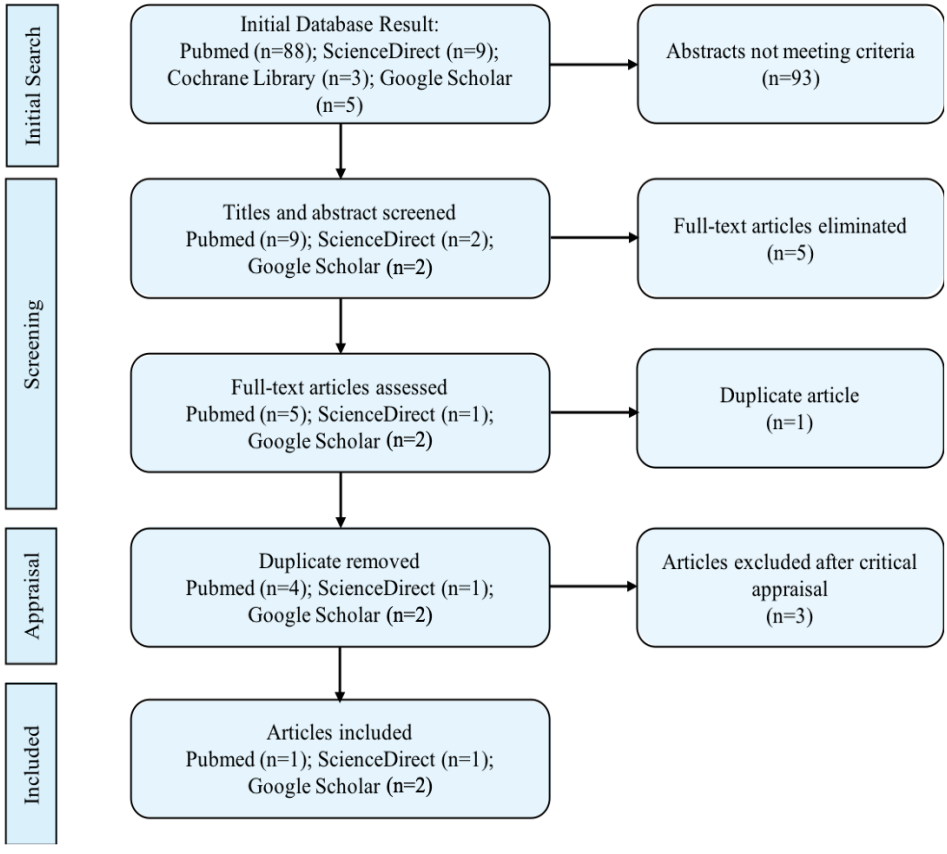

Fig 1. Flowchart of a screening strategy for included studies.

TABLE 3. Newcastle and Ottawa Quality Assessment for Cohort and Case Control Study.

Reference	Year	Design Study	Appraisal Selection	Comparability	Outcome	Score	Quality
Sanz et al[8]	2013	Cohort	****	*	***	8	Good
Csonka et al[9]	2016	Case Control	****	*	***	8	Good
Winther et al[10]	2017	Case Control	***	*	***	7	Good

TABLE 4. Oxford Quality Assessment for Meta-Analysis Study.

Appraisal Cello et al (2023)[11]	Answer
What question (PICO) did the systematic review address?	Yes
Is it unlikely that important, relevant studies were missed?	Yes
Were the criteria used to select articles for inclusion appropriate?	Yes
Were the included studies sufficiently valid for the type of question asked?	Yes
Were the results similar from study to study?	Yes

TABLE 5. Characteristics of Eligible Studies.

Reference	Year Published	Country	Sample Size	Histopathological Grade	Extent of Resection	Follow-Up
Sanz et al.[8]	2013	Spain	135	I, II	Gross Total Resection	1.5 - 25 years (mean: 8 years two months)
Csonka et al.[9]	2016	Hungary	70	I, II, III	Gross Total Resection	Five years
Winther et al.[10]	2017	Norway	160	I, II	Gross Total Resection, Subtotal Resection	0 - 96 months (median: 96 months)
Cello et al.[11]	2023	USA	2811	I, II, III	Gross Total Resection, Subtotal Resection	3 – 17.5 years

Immunohistochemical Markers Relevant to Recurrence

Csonka et al. established two study groups: patients with one or more recurrence/relapses (R/R group), and patients with meningioma without any radiological or postmortem evidence of recurrence/relapse (non-R/R group). The research did not mention the follow-up duration but evaluated the recurrence outcome within five years after resection. Of seventy meningioma patients with meningioma underwent complete surgical removal. The value of markers was measured as the percentage of cell immunopositivity, average labeling intensity score (0-3+), and histoscore (multiple of the percentage of positive cells and average intensity). WHO tumor grade was correlated significantly with MIB-1 Labelling Index (LI) (%) ($p < 0.001$), MIB-1 staining intensity ($p = 0.001$), MIB-1 histoscore ($p < 0.001$), p53 staining intensity ($p < 0.001$), p53 histoscore ($p = 0.031$), Progesterone Receptor (PR) LI (%) ($p < 0.001$), PR intensity ($p < 0.001$), PR histoscores ($p < 0.001$). Comparing the non-R/R and R/R groups, regardless of the grades of the R/R group, there was a significant correlation with the MIB-1 LI (%) ($p < 0.001$), MIB-1 intensity ($p = 0.004$), MIB-1 histoscore ($p < 0.001$), and p53 LI (%) ($p = 0.027$). The study also found a significant correlation between the non-R/R and R/R groups, with only WHO Grade I tumors in the R/R group, with MIB-1 LI (%) ($p = 0.009$), MIB-1 histoscore ($p = 0.029$), p53 LI (%) ($p = 0.032$), and p53 histoscore ($p = 0.038$). The authors concluded that p53 and MIB-1 were sufficient to characterize meningioma immunohistochemically in terms of recurrence risk.[9]

TABLE 6. Summary Table of Tumor Recurrence in Association with Immunohistochemical Markers.

Author, Year	Markers	Tumor Grade	Time of Follow-Up	Effect Size
Sanz et al., 2012[8]	COX-2	I, II	3, 5, and 10-year	95% CI 1.1-9.68; p=0.01
	MIB1/ki67	I, II	3, 5, and 10-year	98% CI 1.12-10.55; p=0.031
Csonka et al., 2016*[9]	p53	I, II, III	5-year	p=0.027
	MIB1/ki67	I, II, III	5-year	p<0.001
	p53	I	5-year	p=0.009
	MIB1/ki67	I	5-year	p=0.032
Winther et al., 2017[10]	MIB1/ki67	I, II	8-year**	95% CI 0.84–4.22; p=0.127
	Topoisomerase IIα	I, II	8-year	95% CI 1.04–4.47; p=0.04
	Mitosin	I, II	8-year	95% CI 1.87–852; p<0.01
Cello et al., 2023[11]	HK327	I, II, III	3, 6, 15 and 17.5 year	(95% CI 1.35–2.15); p<0.01

*markers measured with percentage of cells immunopositivity
**median 96 months

A study by Sanz et al. evaluated 135 patients who underwent complete surgical resection of meningioma (Simpson Grade I, II, III) with a mean follow-up of 8 and two months (range one year and six months to 25 years). Markers were measured as the percentage of cells. COX-2 was considered positive if >10%, Cyclin A considered positive if >3%, MIB-1/Ki-67 was considered positive if >4%, Topoisomerase IIα was considered positive if >4, and TIMP2 was considered positive if >0. Some factors were relevant to RFS, including the expression of immunohistochemical markers COX-2 (9 positive cases and 126 negative cases, p = 0.001), Cyclin A (9 out of 130 valid cases, p = 0.002), MIB-1/Ki-67 (6 out of 133, p = 0.01), Topoisomerase IIα (8 out of 133, p = 0.04), and TIMP2 (16 out of 131, p = 0.04). Multivariate analysis was performed; the study did not include Topoisomerase IIα because of significant co-variation with MIB-1/Ki-67 (p < 0.001) and similar prognostic information. It revealed COX-2 (HR 3.28; 95% CI 1.10-9.68; p = 0.032) and MIB-1/Ki-67 (HR 3.44; 98% CI 1.12-10.55; p = 0.031) were independent variables. A table in the study showed several patients with positive COX-2 related to recurrence over time: 20% of patients had recurrence in 3 years, 30% in 5 years, and 58% in 10 years. The same table also shows the correlation between the positivity of MIB-1/Ki-67 and recurrence: 16.7% of patients had a recurrence at 3 years, 37.5% at 5 years, and 58.3% at 10 years. Another table shows that the expression of COX-2 and MIB-1 was not significantly correlated with the histopathological grade of meningioma (WHO Grade I and II) and grade of resection (Simpson Grade I, II, and III). A Kaplan-Meier curve showed the antagonistic effect of COX-2: patients with negative COX-2 expression had significantly longer RFS than those with positive COX-2 expression. Other markers in this study, such as pAKT, Bcl-2, Cadherin E, Caspase 3a, β-catenin, cathepsin D, CD44, EGFR, HER2, MDM2, MMP9, p21, PDGF, PTEN, progesterone receptor, Survivin, TGF, and VEGF, were not independent variables for recurrence. This study concluded that COX-2 and MIB-1 were independent prognostic factors for recurrence-free survival, and the expression of these markers could predict meningioma recurrence.[8]

Winther et al. included 160 patients, of whom 75.6% underwent gross total resection surgery (Simpson Grade I or II) and 24.4% underwent subtotal resection. The duration of follow-up to evaluate RFS was 0-96 months (median: 96 months). Markers were scored using proliferation indices (PI) based on the percentage of positive immunoreactive nuclei among 1000 tumor cell nuclei with the most significant proliferative activity (hot spots). All analyzed markers (MiB-1, topoisomerase IIα, and mitosin) were expressed at higher levels in atypical meningiomas than in benign meningiomas (p < 0.028). This study showed that topoisomerase IIα and mitosin PI were significant predictors of recurrent tumors (p < 0.039); however, MIB-1 PI was not a significant predictor. (p < 0.497). Among the two markers, mitosin expression was the most accurate discriminator between recurrent and nonrecurrent tumors. Topoisomerase IIα and mitosin expression were significant variables associated with RFS (p < 0.001). In another study, MIB-1 expression and histopathological grade were not associated with RFS (p < 0.127). The table shows that Topoisomerase IIα and mitosin expression were significantly higher in meningioma WHO Grade II than Grade I. Mitosin was the only factor that could significantly predict RFS in multivariate analysis (hazard ratio = 4.80, p < 0.001). In contrast, the association between topoisomerase IIα expression and RFS was not statistically significant (p = 0.052). The MIB-1 PI remained a non-significant factor (p < 0.158).[10]

DISCUSSION

Meningiomas are the most common intracranial primary tumors found in the central nervous system; around 36.4% of all CNS tumors generally appear as benign, slow-growing, and non-infiltrating lesions.[12] However, approximately 10% of the cases appear as histologically malignant lesions and/or are overgrown. Meningiomas originate from arachnoidal cap cells of the leptomeninges.[13] As classified by the World Health Organization (WHO), meningiomas are classified into three grades: benign (grade I), atypical (grade II), and anaplastic/malignant (grade III). Meningiomas that express a malignant phenotype are most susceptible to recurrence. Atypical meningiomas occur in about 4.7-7.2% of all cases and generally have recurrence rates ranging from 29-52% after resection. Anaplastic meningioma only occurs around 1.0-2.8% of all meningioma cases but has a recurrence rate of around 50-94% of cases.[14] The knowledge about immunohistochemistry is needed for patients' education about prognosis and recurrence of meningioma, especially higher grade meningioma. Immunohistochemistry results are also required for effective communication between pathologists and physicians to achieve a diagnosis of malignancy.[15]

Histological level and extent of resection are the two most important predictive factors for recurrence. In higher-grade tumors (i.e., grades II and III), there is an increase in cellularity and a higher level of mitotic and necrotic lesions, which can predict an increased

probability of recurrence, thereby generally resulting in unfavorable outcomes. Based on this, atypical meningiomas have recurrence-free survival, and the median time for recurrence is significantly longer than that for anaplastic meningiomas. Despite recurrence is not only the appearance that occurs in high-grade meningiomas because this can also occur in low-grade meningiomas, even with a lower frequency of occurrence.[16]

The recurrence rate of meningiomas depends on the extent of the resection. The recurrence rate after resection in various studies has shown varying results, ranging from approximately 15% to 25%. Simpson classified the extent of tumor resection into five grades. This resection-level classification system has shown that maximum meningioma treatment can be achieved by gross-total resection, including extensive resection of the attached dura and underlying bone.[17]

Previous research has shown a strong correlation between the risk of recurrence in meningiomas and their molecular profile. In a 2019 study by Ros-Sanjuan et al., atypical meningiomas were observed, and it was found that a high Ki-67 index or histological appearance was commonly present in cases of meningioma recurrence.[18] A study by Sumkovski et al. concluded that the mitotic index is an independent predictor of meningioma recurrence, and the anti-Ki-67 antibody was used to determine the mitotic index.[19] Ning Liu et al. conducted a systematic review, which provided evidence of Ki-67's role in meningioma recurrence.[20] This review found that the marker had a significant association with worse recurrence-free survival and overall survival. A systematic review also showed that Ki-67 was significantly associated with recurrence, except for one study in Norway, which concluded that Ki-67 was not significantly associated with recurrence. Despite this, Ki-67 has been proven in various extensive studies as an immunohistochemical marker that plays a role in recurrence. Ki-67 protein is expressed in cells undergoing mitosis and is detected in routine pathological diagnostics using an MIB-1 antibody clone. Therefore, Ki-67 protein is an excellent marker for detecting cell proliferation in a specific cell population.[16]

The research conducted by Winther et al. demonstrated that topoisomerase IIa is a more effective predictor of recurrence than Ki-67.[10] Their study is supported by numerous previous studies, including one conducted by Korshunov et al., which showed that both Ki-67 and topoisomerase IIa were significantly associated with recurrence. However, the multivariate analysis demonstrated that only topoisomerase IIa had a significant association with recurrence.[21] Other studies by Kunishio et al. showed that topoisomerase IIα was a better predictor of recurrence than Ki-67, but these studies concluded that the two markers had a significant association with recurrence-free survival.[22] Research conducted by Konstantinidou et al. showed that mitosin, a cell proliferation marker, was a significant predictor of early recurrence.[17] Nonetheless, only a few studies have examined the role of mitosin in predicting the prognosis of patients with meningiomas.

Another frequently examined immunohistochemical marker is p53. More than 50% of tumors have a p53 mutation; therefore, this marker is considered to be one of the most critical tumor suppressor proteins. However, the role of p53 in the occurrence of recurrence remains unclear, although it has been observed in various large-scale studies.[17] Cho et al. found that the immunoreactivity of p53 was significantly higher in recurrent meningiomas than in non-recurrent meningiomas.[3] Nevertheless, several studies have shown no significant association between p53 expression and recurrence in meningiomas.[23,24] Our systematic review and research conducted by Csonka et al. showed that p53 expression plays a significant role in meningioma recurrence. The p53 marker was significantly associated with tumor recurrence, regardless of the tumor histology level, and was also an independent predictor of the incidence of recurrence in WHO Grade I meningiomas.

Multivariate analysis by Sanz et al. demonstrated that cyclooxygenase-2/COX-2, along with MIB-1/Ki-67, served as a significant predictor of recurrence. COX-2 functions as a survival factor under various cellular stress conditions and protects cancer cells from apoptosis by regulating the expression of Bcl-2 family proteins. Furthermore, COX-2 inhibits anoikis or the process of cell death during detachment by activating the PI-3K/Akt pathway. This anti-anoikis effect of COX-2 may contribute to tumor development and progression.[25] Research conducted by Ruiz et al. confirmed that COX-2 levels were significantly higher in the recurrent meningioma group.[19] Additionally, Cello et al. noted that H3K27me3 loss was associated with worse prognoses for patients with meningiomas. H3K27me3 loss was significantly linked to higher-grade meningiomas, male gender, recurrent meningiomas, and the requirement for adjuvant radiation therapy. Therefore, H3K27me3 loss can serve as a robust prognostic marker.[11]

Despite our systematic approach to this review, several limitations should be mentioned regarding our findings and wider evidence-based studies. The final analysis did not include several non-English unpublished studies without sufficient data. Therefore, more well-defined and large-scale prospective studies are required to confirm our findings. Further meta-analysis is required

to obtain an association statistical analysis for a better conclusion.

CONCLUSION

The molecular characteristics of tumors are independent risk factors for recurrence of meningiomas, regardless of the histological grade and resection extent. Proliferative markers such as MIB-1/Ki-67, COX-2, p53, topoisomerase IIα, mitosin, and H3K27me3 were identified as independent variables and reliable predictors of meningioma recurrence. Further research is required to discover additional markers to enhance the understanding of meningioma characteristics for researchers and clinicians.

Data Availability Statement

The data supporting the findings of this review article are available from the cited primary literature sources. No new data were generated or analyzed for this study.

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DECLARATION

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There are no grants and funding sources in this research.

Conflict of Interest

The authors have no conflicts of interest to declare.

Registration Number of Clinical Trial

There is no clinical trial number because this study is not a clinical trial/experimental study.

Author Contributions

All the authors contributed to the conception and design of the study. RAA and DRS prepared the materials, DRS and SAHP review article, DRS, RM, SAHP, MRH, and FS collected the data, and RAA and FS performed the analysis. RAA, SAHP and FS drafted the manuscript. All authors have read and approved the manuscript.

Use of Artificial Intelligence

This study did not use artificial intelligence.

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