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Correlation of CD44 and MMP-14 expression with who tumor grade in meningioma

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Abstract

Meningioma is the most common primary brain tumor, classified by the WHO into Grade 1 (benign) to Grade 3 (malignant). The aggressive behavior of these tumors, including invasion, is linked to molecules involved in cell migration and extracellular matrix (ECM) degradation. CD44 (a cell adhesion receptor) and MMP-14 (a proteolytic enzyme) are hypothesized to play a synergistic role in driving tumor aggressiveness. This study aimed to analyze the individual and synergistic correlation between the expression of CD44 and MMP-14 and the histological grade of meningioma. This was an analytical observational, cross-sectional study involving 44 meningioma samples obtained from Dr. Soetomo General Academic Hospital. The expression of CD44 and MMP-14 was evaluated using immunohistochemistry (IHC). Correlations with meningioma grade were analyzed using the Spearman correlation test, and differences across grade groups were assessed using the Kruskal-Wallis test. The majority of samples were Grade 1 (54.5%), followed by Grade 2 (38.6%) and Grade 3 (6.8%). CD44 expression was significantly and positively correlated with meningioma grade ($p = 0.011$) and was significantly different across grade groups ($p = 0.040$). MMP-14 expression showed a descriptive trend of increasing with higher grades but was not statistically significant ($p = 0.080$). Crucially, a highly significant correlation was observed between CD44 and MMP-14 expression ($p = 0.000$). CD44 expression is significantly correlated with meningioma grade, suggesting its potential as a prognostic biomarker for aggressiveness. While MMP-14 expression lacked a statistically significant correlation with grade, the strong synergistic relationship observed between CD44 and MMP-14 indicates that their combined interaction is likely pivotal in tumor invasion mechanisms, warranting further investigation as a potential therapeutic target pair.

Keywords: Meningioma, CD44, MMP-14, WHO grade, Prognostic biomarker, Immunohistochemistry

Introduction

As the most common primary central nervous system tumor, meningioma contributes to roughly 37.6% of all cases. While most meningiomas are benign tumors arising from the meninges, their risk of recurrence and malignant transformation varies with histopathological grade. Under the WHO classification system, meningiomas are classified into Grade 1, Grade 2, and Grade 3, with higher grades linked to increased aggressiveness and recurrence potential [1]. In the United States, meningioma is recognized as the most prevalent primary brain tumor among adults, with an estimated annual incidence of 8.58 per 100,000 individuals [2]. Accounting for approximately 37.6% of primary neoplasms of the central nervous system, these tumors also make up more than 53.3% of benign CNS cases. The incidence of meningioma increases with age, with the average age at diagnosis reported to be approximately 66 years, and it is observed more often in women than in men. In contrast, high-grade meningiomas are more frequently encountered in pediatric populations and are linked to higher recurrence rates and poorer overall survival. In addition, benign and malignant meningiomas are more frequently observed in Black individuals compared to White individuals [3].

Early diagnosis and accurate assessment of tumor severity are important for determining optimal clinical management. Diagnosis is based on clinical history, physical examination, and radiological imaging. Many patients with meningioma remain asymptomatic and may undergo conservative management with periodic imaging follow-up. Symptomatic cases generally require surgical intervention to reduce recurrence risk and disease severity. Treatment planning varies according to tumor grade and clinical presentation [1].

Cluster of Differentiation 44 (CD44) is implicated in tumor invasion and metastatic potential. CD44 has been studied across multiple tumor types, including meningioma [4]. This transmembrane glycoprotein exists in various molecular isoforms and is involved in several physiological processes. Dysregulation of CD44 has been linked to tumorigenesis and cancer

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progression. CD44 functions as a cancer stem cell marker and contributes to epithelial–mesenchymal transition by regulating signaling pathways involved in proliferation, invasion, metastasis, and resistance to anticancer treatment [5]. In addition, CD44 binds to various extracellular matrix components, including hyaluronan, osteopontin, collagen, and matrix metalloproteinases, thereby further shaping malignant cell behavior [6], [7]. While multiple investigations have explored the association between CD44 expression and invasive characteristics in meningioma, the available evidence remains inconsistent and has yet to yield definitive conclusions [4].

Matrix Metalloproteinases (MMPs) have also been identified as therapeutic targets in various cancers [8]. In aggressive tumors, specific MMP family proteins are known to contribute to increased cell proliferation and invasion [9]. MMP-14, a membrane-type metalloproteinase, is upregulated in several malignancies, promoting angiogenesis, inflammation, cell proliferation, invasion, and metastasis [10]– [12]. MMP-14 regulates extracellular matrix degradation and remodeling, thereby facilitating cancer cell invasion and metastatic spread [11].

Limited data are available regarding the relationship between CD44 and MMP-14 expression in meningioma. Accordingly, this study aims to assess the variation and correlation of CD44 and MMP-14 expression across WHO Grade 1, Grade 2, and Grade 3 meningiomas. The findings are expected to contribute to their potential role as prognostic markers and support improved clinical management to reduce morbidity in patients with meningioma.

Materials and Methods: This observational analytic study employed a cross-sectional approach to assess the relationship between CD44 and MMP-14 expression across WHO meningioma grades. Archived meningioma specimens preserved as formalin-fixed, paraffin-embedded tissue blocks from the Anatomical Pathology Laboratory of Dr. Soetomo General Hospital, Surabaya, collected between January 2016 and December 2023, were examined. Samples were selected using purposive sampling based on inclusion criteria: confirmed meningioma diagnosis, adequate tissue for immunohistochemical staining, and determinable WHO grade; cases with concurrent tumor types were excluded. Immunohistochemistry was performed on 4–6 µm sections using monoclonal antibodies against CD44 and MMP-14. Staining results were evaluated according to predefined scoring criteria, and data were recorded systematically. Descriptive analysis was conducted to summarize clinicopathological characteristics. Statistical inference was carried out using SPSS software. Data distribution was first evaluated through normality testing, after which intergroup differences in marker expression across tumor grades were examined using Statistical comparisons were conducted using either one-way ANOVA or the Kruskal–Wallis test based on data characteristics, and results with a p-value below 0.05 were considered statistically significant. The association between CD44 and MMP-14 expression was subsequently assessed using Pearson or Spearman correlation analyses based on the distribution characteristics of the data.

Results: An observational analytic study with a cross-sectional framework was conducted on 44 meningioma tissue samples sourced from the Anatomical Pathology Laboratory of Dr. Soetomo General Hospital, Surabaya, spanning January 2016 to December 2023. All samples met the inclusion criteria of having sufficient tissue for immunohistochemical examination of CD44 and MMP-14 expression and were assigned an accurate WHO grade.

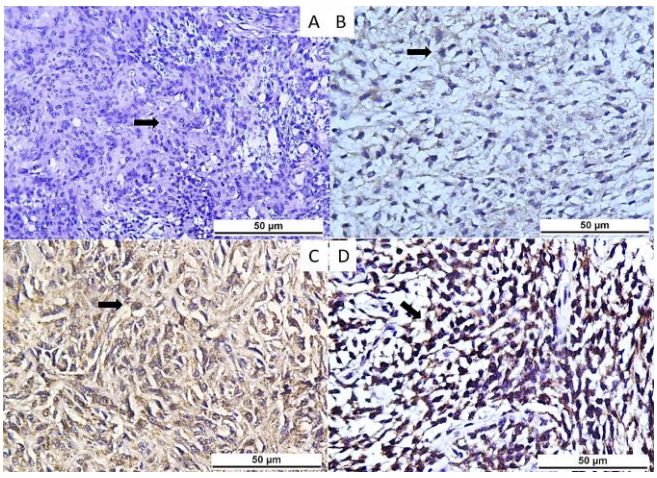

Figure 1. CD44 expression in meningioma tumor cells. Tumor cells show membranous staining. (A) no expression; (B) weakly positive; (C) moderately positive; (D) strongly positive. Magnification 400×.

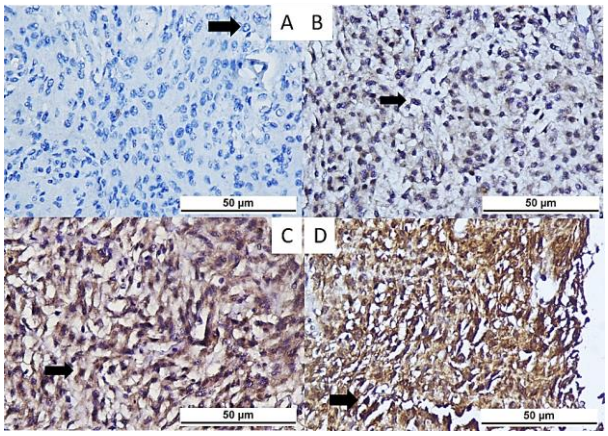

Figure 2. MMP-14 expression in meningioma tumor cells. Tumor cells show cytoplasmic staining. (A) no expression; (B) weakly positive; (C) moderately positive; (D) strongly positive. Magnification 400×

. **Table 1.** Characteristics of Study Subjects (n = 44)

Characteristics	Number (n)	Percentage (%)
Sex		
Male	4	9.1
Female	40	90.9
Age (years)		
- < 40	11	25.0
- 40–59	30	68.2
- ≥ 60	3	6.8
Meningioma Grade		
- Grade 1	24	54.5
- Grade 2	17	38.6
- Grade 3	3	6.8

The majority of subjects were female (40 cases, 90.9%), while 4 cases (9.1%) were male. The most common age group was 40–59 years (30 cases, 68.2%), followed by those under 40 years (11 cases, 25.0%) and those aged 60 years and older (3 cases, 6.8%). Based on WHO grading, 24 cases (54.5%) were classified as Grade 1, 17 cases (38.6%) as Grade 2, and 3 cases (6.8%) as Grade 3. All Grade 1 and Grade 3 cases were found in female patients, while Grade 2 cases consisted of 4 males and 13 females

CD44 expression was detected in all grades of meningioma (Grades 1, 2, and 3) and was localized to the cell membrane of tumor cells. Immunoreactivity was evaluated using the semi-quantitative Histochemical Scoring Assessment (H-score, range 0–300). Overall, moderate positive expression was the most frequent profile (42 samples, 95.5%). Specifically, Grade 1 samples predominantly demonstrated moderate positive expression (91.7%), Grade 2 samples predominantly showed weak positive expression (100%), and Grade 3 samples consistently showed moderate positive expression (100%). The Kruskal–Wallis test revealed significant differences in CD44 expression across the three meningioma grades ($p = 0.04$). Pairwise comparisons performed with the Mann–Whitney U test showed significant differences between Grade 1 versus Grade 2 ($p = 0.049$), Grade 2 versus Grade 3 ($p = 0.046$), and Grade 1 versus Grade 3 ($p = 0.018$), indicating an association between increasing CD44 expression and greater tumor malignancy.

Table 2. Comparison of CD44 and MMP-14 expression across meningioma grades using the Kruskal-Wallis Test

Interpretation	Grade 1	Grade 2	Grade 3	Total (n)	p-value
CD44 Expression					
Negative	1	0	0	1	
Weak Positive	1	0	0	1	0.04
Moderate Positive	22	17	3	42	
Strong Positive	0	0	0	0	
MMP-14 Expression					
Negative	0	1	0	1	
Weak Positive	2	0	0	2	
Moderate Positive	18	14	2	34	0.08
Strong Positive	4	2	1	7	
Total (n)	24	17	3	44	

MMP-14 expression was observed in all meningioma grades, with positive staining localized to the cytoplasm. Evaluation using the H-score showed that moderate positive expression was the most prevalent overall (34 samples, 77.3%). Moderate positive expression occurred in 75% of Grade 1 cases, 82.35%

of Grade 2 cases, and 66.67% of Grade 3 cases. Although the mean rank of MMP-14 expression tended to increase with tumor grade (Grade 1: 19.85; Grade 2: 24.09; Grade 3: 34.67), no significant variation among the three groups was observed based on the Kruskal–Wallis test ($p = 0.08$). Furthermore, pairwise analysis with the Mann–Whitney U test did not demonstrate any statistically significant differences, including the comparison between Grade 1 and Grade 2 ($p = 0.265$).

Spearman's correlation analysis revealed a statistically significant, moderately positive association between CD44 expression and meningioma grade ($\rho = 0.382$, $p = 0.011$), indicating that increased CD44 expression is linked to higher tumor malignancy. Conversely, although a positive trend was observed between MMP-14 expression and tumor grade, this relationship did not reach statistical significance ($\rho = 0.267$, $p = 0.080$). Additionally, Chi-square and Spearman's correlation analyses demonstrated a significant positive association between CD44 and MMP-14 expression ($p < 0.001$), suggesting co-expression of these markers in meningioma tissues.

Discussion

This study analyzed 44 meningioma samples, an aggressive form of primary brain neoplasm [13]. The demographic findings are largely consistent with global and local epidemiology, confirming a strong female predominance (90.9% vs. 9.1% male), aligning with reported global ratios of 2–3:1 and local data [14]–[16]. This gender disparity is primarily attributed to hormonal influence, as meningiomas, particularly lower-grade types, express progesterone and estrogen receptors [17]. The lower incidence in males is often associated with a higher tumor grade, poorer prognosis, and increased recurrence risk [17], [18]. The mean patient age was 46.0 years, with the highest incidence in the 4th and 5th decades (40–59 years), consistent with WHO reports placing the incidence peak in mid-to-late adulthood [14]. Notably, the observed incidence pattern in this Indonesian cohort appears earlier than some international reports, mirroring other local studies that found the peak incidence in the productive age group (35–54 years) [16], [17]. WHO grading showed Grade 1 (54.5%) as the most common, confirming the benign nature of most meningiomas [16]. However, the proportion of Grade 2 (38.6%) was relatively high compared to the literature, suggesting that atypical and anaplastic meningiomas (Grade 2–3) account for only 5–20% of cases, which may reflect a referral bias to this tertiary center, selecting for more aggressive or complex cases [14], [18].

The analysis demonstrated a significant positive correlation between CD44 expression and meningioma grade, supported by a significant difference across grades. This finding is consistent with the known biological role of CD44—a transmembrane glycoprotein—in tumor aggressiveness, facilitating adhesion, migration, and invasion [19], [20]. CD44 acts as a hyaluronan receptor, promoting tumor cell movement through the extracellular matrix (ECM) [13]. Previous studies support this finding, reporting that higher CD44 expression correlates with more aggressive meningiomas and higher recurrence risk, particularly noting its strong expression on the cell membrane in malignant meningiomas [4], [13], [20]. Our result affirms CD44 as a relevant biomarker for identifying the degree of malignancy and potentially predicting prognosis and recurrence risk in meningioma.

MMP-14 expression showed a tendency to increase with meningioma grade (Mean Rank: Grade 1 = 19.85; Grade 3 = 34.67), supporting its hypothesized role as a key proteolytic enzyme in ECM degradation and local invasion [13], [21]. However, the Spearman's correlation test was not statistically significant, and the Kruskal-Wallis test showed no significant difference across grades. This non-significant finding, while contrasting with its expected biological role in promoting invasiveness, aligns with literature suggesting that MMP-14 expression may reflect local invasion mechanisms (e.g., penetrating dura mater or bone) rather than solely the proliferative activity (mitosis, atypia) used to determine the WHO grade [22]. The lack of a significant correlation suggests that MMP-14 is not a single, sufficient determinant of meningioma aggressiveness, as its regulation may be influenced by other factors like Tissue Inhibitors of Metalloproteinases (TIMPs) or tumor heterogeneity.

Crucially, Chi-square analysis demonstrated a highly significant relationship between CD44 and MMP-14 expression. This supports the hypothesis that the two

biomarkers act synergistically to drive tumor invasion [22], [23]. Biologically, CD44 has been shown to anchor MMP-14 (MT1-MMP)—a crucial activator of other MMPs like MMP-2 and MMP-9—on the cell surface, creating a localized proteolytic machine. This strategic interaction enhances the cell's ability to degrade the basement membrane and invade surrounding tissues, a mechanism also observed in other cancers [21], [24].

The findings establish that CD44 expression is a stronger prognostic indicator associated with meningioma grade compared to MMP-14. High CD44 expression can therefore serve as a valuable biomarker for risk stratification, guiding pathologists and neurosurgeons in identifying patients with a higher risk of recurrence or progression and warranting more intensive follow-up [4]. Furthermore, the robust CD44–MMP-14 synergy provides a strong biological rationale for developing molecular inhibitor therapies targeting this specific interaction to potentially mitigate tumor invasion in more aggressive meningiomas [13], [20], [24].

This study is limited by its cross-sectional nature, which restricts causal inference, and by the relatively small and imbalanced sample size of Grade 3 meningiomas, potentially affecting the ability to detect statistically significant associations for MMP-14.

Conclusion

This study confirms the strong female predominance and middle-aged onset of meningioma, consistent with global epidemiology and hormonal influence. We found a significant positive correlation of moderate strength between CD44 expression and increasing meningioma WHO grade, establishing CD44 as a relevant biomarker for tumor aggressiveness and prognosis. While Matrix Metalloproteinase-14 (MMP-14) expression showed a descriptive trend toward increasing with grade (mean rank increase from Grade 1 to Grade 3), this relationship was not statistically significant ($p = 0.080$). Crucially, a highly significant relationship was demonstrated between CD44 and MMP-14 expression ($p = 0.000$), supporting the hypothesis that these two molecules interact synergistically on the cell membrane to facilitate local tumor invasion. In clinical practice, the strong prognostic value of CD44 expression can aid in the risk stratification of meningioma patients, while the synergistic interaction between CD44 and MMP-14 offers a potential molecular target for anti-invasive therapies.

Author contribution statement

All authors were involved in developing the study concept and design, and each author reviewed and gave approval to the final version of the manuscript.

Ethical declaration

This study received ethical clearance from the Research Ethics Committee of Dr. Soetomo General Academic Hospital on September 26, 2025, under approval number 3947/120/4/IX/2025.

Conflict of Interest

All authors declare that there are no conflicts of interest.

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