

Could Moesin Be a New Marker for Indicating Progression in Endometrial Cancer?

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Aim: This study aims to determine an important parameter in progression from pre-invasive lesions of endometrium to endometrial cancer and also evaluate the effect of this parameter on the progression of endometrial cancer.

Material and Method: In our study, 30 patients with normal endometrial tissue (group 1), 56 patients who had endometrial hyperplasia without atypia (group 2), 36 patients who had endometrial hyperplasia with atypia (group 3), and 63 patients with endometrial cancer (group 4) were included. Age, parity, body-mass index, systemic diseases, and tumor markers of patients were evaluated. Expression levels of Ezrin, Radixin, and Moesin proteins were immunohistochemically evaluated in terms of frequency, intensity, and score value.

Results: When we compared hyperplasia cases with or without atypia; frequency, and score value of ezrin expression and frequency, intensity, and score value of moesin expression was significantly higher in patients who had hyperplasia with atypia ($p:0.000$ $p:0.001$ $p:0.003$, $p:0.032$ $p:0.035$ $p:0.015$ $p:0.005$, respectively). It was observed that the frequency and score value of moesin expression were significantly higher in patients with endometrial cancer when compared with patients who had hyperplasia with atypia ($p:0.003$ $p:0.045$). The frequency of moesin expression was significantly higher in patients who had postoperative mortality ($p:0.030$ $p:0.039$).

Conclusion: Increased frequency of moesin expression in the preoperative period in patients with atypical hyperplasia should alert the surgeon in terms of malignancy. If the frequency of moesin expression increases in cases with endometrial cancer, the patient should be followed closely in terms of progression in the postoperative period.

Keywords: hyperplasia, endometrial cancer, moesin, progression

Introduction

Endometrial cancer is the most common gynecological malignancy in high-income countries. It is the second most common after cervical cancer in low- and middle-income countries. The most common histological type of uterine cancer is endometrial adenocarcinoma.¹

Pre-invasive lesions (with or without atypia) are extremely important for the early diagnosis and treatment of endometrial cancer. Surgical and medical options are present in the treatment of these lesions.² Medical treatment (progesterone) is at the forefront, especially in the treatment of patients who had hyperplasia without atypia.³ However, surgery should be considered as the first option in the atypical hyperplasia because of the high risk for malignancy (8–29%) and frozen section examination should be made during surgery.⁴ But if we could determine the patient group, among patients who had atypical hyperplasia, without risk of malignancy at a ratio of 70–80% before surgery; we could be able to treat these patients with medical treatment. Also, frozen section examination might not be needed in these patients even if we made a surgical approach. We still need markers that can alert us for patients with a risk of malignancy in the preoperative period.

Ezrin, radixin, and moesin (ERM) protein family consist of three closely related proteins: ezrin, radixin, moesin. These proteins are responsible for the connection between plasma membrane proteins and the actin cytoskeleton. ERM proteins have three domains named as N-terminal domain (also named as FERM domain that interacts lipid with

membrane), an α -helical domain which is folded in the center, and C-terminal domain which connects F-actin.⁵ ERM proteins are concentrated in actin-rich surfaces such as microvilli, filopodia, and membrane ruffles. Active ERM proteins play a role in many processes such as taking shape of the microvillus, the possible regulation of canal organization, and adhesions. These proteins are important in cell shapes changes, cell attachments, and adhesions.⁶ ERMs have a supportive role in cortical activity during cytokinesis. It also provides insight into the selective mechanism that associates cytokinesis-related proteins preferentially with cleavage sites.⁷ Ezrin is synthesized in epithelial and mesothelial cells, and moesin is synthesized in endothelial cells.⁵ For this reason, we think that these markers are important for the early diagnosis of invasive cancers with malignant potential. In this study, we planned to immunohistochemically evaluate the expression of ezrin, moesin, and radixin (ERM protein family) in benign, hyperplastic, and malignant preparations to early diagnose endometrial cancer and prevent unnecessary surgical approaches.

There are various studies about ezrin and moesin in endometrial pathologies, but no study was conducted about the ERM family in the literature. Very few studies were found about ezrin and moesin in the literature and comprehensive studies are needed as clear evidence is not available. We planned this study to show whether certain markers correlated with hyperplastic and invasive lymph node positivity and survival for early diagnosis and progression of endometrial cancer which have many deficiencies in the literature and need to be investigated.

Materials and Methods

Patients, to whom probe curettage was applied due to abnormal uterine bleeding, postmenopausal bleeding, or endometrial thickness between January 2014 – December 2019 in Dicle University Faculty of Medicine, Gynecology and Obstetrics Clinic, were included in this study. Our study was approved by the Ethics Committee of Dicle University (Date:13.10.2021-Number:450). According to the Declaration of Helsinki, an informed consent form was obtained from all participants, stating that they agreed to participate in the study. In our study, 30 patients with normal endometrial tissue (group 1), 56 patients who had endometrial hyperplasia without atypia (group 2), 36 patients who had endometrial hyperplasia with atypia (group 3), and 63 patients with endometrial cancer (group 4) were included. All our patients with endometrial cancer were diagnosed with endometrioid adenocarcinoma. Age, gravida, weight, current systemic diseases, additional malignancies, and tumor markers were obtained from patient files. Patients with hereditary cancer syndromes, receiving exogenous estrogen treatment, and BMI (body mass index) higher than 35 were excluded. A total of 4 groups were constituted including normal, hyperplasia with and without atypia, and malignant groups. The expression of ezrin, radixin and moesin antibodies was evaluated with an immunohistochemical method. Then expression levels of ERM proteins were evaluated according to the stage, myometrial invasion, stage, lymph node positivity, mortality, and survival of patients diagnosed with endometrial cancer.

Immunohistochemical Staining

Four-micrometer sections were prepared from routinely processed paraffin blocks and mounted on positively charged slides. The sections were mounted on positively charged slides and were incubated at 57 °C for 60 minutes for the removal of paraffin. Immunohistochemical staining was performed with the automated BenchMark XT immunohistochemical system (Ventana, AZ, USA). Ezrin, radixin and moesin, were detected by using a monoclonal anti-moesinantibody (catalog no:m7060, Sigma-Aldrich Chemie GmbH, 82024 Taufkirchen, Germany), anti-ezrin antibody (catalog no:e8897, Sigma-Aldrich Chemie GmbH, 82024 Taufkirchen, Germany), and anti-radixin antibody (catalog no:r3653, Sigma-Aldrich Chemie GmbH, 82024 Taufkirchen, Germany).

Immunohistochemical staining was evaluated by a previous study of Bartova et al, Yu et al, and Ferrari et al^{8–10} The intensity and extent of staining were evaluated and scored for each sample. The distribution of ezrin, radixin, and moesin immunoreactivity was semi-quantitatively scored by using a 0–3 scale for the percentage of stained cells. A score of 0 represented that none of the cells were stained, 1+ was 1–9% of cells were stained, 2+ was 10–50% of cells were stained and 3+ was 51–100% of cells were stained. Immunohistochemical staining intensity was graded from 0 to 3, with 0 as none, 1 as weak, 2 as moderate and 3 as strong. The combined scores were calculated by multiplying the extent and intensity scores. Finally, the combined scores were graded as: negative = 0, weak = 1 or 2, moderate = 3 or 4 and strong = 5–9. Finally, the combined scores were grades as negative=0, weak=1 or 2, moderate=3 or 4, and strong=6 or 9.

All statistical analyses were performed with SPSS statistical package program (SPSS15 SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test for normality was used to test whether the data of our study are normally distributed. Mann Whitney *U*-test was used for the comparison of two independent groups with non-normal distribution. Kruskal–Wallis statistical method was used in the comparison of the 4 groups. Student's *t*-test was used in the presence of normal distribution. Chi-square test was used for categorical data. Linear regression analysis was used for demographic parameters with significant differences. Evaluation of the relationship between expression levels and demographic parameters was conducted with Spearman correlation analysis. Kaplan-Mayer statistical method was used to evaluate the change of expression levels according to survival. $P < 0.05$ was considered statistically significant. Morphometric measurements were made with a Trinocular Headed Image Research microscope, and after statistical analysis, they were viewed and illustrated under the same microscope.

Results

Totally, 30 patients with normal endometrial tissue (group 1), 56 patients who had endometrial hyperplasia without atypia (group 2), 36 patients who had endometrial hyperplasia with atypia (group 3), and 63 patients with endometrial cancer (group 4) were included in our study according to pathological report. Among patients with endometrial cancer; 22 patients who were limited to the endometrium, 25 patients with invasion of more than $\frac{1}{2}$ of the myometrium, 5 patients with invasion of the cervix, 9 patients with adnexal and parametrial involvement, and 2 patients with lymph node invasion were included. Among our patients with endometrial cancer; 47 were stage 1 (74.6%), 5 were stage 2 (7.9%), 10 were stage 3 (15.9%), 1 was stage 4 (1.6%), and 48 were grade 1 (76.2%), 8 were grade 2 (12.7%), 7 of them were grade 3 (11.1%). There were 27 patients (43.5%) taking radiation therapy and 14 patients (22.6%) taking chemotherapy. Two patients had lymph node invasion (3.2%). Mortality was seen in 7 (11.1%) patients. The average age of our patients was 52.4 ± 10.3 . A significant difference was found between groups in terms of average age. Hypertension was significantly higher in group 4 patients (Table 1). Linear regression analysis was performed against the possibility that age and hypertension factors can be a confounder for our results. In linear regression analysis, age ($p: 0.412$ $t: 0.822$) and hypertension ($p: 0.087$, $t: 1.723$) were not found to be effective parameters. Our average follow-up time was 49.0 ± 14.8 months.

Ezrin expression was evaluated immunohistochemically in normal (Figure 1A), without atypia (Figure 1B), with atypia (Figure 1C) and endometrial cancers (Figure 1D), radixin expression in normal (Figure 2A), without atypia (Figure 2B), with

Table 1 Comparison of Demographic Data Between Groups

		Group 1	Group 2	Group 3	Group 4	p
Age		45.4±4.7	48.0±8.7	53.1±10.0	57.0±9.9	0.000
Parity		3.2±1.5	2.1±0.7	2.2±0.7	2.2±0.8	0.057
BMI	25↓	10 (66.7%)	47(83.9%)	27(75%)	40(63.5%)	0.087
	25–30	3 (20%)	7(12.5%)	8(22.2%)	19(30.2%)	
	30↑	2(13.3%)	2(3.6%)	1(2.8%)	4(6.3%)	
Hypertension	Yes	2(13.3%)	9(16.1%)	12(33.3%)	24(38.1%)	0.026
	No	13(86.7%)	47(83.9%)	24(66.7%)	39(61.9%)	
Diabetes Mellitus	Yes	1 (6.7%)	4 (7.1%)	3(8.3%)	10(15.9%)	0.395
	No	14(93.3%)	52(92.9)	33(91.7%)	53(84.1%)	
Heart Disease	Yes	0	1(1.8%)	4(11.1%)	8 (12.7%)	0.078
	No	15	55(98.2%)	32(88.9%)	55(87.3%)	
CA 125		24.0±5.9	14.8±8.0	13.9±9.1	29.9±33.3	0.094

Notes: Kruskal–Wallis statistical method. $P < 0.05$ was considered to be statistically significant (in bold).

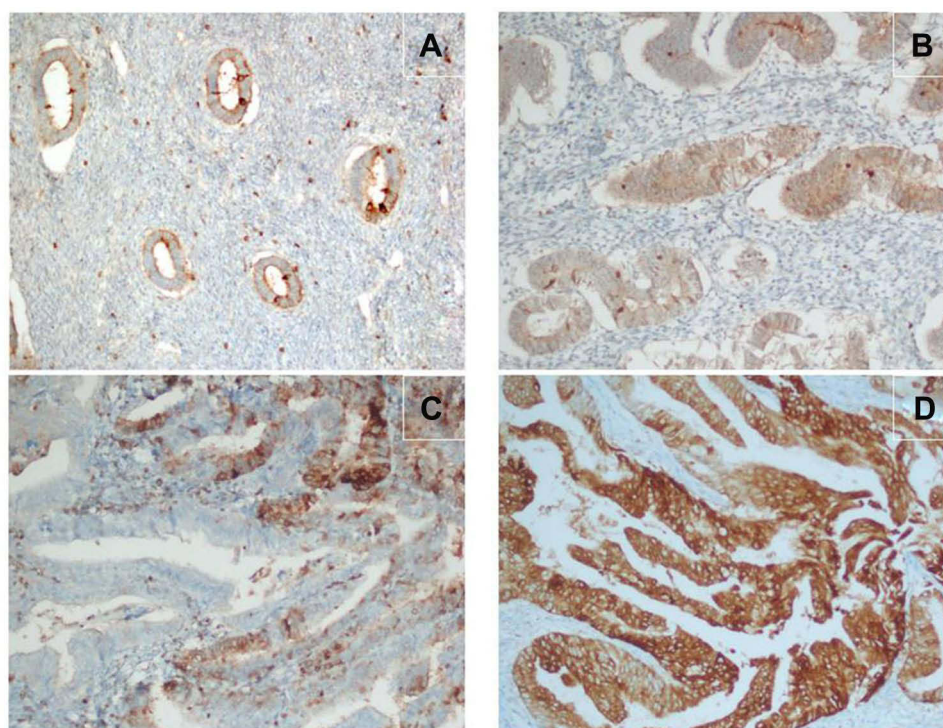


Figure 1 (A) Very mild ezrin expression in proliferative endometrial tissues. (B) Weak ezrin expression in cases of endometrial hyperplasia without atypia. (C) Moderate ezrin expression in patients with endometrial hyperplasia with atypia. (D) Severe ezrin expression in endometrial cancer cases.

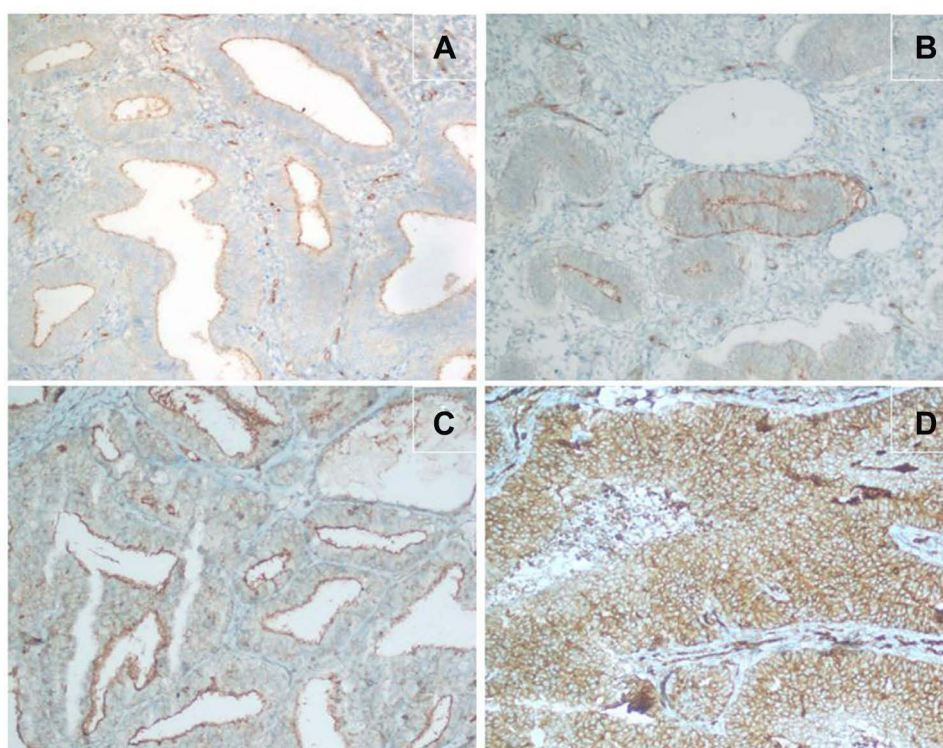


Figure 2 (A) Negative radixin expression in proliferative endometrial tissues. (B) Weak radixin expression in cases of endometrial hyperplasia without atypia. (C) Moderate radixin expression in cases of endometrial hyperplasia with atypia. (D) Severe radixin expression in endometrial cancer cases.

atypia (Figure 2C) and endometrial cancers (Figure 2D), and moesin expression levels in normal (Figure 3A), without atypia (Figure 3B), with atypia (Figure 3C) and endometrial cancers (Figure 3D). When we compared hyperplasia cases with or without atypia; frequency, and score value of ezrin expression and frequency, intensity, and score value of moesin expression was significantly higher in patients who had atypical hyperplasia ($p:0.000$ $p:0.001$ $p:0.003$, $p:0.032$ $p:0.035$ $p:0.015$ $p:0.005$, respectively). The frequency and score value of ezrin and radixin expression in patients with endometrial cancer were found significantly higher than patients who had hyperplasia without atypia ($p:0.000$ $p:0.000$ $p:0.019$ $p:0.004$). Additionally, frequency, intensity, and score value of moesin expression were found as significantly higher in patients with endometrial cancer ($p:0.000$ $p:0.001$ $p:0.000$). The frequency and score of moesin expression in patients with endometrial cancer were significantly higher than patients with atypical hyperplasia ($p:0.003$ and $p:0.045$, respectively) (Table 2). Relation of demographical data (age, parity, weight) and tumor markers with expression levels of ERM proteins were evaluated with correlation analysis. No correlation was found between expression levels and demographic data. A positive significant correlation was found between tumor markers, and frequency and score value of ezrin expression ($p:0.005$ $r:0.337^{**}$ $p:0.017$ $r:0.286^{*}$ $p:0.022$ $r:0.276^{*}$).

When we only evaluate patients with endometrial cancer, a significant difference was not found in expression levels of ERM proteins according to the grade and stage of patients with endometrial cancer. When stage 1 endometrial cancer patients with or without myometrial invasion of more than half were evaluated, a significant difference was not observed in terms of frequency, intensity, and score value of ezrin expression ($p:0.525$, $p:0.682$, $p:0.380$, $p:0.167$). A significant increase in frequency and score value of radixin expression was observed in patients who had more than half myometrial invasion when frequency, intensity, and score value were evaluated ($p:0.043$, $p:0.336$, $p:0.024$, $p:0.230$). Additionally, a significant increase in the frequency of moesin expression was observed when frequency, intensity, and score value of moesin expression were evaluated in patients who had more than half myometrial invasion ($p:0.031$, $p:0.408$, $p:0.055$, $p:0.056$) (Table 3). No significant difference was found between patients with or without lymph node invasion. No significant difference of expression levels of ERM proteins was found between patients who received and did not receive postoperative chemotherapy and radiation therapy. It was seen in patients with postoperative mortality that the frequency of moesin expression was significantly higher ($p:0.030$ $p:0.039$) (Table 4). When

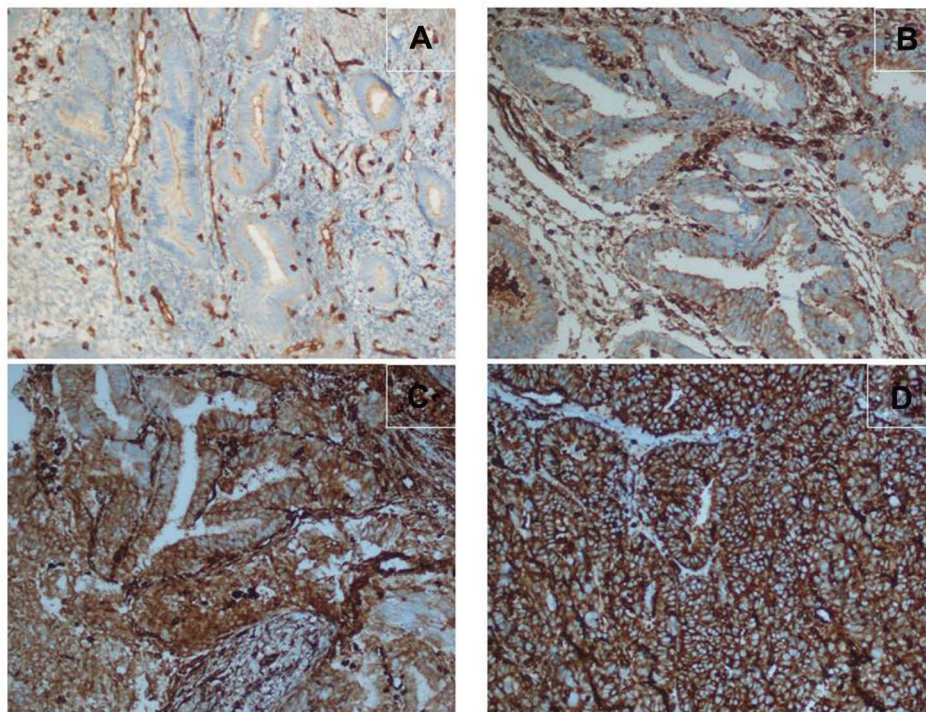


Figure 3 (A) Negative moesin expression in proliferative endometrial tissues. (B) Weak moesin expression in cases of endometrial hyperplasia without atypia. (C) Moderate moesin expression in cases of endometrial hyperplasia with atypia. (D) Severe moesin expression in endometrial cancer cases.

Table 2 Diffusiveness, Density and Score of ERM Proteins Between Groups

	Group 1	Group 2	Group 3	Group 4	p
Ezrin Diffusiveness	1.0±0.9	1.1±0.7	1.8±1.0	2.1±1.0	0.688 ^β 0.020[€] 0.002[¥] 0.000^{&} 0.000[♢] 0.210 ^α
Ezrin Density	1.0±0.9	1.6±1.1	1.8±0.9	2.0±0.9	0.100 ^β 0.028[€] 0.004[¥] 0.070 ^{&} 0.480 [♢] 0.303 ^α
Ezrin Score	1.7±1.7	2.2±1.7	3.9±2.5	4.9±3.0	0.389 ^β 0.014[€] 0.002[¥] 0.000^{&} 0.001[♢] 0.105 ^α
Radixin Diffusiveness	0.3±0.6	1.0±1.1	1.5±1.2	1.7±1.3	0.025^β 0.002[€] 0.004[¥] 0.019^{&} 0.063 [♢] 0.727 ^α
Radixin Density	0.2±0.4	0.7±0.7	0.9±0.8	1.3±1.2	0.017^β 0.003[€] 0.003[¥] 0.006 ^{&} 0.205 [♢] 0.145 ^α
Radixin Score	0.3±0.6	1.5±2.1	2.2±2.3	3.7±3.6	0.025^β 0.003[€] 0.003[¥] 0.004^{&} 0.065 [♢] 0.164 ^α
Moesin Diffusiveness	0.5±0.7	1.3±0.9	1.8±1.0	2.3±1.0	0.009^β 0.001[€] 0.000[¥] 0.000^{&} 0.032[♢] 0.003^α
Moesin Density	0.4±0.5	1.3±0.9	1.8±1.0	1.9±1.0	0.004^β 0.000[€] 0.000[¥] 0.001^{&} 0.035[♢] 0.433 ^α

(Continued)

Table 2 (Continued).

	Group 1	Group 2	Group 3	Group 4	p
Moesin Score	0.5±0.7	2.5±2.5	3.9±2.8	5.3±3.2	0.004^β 0.000^ε 0.000^κ 0.000^κ 0.015^δ 0.045^α

Notes: Group 1 versus Group 2:^β, Group 1 versus Group 3:^ε, Group 1 versus Group 4:^κ, Group 2 versus Group 4:^δ, Group 2 versus Group 3:^δ, Group 3 versus Group 4:^α. Normal endometrial tissue (group 1 (n:30)), Endometrial hyperplasia without atypia (group 2 (n:56)), Endometrial hyperplasia with atypia (group 3 (n:36)), Endometrial cancer (group 4 (n:63)). Data are presented as mean±standard deviation (min-max) and comparisons are made to Mann Whitney U-Test. P<0.05 was considered to be statistically significant (in bold).

the frequency of moesin expression was evaluated according to postoperative survival, no significant difference was observed (Figure 4).

Discussion

Our study was planned for early diagnosis in patients with endometrial hyperplasia and cancer, and a significant increase was observed in the frequency of moesin expression in patients with endometrial cancer. We especially think that increased frequency of moesin expression in patients with atypical hyperplasia in the preoperative period may be instructive for a surgeon in terms of being malignancy in the preoperative period. Increased frequency of moesin expression in the preoperative period in patients with atypical hyperplasia should alert the surgeon in terms of malignancy.

In a study, showing that ezrin overexpression is significantly correlated with poor survival, a positive correlation was observed between tumor metastasis and expression of ezrin in bone and soft tissue sarcomas. This suggests that ezrin may be a valuable prognostic biomarker and a potential therapeutic target.¹¹ In our study, Ezrin was not determined as a prognostic marker in endometrial cancers. But an extensive-expression was shown in atypical hyperplasia and endometrial cancer when compared to hyperplasia without atypia. Ezrin showed a positive correlation with CA125 in our study. The role of the CA 125 level in the evaluation of malignancy in endometrial cancer is uncertain, not verified, and has low value. The high level of CA125 can be used for following the treatment. It can be associated with metastatic disease.¹² We think that Ezrin can be used as an important prognostic marker in advanced endometrial cancer as it correlates especially with tumor markers. Our cases in this study were generally early stage, and one of our patients (1.6%) was stage 4 endometrial cancer. When evaluated according to myometrial infiltration in patients with endometrial cancer; several studies are present showing that the expression level of ERM/ETV5 gene and protein can be associated with myometrial infiltration.¹³ In our study, a significant increase of moesin expression was observed in patients with more than half myometrial invasion. We determined in our study that increased expression of moesin at tissues is associated with a poor prognosis.

Several studies in the literature claim that expression of Ezrin does not have a significant relation both with the stage and grade of endometrial cancer.¹⁴ In our study, similar to the literature, no significant difference was observed for ERM proteins in patients with endometrial cancer when evaluated according to stage and grade. We think this is related to the fact that most of our patients were early-stage and had a low grade.

In a study that evaluated the expression of moesin as a prognostic marker in patients with oral squamous cell carcinoma, it was found that the expression of moesin has a strong positive correlation with mortality and a significant negative correlation with survival.¹⁵ Similar to this study, a significant positive correlation was found between mortality and expression of moesin in our study. However, no relation was found between survival and the expression of moesin. The reason for this might be due to the presence of a mean postoperative follow-up period of 49.0±14.8 months in our study. More significant results can be achieved if the postoperative follow-up period is prolonged.

Table 3 Diffusiveness, Density and Score of ERM Proteins According to Myometrial Infiltration, Stage and Grade in Endometrial Cancers

	Myometrial Infiltration			Stage					Grade			
	Yes	No	p	Stage 1	Stage 2	Stage 3	Stage 4	p	Grade 1	Grade2	Grade3	p
Ezrin Diffusiveness	2.0±1.0	2.2±1.0	0.452	2.1±1.1	1.8±0.8	2.4±0.7	2.0±0.0	0.605	2.1±0.9	1.8±1.2	2.2±1.2	0.663
Ezrin Density	1.9±0.9	2.0±0.9	0.666	1.9±0.9	1.6±0.5	2.5±0.7	3.0±0.0	0.063	2.0±0.9	1.8±1.1	2.1±1.0	0.847
Ezrin Score	4.7±3.1	5.3±3.0	0.506	4.9±3.1	3.0±2.0	6.4±2.8	6.0±0.0	0.216	4.8±2.9	4.6±3.4	5.8±3.6	0.687
Radixin Diffusiveness	1.6±1.4	1.7±1.2	0.858	1.7±1.3	0.6±1.3	2.0±1.3	3.0±0.0	0.200	1.5±1.3	2.0±1.5	2.1±1.2	0.454
Radixin Density	1.2±1.2	1.6±1.1	0.214	1.4±1.1	0.6±1.3	1.6±1.2	3.0±0.0	0.199	1.3±1.2	1.3±1.2	1.8±1.2	0.518
Radixin Score	3.5±3.6	4.0±3.5	0.423	3.7±3.5	1.8±4.0	4.4±3.5	9.0±0.0	0.210	3.4±3.6	4.0±3.6	4.8±3.6	0.572
Moesin Diffusiveness	2.4±1.0	2.0±1.1	0.031	2.2±1.1	2.0±1.4	2.6±0.5	3.0±0.0	0.792	2.3±0.9	1.8±1.4	2.4±1.1	0.616
Moesin Density	2.0±1.0	1.8±1.0	0.408	1.8±1.0	1.6±1.1	2.4±0.7	3.0±0.0	0.288	2.0±1.0	1.5±1.2	2.1±1.2	0.449
Moesin Score	5.8±3.2	4.2±3.2	0.055	5.0±3.3	4.4±3.7	6.5±2.5	9.0±0.0	0.332	5.3±3.2	4.4±3.6	6.0±3.4	0.639

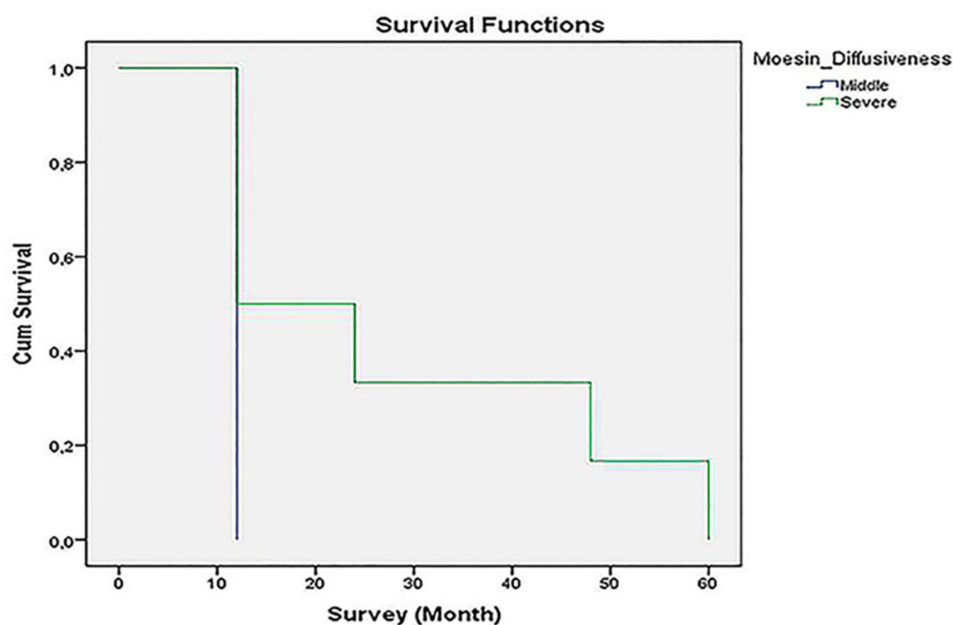
Notes: Chi-square test and Kruskal–Wallis statistical method. P<0.05 was considered to be statistically significant (in bold).

Table 4 Diffusiveness, Density and Score of ERM Proteins According to Lymph Node Invasion, Radiotherapy, Chemotherapy and Mortality in Endometrial Cancers

	Lymph Node Invasion			Radiotherapy			Chemotherapy			Mortality		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Ezrin Diffusiveness	2.5±0.7	2.1±1.0	0.704	2.1±0.8	2.0±1.1	0.963	2.0±1.0	2.1±1.0	0.518	2.1±1.1	1.7±1.0	0.213
Ezrin Density	3.0±0.0	1.9±0.9	0.078	2.1±0.8	1.9±1.0	0.488	2.1±1.0	1.9±0.9	0.402	1.7±0.9	1.8±1.0	0.787
Ezrin Score	7.5±2.1	4.8±3.0	0.228	5.1±2.9	4.9±3.1	0.844	5.0±3.2	5.0±3.0	0.906	4.5±3.3	3.7±2.7	0.521
Radixin Diffusiveness	1.5±2.1	1.7±1.3	0.849	1.7±1.4	1.6±1.3	0.747	1.7±1.4	1.7±1.3	0.993	2.0±1.3	1.4±1.2	0.212
Radixin Density	0.5±0.7	1.4±1.2	0.309	1.3±1.2	1.4±1.1	0.814	1.5±1.4	1.3±1.1	0.676	1.4±1.1	1.0±0.9	0.256
Radixin Score	1.5±2.1	3.7±3.6	0.420	3.9±3.6	3.6±3.5	0.948	4.4±4.0	3.5±3.4	0.654	3.7±3.1	2.5±3.0	0.201
Moesin Diffusiveness	3.0±0.0	2.3±1.0	0.309	2.5±0.8	2.1±1.1	0.127	2.5±0.8	2.2±1.1	0.576	2.5±1.0	1.8±1.0	0.030
Moesin Density	2.5±0.7	1.9±1.0	0.522	2.1±0.9	1.8±1.1	0.347	2.2±0.9	1.8±1.0	0.333	2.2±1.2	1.6±1.0	0.119
Moesin Score	7.5±2.1	5.2±3.3	0.353	5.9±3.0	4.7±3.3	0.136	6.0±2.9	5.0±3.3	0.275	6.3±3.5	3.8±3.0	0.039

Notes: Chi-square test statistical method. P<0.05 was considered to be statistically significant (in bold).

In a study, in which the relation between pancreas cancer and the expression of moesin was evaluated, a significant positive correlation of pathological stage and neural invasion with the expression of moesin was determined. It has been considered that moesin contributes to the progression of pancreas cancer by increasing the release of Matrix metallo-proteinase 7, TNF-6, and IL-6.¹⁶ In our study, like literature, the expression of moesin was significantly increased in stage 1 endometrioid adenocarcinomas, especially in patients with myometrial invasion. But in our study, no significant change in expression was observed with stage in endometrial cancer. However, most of our cases were early-stage cancer. As there was a significant correlation between mortality and frequency of moesin expression, this marker can contribute to the follow-up of progression.

**Figure 4** Relationship between moesin diffusiveness and survival.

In a study, which evaluate the expression of moesin in cases with Glioblastoma, the level of moesin was evaluated with PCR and Western blot methods. An increase in the expression of moesin was observed especially with cellular invasion and migration. Then it was determined that it increases invasion and proliferation by increasing the expression of β -catenin.¹⁷ In a study evaluating RNA expression in endometrial cancer progression, a positive correlation was found between estradiol, which plays an important role in prognosis, and up-regulation of SRA, H19, and HOTAIR, and lncRNA expression levels. It has been observed that lncRNAs are increased in advanced endometrial cancers.¹⁸ In another study, it was stated that nc886 is an important oncogene in endometrial cancer progression and that by suppressing this oncogene, increasing caspase 3 and decreasing VEGF and NF- κ B may provide benefit in the follow-up and treatment of endometrial cancer.¹⁹ To the best of our knowledge, this is the first study that evaluates ERM proteins in pre-invasive and malignant endometrial lesions. In literature, augmentation of these proteins with especially invasion and proliferation alert obstetricians for cases with endometrial cancer that spread through invasion. Determination of increased moesin expression as a poor prognostic factor has shown us that more extensive studies are needed on this subject.

Studies about moesin with patients who have a malignancy in the literature showed that moesin is an independent prognostic marker in patients with estrogen receptor (ER)-positive breast cancer.⁹ In another study conducted in patients with breast cancer, it was stated that the loss of miR-200c as a result of mutation of the P53 tumor suppressor gene provides upregulation of moesin and thus increases carcinogenesis.²⁰ Similarly, our study drew attention to moesin as the frequency of moesin expression significantly increases in patients with endometrial cancer, especially in more progressive cases with myometrium invasion and the presence of mortality. This made us think that this marker can be an important marker in neoplastic progression. Absence of expression in benign cases, a significant increase of expression in atypical hyperplasia cases compared to hyperplasia without atypia, and a significant increase in endometrial cancer when compared with atypical hyperplasia are important. This circumstance, which has not been detected in the literature before, shows that our study is the first study in the literature to our knowledge.

In another study, in which the expression of moesin was evaluated in patients with breast cancer, a significant relation was determined between metastasis and moesin expression.²¹ In studies evaluating malignant cases and the expression of moesin, moesin drew attention as an important prognostic marker. However, studies about the relation between endometrial cancer and the expression of moesin are very limited in the literature. To our knowledge, this is the first study on this subject, and the low number of cases and short follow-up period are our limitations. Therefore, more comprehensive studies are needed.

In conclusion; increased frequency of moesin expression in the pathological evaluation of preinvasive and invasive lesions should alert the surgeon in terms of being a poor prognostic factor. However, more comprehensive studies with longer follow-up periods are needed.

Disclosure

The authors report no conflicts of interest in this work.

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