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Original Article

Differences in the Expression of CD44 and EMMPRIN in Various Spectra of Mucinous Ovarian Tumors

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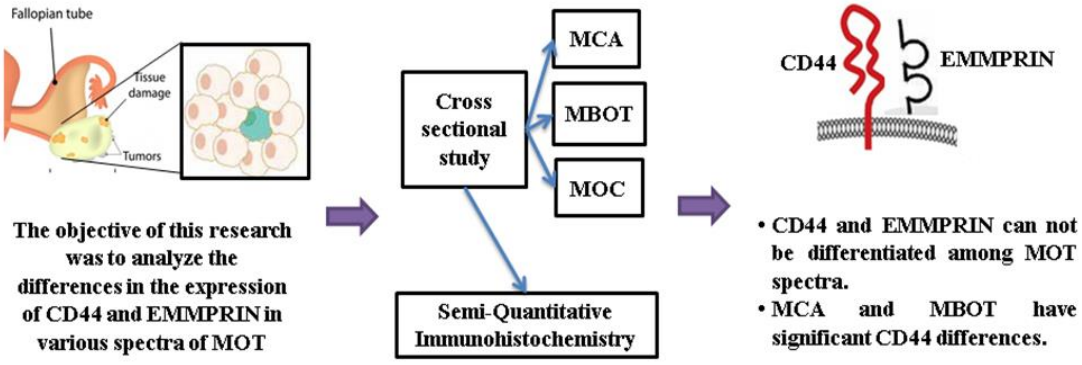
ABSTRACT

Mucinous ovarian carcinoma (MOC) accounts for only 4% of epithelial ovarian carcinoma, but the incidence rate in Indonesia is higher. Mucinous ovarian tumors (MOT) consist of mucinous cystadenoma (MCA), mucinous borderline tumor (MBOT), and MOC, but the diagnosis still needs further study. Carcinogenesis of ovarian cancer involves the regulation of proliferation and invasion. CD44 is a cancer stem cell (CSC) marker that mainly plays a role in tumor cell proliferation. A glycoprotein called EMMPRIN contributes to cancer biology, particularly the invasion process. The objective was to analyze the differences in the expression of CD44 and EMMPRIN in various spectra of MOT. A retrospective cross-sectional study was performed using 53 paraffin blocks from patients with MOT after approval by the Ethical Committee. The samples were divided into 3 groups, including mucinous cystadenoma (MCA), MBOT, and MOC grade 1. The expression of CD44 and EMMPRIN were evaluated using semi-quantitative immunohistochemistry method. There were differences in CD44 expression in various spectra of MOT (p=0.025), with significant differences in expression between MCA and MBOT (p=0.010), but there was no correlation (p = 0.432). There was no difference in EMMPRIN expression in various spectra of MOT (p=0.207), and there was no correlation (p=0.113). There was a positive correlation between CD44 expression and EMMPRIN expression in various spectra of MOT (p=0.0003) with weak strength (r = 0.478). This study concluded that there were significant differences in CD44 expression between MCA and MBOT.

GRAPHICAL ABSTRACT



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Introduction

Ovarian cancer was the eighth most frequent cancer diagnosis and cause of death for women in 2018 [1]. It was characterized by tumor heterogeneity, early metastases, and resistance to therapy [2-4]. Even after receiving multimodality therapy, the clinical result for most ovarian cancer patients remains poor since they are discovered at an advanced stage with intraperitoneal tumor progression and metastases [4, 5]. Mucinous ovarian carcinoma (MOC) accounts for only 4% of ovarian epithelial cancer (EOC), but its incidence in Indonesia, Singapore, and Korea is higher [6-9].

Multiple diagnostic difficulties can arise with mucinous ovarian tumors (MOT). There is a broad histological spectrum in these tumors, from benign cystadenoma, borderline to malignant carcinoma [10]. Differentiating between mucinous borderline tumor (MBOT) and mucinous cystadenoma (MCA) is sometimes difficult, especially if epithelial proliferation is found [11]. Distinguishing MBOT from MOC, especially well-differentiated, can be difficult, even for experienced pathologists, which can lead to misdiagnosis [12]. This misdiagnosis has an impact on patient survival [13].

The carcinogenesis and tumor progression involve the regulation of proliferation and invasion. Regulation of proliferation involves tumor suppressor genes, protooncogenes, and cancer stem cells (CSC) [14, 15]. One of CSC markers is CD44. It is a cell surface glycoprotein that regulates cellular reactions to the microenvironment and plays a role in various solid tumors, especially in tumor cell proliferation [16, 17]. The invasion regulation involves the epithelial-to-mesenchymal transition (EMT), tight junction disruption, degradation of the basement membrane, and angiogenesis [14]. One of EMT regulations involves EMMPRIN. EMMPRIN is cell surface glycoprotein with multiple roles in cancer biology, particularly promoting invasion by increasing MMP activity [18-20].

Thus, this study had hypotheses that there were differences in CD44 and EMMPRIN expression in various spectra of MOT, correlations between those proteins expression and various spectra of MOT, correlation between CD44 and EMMPRIN expression in different spectra of MOT. Studies analyzing CD44 and EMMPRIN expression in MOT have been limited to date. This study aim was to analyze differences in the expression of CD44 and EMMPRIN in various spectra of MOT.

Materials and Methods

Research designs

This study used a cross-sectional, retrospective, and analytical observational design. 53 paraffin blocks from surgical specimens of patients who had been diagnosed with MOT in the Anatomical Pathology Laboratory at Dr. Soetomo General Academic Hospital, Surabaya for the months of January 2018 through December 2021 were used as samples in this study. The Dr. Soetomo General Academic Hospital in Surabaya, Indonesia's Ethic Committee of Health Research had approved this study with No. 0596/KEPK/II/2023. The inclusion criteria were good quality paraffin blocks and sufficiently representative tumor cells for immunohistochemistry examination. The exclusion criteria were patients who had coexistent tumors in gastrointestinal tract or other organs.

Immunohistochemistry staining

The expression of CD44 and EMMPRIN was examined by immunohistochemistry method. Block paraffin samples were cut into 4 μm sections, xylol was used to deparaffinize the section three times, and followed by rehydrating with 96%, 90%, and 80% ethanol. Slides were warmed in the target retrieval solution (TRS)/buffer citrate at pH 6 in the microwave for 15 minutes, and then PBS was used to wash for 5

minutes after being immersed in the 3% hydrogen peroxide for 15 minutes. The tissue samples were then treated overnight with monoclonal antibodies for CD44 (DF1485) sc-7297 (dilution 1:200, Santa Cruz Biotechnology) and EMMPRIN (1.BB.218) sc-71038 (dilution 1:250, Santa Cruz Biotechnology). At room temperature, the secondary antibody was applied for ten minutes. The sections were counterstained with Meyer Hematoxylin. The final step was dehydration and 95% alcohol [21].

Evaluation of immunohistochemistry expression

Two researchers examined each sample in a blinded manner. Interobserver agreement was used to resolve any discrepancies. The percentage of stained tumor cells and the staining intensity of the stained tumor cells were used to evaluate the expression of CD44 and EMMPRIN. Both CD44 and EMMPRIN staining intensity was graded as 0 (absent), 1 (weak), 2 (moderate), and 3 (high).

The following criteria were used to evaluate CD44 expression: 0, no tumor cells, 1, 1-25%, 2, 26-50%, 3, 51-75%, and 4, >75%. The IRS score was then calculated by multiplying the staining intensity score by the proportion of stained cells; a score of 0 was regarded as negative, a score of 1-4 as weak, a score of 5-8 as moderate, and a score of 9–12 as strong [22]. The percentage of stained tumor cells was rated as follows for EMMPRIN evaluation: 0 for 0–10% positive cells; 1, 10%-24%; 2, 25%-49%; 3, 50%-74%; and 4, 75%. This was a little variation from CD44. The total EMMPRIN score was then calculated as the addition of the proportion of stained tumor cells score and the staining intensity score. Total scores between 0 and 1 were regarded as negatives, between 2 and 3 as weak, between 4 and 5 as moderate, and between 6 and 7 as strong [21, 23].

Statistical analysis

Differences between CD44/EMPPRIN expression and various spectra of MOT were analysed using the Kruskal-Wallis test. The Mann-Whitney test was used to evaluate differences in CD44/EMPPRIN expression between two groups of MOT (MCA-MBOT, MCA-MOC grade 1, and MBOT-MOC grade 1). The Spearman test, which has a significance level of 0.05 (p 0.05), was used to analyse the correlation.

Results and Discussion

The population consisted of 46 (38.98%) MCA, 17 (14.41%) MBOT, and 55 (46.61%) grade 1 MOC. The sample for the MBOT group was taken entirely from population of 17 samples (32.08%), while the MCA and MOC grade 1 groups were sampled, each with a total of 18 samples (33.96%).

Table 1: Characteristics of MOT patients

Characteristics	MCA N (%)	MBOT N (%)	MOC grade 1 N (%)
Populations	46 (38.98 %)	17 (32.08 %)	55 (46.61 %)
Samples	18 (33.96 %)	17 (32.08 %)	18 (33.96 %)
Age			
11-20 years	1 (1.89 %)	2 (3.77 %)	2 (3.77 %)
21-30 years	7 (13.21 %)	5 (9.43 %)	0 (0 %)
31-40 years	1 (1.89 %)	2 (3.77 %)	4 (7.55 %)
41-50 years	2 (3.77 %)	2 (3.77 %)	3 (5.66 %)
51-60 years	4 (7.55 %)	3 (5.66 %)	4 (7.55 %)
61-70 years	3 (5.66 %)	3 (5.66 %)	5 (9.43 %)
Tumor location/laterality			
Right ovary	7 (13.21 %)	9 (16.98 %)	11 (20.75 %)
Left ovary	11 (20.75 %)	8 (15.09 %)	7 (13,21 %)
Bilateral	0 (0 %)	0 (0 %)	0 (0 %)

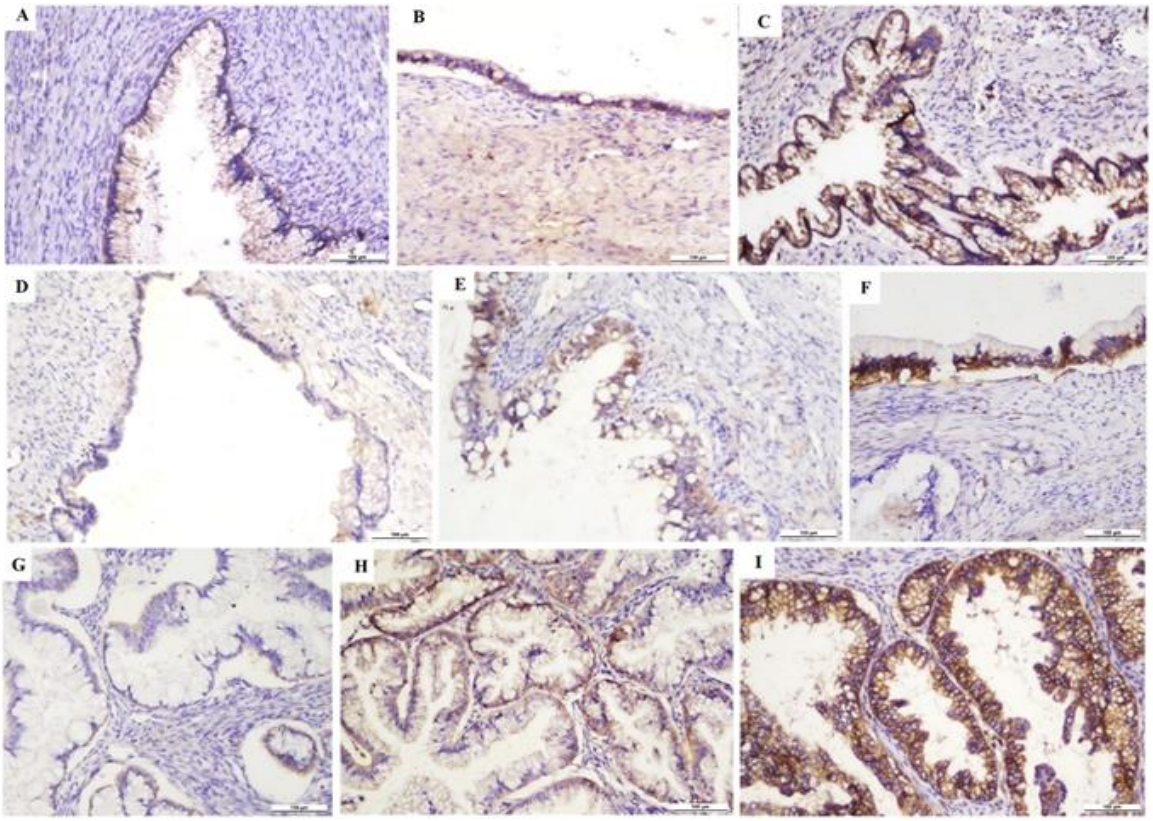

Figure 1: CD44 expression in MCA [weak (A. 200x), moderate (B. 200x), and strong (C. 200x) intensities]. MBOT [weak (D. 200x), moderate (E. 200x), and strong (F. 200x) intensities], and MOC grade 1 [weak (G. 200x), moderate (H. 200x), and strong (I. 200x) intensities]

Table 2: The result for differences in CD44 and EMMPRIN expression in various spectra of MOT using Kruskal-Wallis test

Expression	Interpretation	MCA (n=18)	MBOT (n=17)	MOC grade 1 (n=18)	Kruskal-Wallis (p)
IRS score of CD44	Negative	0 (0 %)	1 (5.88 %)	2 (11.11 %)	0.025
	Weak	6 (33.33 %)	8 (47.06 %)	2 (11.11 %)	
	Moderate	6 (33.33 %)	8 (47.06 %)	12 (66.67 %)	
	Strong	6 (33.33 %)	0 (0 %)	2 (11.11 %)	
Total score of EMMPRIN	Negative	0 (0 %)	0 (0 %)	0 (0 %)	0.207
	Weak	2 (11.11 %)	2 (11.76 %)	2 (11.11 %)	
	Moderate	13 (72.22 %)	12 (70.59 %)	9 (50 %)	
	Strong	3 (16.67 %)	3 (17.65 %)	7 (38.89 %)	

The age range of MOT patients was 15-70 years, with mean of 42.64 and median of 46. The age range of 21-30 had the highest percentage of MOT patients (22.64%), followed by 51 to 60 and 61 to 70 (20.75%). All samples (100%) had tumors located on one ovary only/unilateral (Table 1).

CD44 expression in various spectra of MOT

Tumor cells expressed CD44 in both their cytoplasm and membrane (Figure 1). According to the results of the Kruskal-Wallis test, various MOT spectra expressed CD44 differently (p=0.025) (Table 2 and Figure 2). However, according to the results of the Spearman correlation test, there was no association between the expression of CD44 and various MOT spectra (p=0.432) (Table 3). The results of the Mann-Whitney test showed differences in CD44 expression between MCA and MBOT (p=0.010), but there were no differences in CD44 expression between MCA and MOC grade 1

(p=0.392) or between MBOT and MOC grade 1 (p=0.052) (Table 4). CD44 expression levels were the highest in the MCA group, decreased in the MBOT group, and then increased again in the MOC grade 1 group.

A study by Matuura *et al.* on MOT showed differences in CD44 expression between MCA, MBOT, and MOC groups, in accordance with the results of this study. However, in contrast to the results of this study, strong CD44 expression was higher in MBOT than MCA, while strong CD44 expression was lower in MOC than MBOT, which indicates that CD44 expression is increased in the process of malignant transformation and decreased during the invasive process [24, 25]. High-grade serous, mucinous, and endometrioid tumors were linked to high CD44 expression (73%) in a study by Kar *et al.*, which indicated that high-grade ovarian cancers had a considerably higher CD44 positive rate [26]. A meta-analysis study by Shi and Jiang concluded that CD44 is not correlated with tumor grade, patient age, residual tumor size, or response to chemotherapy. CD44 expression is correlated with lymphatic tumor metastasis, TNM-stage tumors, and decreased overall survival in ovarian cancer patients [27]. In ovarian cancer, cell-surface CD44 expression is linked to CSC. The majority of research on CD44's significance in ovarian cancer development emphasizes the maintenance relationship between CD44 and CSC. The CSC group is a subpopulation of tumor cells with stem cell-like properties, high self-renewal, and low differentiation capacity. This allows CSC to develop into tumors and cause recurrences [16, 28].

EMMPRIN expression in various spectra of MOT

Tumor cells expressed EMMPRIN in both their cytoplasm and membrane (Figure 3).

The results of Kruskal-Wallis test showed that various MOT spectra did not differ in how EMMPRIN was expressed (p=0.207) (Table 2 and Figure 2), and Spearman correlation test showed that EMMPRIN expression did not correlate with various MOT spectra (p=0.113) (Table 3).

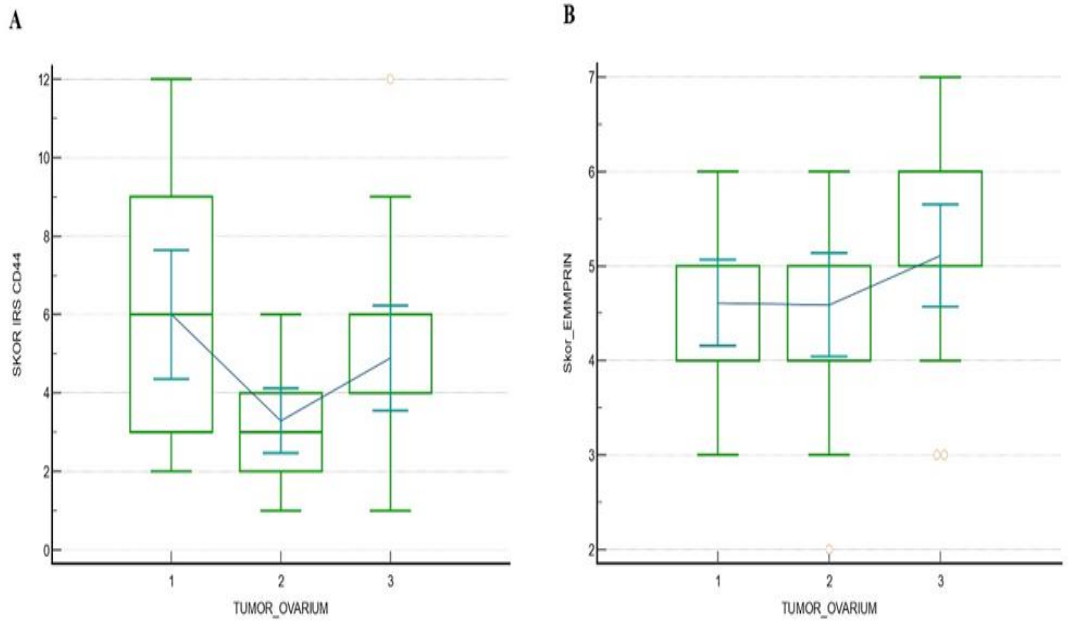

Figure 2: Distribution of CD44 expression values (A) and EMMPRIN expression values (B) in various spectra of MOT (1=MCA, 2=MBOT, 3=MOC *grade* 1)

Table 3: The differences expression of CD44 and EMMPRIN between two groups of MOT by Mann-Whitney test

Differences between the two groups of MOT	CD44 expression (p)	EMMPRIN expression (p)
MCA and MBOT	0.010	0.917
MCA and MOC grade 1	0.392	0.116
MBOT and MOC grade 1	0.052	0.142

Table 4: The results of Spearman correlation test

Correlation	r_s	p
Correlation between CD44 expression and various spectra of MOT (n=53)	-0.110	0.432
Correlation between EMMPRIN expression and various spectra of MOT (n=53)	0.220	0.113
Correlation between CD44 expression and EMMPRIN expression in various spectra of MOT (n=53)	0.478	0.0003

According to the Mann-Whitney test, EMMPRIN expression was not different between MCA and MBOT (p=0.917), between MCA and MOC grade 1 (p=0.116), or between MBOT and MOC grade 1 (p=0.142).

EMMPRIN expression levels were found to be the lowest levels in MCA group, slightly increased in MBOT group, and the highest levels in grade 1 MOC group (Table 4). A study by Alici *et al.* in MOT showed no significant difference in EMMPRIN expression in MCA, MBOT, or the MBOT group.

Strong EMMPRIN expression was found to be the highest in the MOC group, followed by the MBOT and MCA groups. These findings match those in this study [29]. According to a study by Jin *et al.*, EMMPRIN expression was significantly upregulated in serous carcinoma, MOC, endometrioid carcinoma, yolk sac tumor, dysgerminoma, granulosa cell tumor, and Brenner tumor compared to normal ovarian tissue free of tumor, where expression was either weak or absent. This shows that EMMPRIN, particularly in the early and late stages of carcinogenesis, plays a significant role in the clinical aggressiveness of ovarian cancers.

Intense EMMPRIN positivity in malignant ovarian tumors shows that EMMPRIN may play a function in promoting MMP production in stromal cells and promoting the metastatic spread to other organs [29, 30]. In contrast to normal ovaries and benign tumors, EMMPRIN expression was shown to be higher in borderline tumors and carcinomas in a study on epithelial ovarian carcinoma by Zhao *et al.* The degree of tumor differentiation and FIGO stage are strongly correlated with EMMPRIN expression [31].

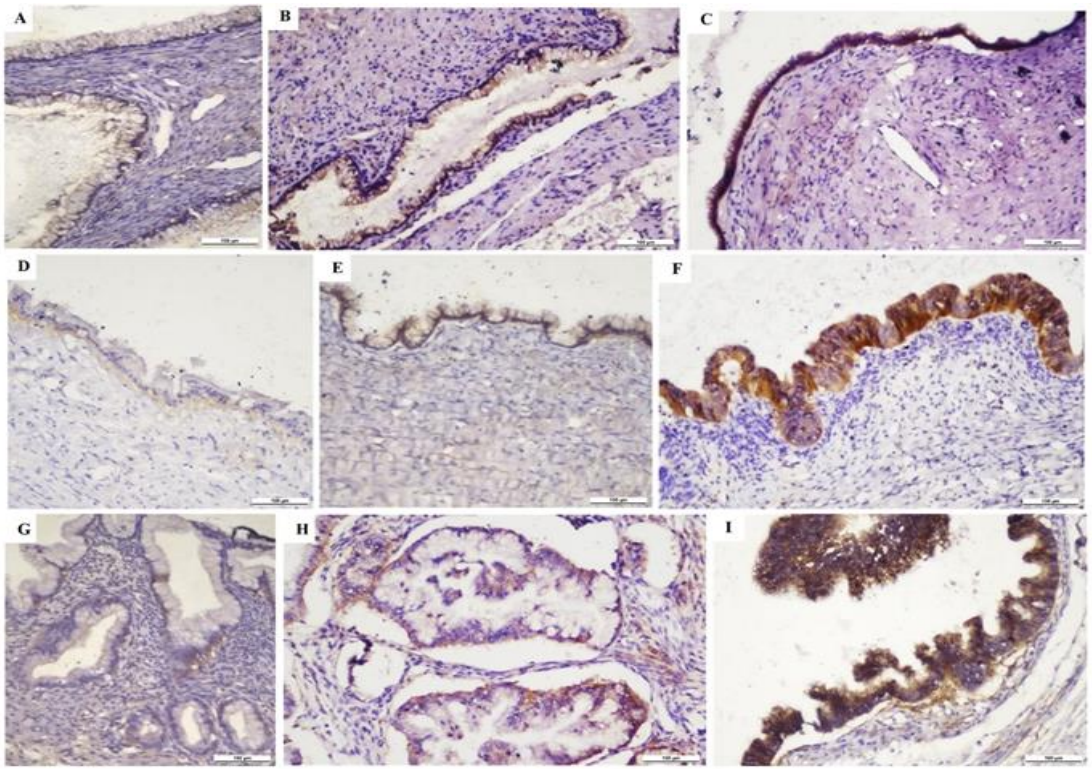

Figure 3: EMMPRIN expression in MCA [weak (A. 200x), moderate (B. 200x), and strong (C. 200x) intensities]. MBOT [weak (D. 200x), moderate (E. 200x), and strong (F. 200x) intensities], and MOC grade 1 [weak (G. 200x), moderate (H. 200x), and strong (I. 200x) intensities]

Correlation between CD44 and EMMPRIN expression

The results of the Spearman test revealed a significant weak positive correlation between the expression of CD44 and EMMPRIN (p=0.0003 and r=0.478) (Table 3). These findings demonstrated that the elevated expression of CD44 in various spectra of MOT was consistent with the elevated expression of EMMPRIN. There were no other studies that assessed the correlation between CD44 and EMMPRIN expression in ovarian tumors, but there was a study in another organ that assessed this correlation. In a study by Yang *et al.* in hypopharyngeal squamous cell carcinoma, there was a significant correlation between CD44 and EMMPRIN expression [32]. These results are similar to this study. EMMPRIN activates the EGFR-Ras-ERK pathway to cause invasion. This partially depends on EMMPRIN-induced increases in hyaluronan acid (HA) synthesis and the interaction with CD44. Increased expression of EMMPRIN causes the redistribution of EGFR, CD44, and EMMPRIN to form the lipid raft domain complex of EMMPRIN-EGFR-CD44 on the cell surface. EMMPRIN enhances HA synthesis and EGFR-Ras-ERK activation via HA-CD44 interaction, and Ras activity ultimately increases EMMPRIN expression, implying that EMMPRIN is integrated into the HA-CD44-EGFR-Ras signalling module via a positive feedback loop [20]. This shows that increasing EMMPRIN expression indirectly increases the CD44 expression. CD44 and EMMPRIN expression could not distinguish between MOT spectra, although CD44 expression could distinguish MCA and MBOT. Further research is needed to determine the molecular activation pathway related to differences in carcinogenesis in each group of MOT that affect the expression of CD44 and EMMPRIN. One study showed that not all MOC originates from MCA and MBOT but can occur de novo. This is related to KRAS and BRAF mutations. MCA with KRAS mutations may progress into MOC through MBOT, while MBOT with BRAF mutations generally may not progress into MOC. In addition, TP53 mutations affect the process of MOC carcinogenesis [33, 34]

Conclusion

There were differences in CD44 expression in various spectra of MOT, with significant differences between MCA and MBOT. However, there was no difference in EMMPRIN expression in various spectra of MOT. There was significant weak positive correlation between the expression of CD44 and EMMPRIN in various spectra of MOT. These findings suggest role of these proteins in MOT carcinogenesis, but still need further study involving the other related proteins.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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