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Evaluation of Immunohistochemical Expression of Matrix Metallo-Proteinase14 (MMP14) in Endometrial Carcinoma Type I: Relation with β1- Integrin & Yes-Associated Protein 1(YAP1)

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ABSTRACT

Background: Endometrial carcinoma (EC) is a common gynecological malignancy, yet the mechanisms that lead to tumor development and progression are still not fully known.

Objectives: We aimed to evaluate immunohistochemical (IHC) expression of MMP14, β1 integrin and YAP1 in EC type I and its relation to clinic-pathological parameters.

Subjects and Methods: IHC expression of MMP14, β1-integrin & YAP1 in 52 cases of EC type I (endometrioid type) were studied. The association of these markers with each other as well as with clinic-pathological parameters were evaluated. **Results:** Positive membranous and cytoplasmic IHC expression of MMP14 was detected in 36 (69.2%) of studied EC cases. Comparison of MMP14 IHC expression with the clinic-pathological data revealed higher expression of MMP 14 in high grades EC (II & III) and higher stages (II& III), compared to lower grades and stages but did not reach significant difference (P=0.077, P=0.925 respectively). No significant statistical difference with other variables (P>0.05 for all) were detected. Cytoplasmic localization of β1 integrin was detected in 33 (63.5%) of studied EC cases. Significant statistical difference with grade, depth of invasion (p<0.001 for both), LVI (P=0.001) and LNs metastasis (P=008) were detected. No significant statistical difference with other variables (P>0.05 for all). Nuclear IHC expression of YAP1 was detected in 34(65.4%) of studied EC cases. There was significant statistical difference with grade & depth of invasion (p=0.001 for both), mean tumor size (P=0.033), LVI (p<0.001), LN metastasis (P<0.001) and TNM stage (P=0.007).

Conclusion: MMP14, β1-integrin and YAP1 were upregulated in EC and associated with malignant potential. This pattern of expression may represent promising markers for tumor development and progression and may be used as therapeutic targets.

Keywords: Endometrial carcinoma, Immunohistochemistry, MMP14, β1-integrin, YAP 1.

INTRODUCTION

Endometrial cancer (EC) worldwide represents the seventh common malignancy among females. Developed countries have increased incidence of EC [(1)]. In United States, EC is the commonest gynecologic cancer, and the fourth most frequently diagnosed cancer in female (coming after breast, lung and colorectal cancers) [(2)].

In Egypt, it comes in the 14th rank among all cancers representing 1.5%. At NCI it is the third most common gynecological cancer after ovary and cervix [(1,3)]. EC is divided into two entities: type 1 cancer (80%), which occur in young and obese patients, is associated with excess estrogen, a favorable prognosis, and endometrioid histology, and is often accompanied by and/or following endometrial hyperplasia (EH). Type 2 cancers (10-20%), which represent tumors that arise in older and non-obese patients, are related to poor prognosis and non-endometrioid histotypes, and are typically of serous histology, without associated hyperplastic lesions [(4)].

The development and progression of EC are related to its secretion of a variety of matrix metalloproteinases (MMPs) involving the degradation of extracellular matrix (ECM) components [(5,6)].

MMP-14, one of the members of thin-film MMP, not only reduces a variety of ECM components but also, activates matrix metalloproteinase-2 (MMP-2). In addition, MMP14 plays an important role in the development and invasion of cancers such as breast cancer, colorectal cancer, pancreatic cancer, and oral squamous cell carcinoma [(7)].

Many studies revealed that there is a relation between MMP14 and β1-integrin. MMP14 accumulates at the bud tip of the invasive mammary gland, so activate β1-integrin to promote cell invasion to regulate the invasion to interstitial tissue [(8)]. YAP1 is a main effector downstream of the Hippo signaling pathway, which activated during the development of many solid tumors. Also it is a driving factor to increase the proliferation and invasion of tumor cells[(9)].

The regulation of this pathway occurred by phosphorylation and subcellular localization of YAP1. Activation of the Hippo signaling pathway induces phosphorylation of YAP1, which prevents translocation to the nucleus. When this pathway is inactivated, dephosphorylated YAP1 translocate to the nucleus and interacts with transcription factors, resulting in cell proliferation in many organs [(10)].

Many studies have shown that upregulation of YAP1 can induce epithelial–mesenchymal transformation (EMT), inhibit apoptosis and promote the production of tumor stem cells [(11-12)]. These concepts inform possible strategies for effectively inhibiting YAP1 activity in cancer patients, such as conventional chemotherapy, radiotherapy or immunotherapy. However, there are a few studies on the expression of YAP1 in EC and its correlation with MMP and β1-integrin.

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AIM OF THE STUDY

This study aims to evaluate the IHC expression of MMP14, β1-integrin and YAP1, in EC cases, as well as their correlation to clinic-pathological parameters.

SUBJECTS AND METHODS

This retrospective study included formalin fixed blocks of 52 cases diagnosed as EC type I (endometrioid type) in the form of hysterectomy specimens. Blocks were collected from archives of Pathology Department and Early Cancer Detection Unit, Faculty of Medicine, Benha University, Egypt from January 2015 to January 2021. Patients' relevant demographic and pathological data were retrieved.

Ethical approval:

Being a retrospective study, a written informed consent was not needed from the patients. The study was approved by the Research Ethics Committees of Faculty of Medicine, Benha University, Egypt (RC: 6-11-2022).

Hematoxyline and eosin-stained slides of all cases were reviewed for confirmation of the original diagnosis independently by 2 pathologists. Cases were graded according to FIGO grading system. Staging according to TNM classification of the American Joint Committee on International Union against Cancer AJCC [(13)] was applied for each case.

Immunohistochemical study:

For IHC staining of MMP-14, β1-integrin and YAP1, 4-mm sections were cut from paraffin blocks and placed on positive charged slides. Antigen retrieval by citrate buffer (pH6) was performed. The primary antibodies used were MMP14 antibody (rabbit polyclonal, NBP1-77276; Novus Biologicals, Littleton, CO 80120, USA) at a dilution of 1:100, β1 integrin antibody (mouse monoclonal,NBP1-47440; Novus Biological , Littleton, Colorado, USA) at a dilution of 1:200, and YAP1 antibody (rabbit polyclonal, NBP2-62669; Novus Biological, Littleton, Colorado, USA) at a dilution of 1:200,overnight at room temperature. The color development was performed using 3,3′-Diaminobenzidine tetrahydrochloride (DAB) as chromogen. Negative (cold phosphate-buffered saline) and positive controls (Heart tissue for MMP14, Melanoma for β1 integrin and colonic carcinoma for YAP 1) were enclosed in each run.

Interpretation of results:

MMP-14, IHC expression was membranous and cytoplasmic. The intensity and extent of staining was multiplied yielding a scoring on a scale from 0 to 9. Sections with score equal to 0 were considered negative, those with less than or equal to 4 were weakly positive, and those with greater than 4 were strongly positive. Results were also further simplified as positive and negative for statistical purpose [(13)].

IHC expression of β1-integrin antibody was cytoplasmic, while, YAP1 antibody was nuclear. Both were scored according to (14), a score that ranged from 0 to 9.A score ranged from (0-3) is negative, while a score (4-9) is positive, using Olympus Light Microscope (Tokyo, Japan).

Statistical analysis

Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation (SD). Chi square test (χ^2), or Fisher's exact test were used to analyze categorical variables. Quantitative data were tested for normality using Shapiro-Wilks test, assuming normality at P>0.05, using Student "t" test if normally distributed, or Man-Whitney U test and Kruskal-Wallis test if not normally distributed for analyzing the difference. Pearson's correlation test was used for correlation. Differences were considered significant at a calculated P value of <0.05. Statistical analysis was performed using SPSS version 20 (SPSS Inc, Chicago, IL, USA).

RESULTS

Demographicand histopathological results:

The current study included 52 cases of EC type 1 (endometrioid type). Thirty five cases were below the age of 60 (67.3%). All clinico-pathological data are listed in **table 1.**

Table (1): Clinico-pathological findings of all EC patients

Clinico-pathological data	No	%
Age group		
<60	35	67.3
≥60	17	32.7
Mean tumor size	25	48.1
<3.6	27	51.9
≥3.6		
Depth of invasion		
No invasion	2	3.8
<50%	27	51.9
≥50%	23	44.2
Grade:		
G1	11	21.2
G2	26	50.0
G3	15	28.8
LVI:		
Positive	18	34.6
Negative	34	65.4
LNS metastasis:		
Positive	13	25.0
Negative	39	75.0
TNM Stage		
I	26	50.0
II	11	21.2
III	15	28.8

LVI, Lympho-vascular invasion; LNS, Lymph nodes

Immunohistochemical Results:

A- MMP14 IHC expression:

Positive membranous and cytoplasmic IHC expression of MMP14 was detected in 36 (69.2%) of studied EC cases.

Comparison of MMP14 IHC expression with the clinic-pathological data revealed higher expression of MMP 14 in high tumor grades (grade II & III) and higher stages (stage II& III), compared to lower tumor grades and stages but did not reach statistical significant difference (P=0.077, P=0.925 respectively).

No significant statistical difference with other variables including, age of the patient, mean tumor size, LVI or lymph node metastasis (P>0.05 for all) were detected. **Table- 2&Fig 1**.

B- β1-integrin IHC expression:

IHC expression of β1-integrin was localized in the cytoplasm of 33(63.5%) of studied EC cases. Significant statistical difference with grade, depth of invasion (p<0.001 for both), LVI (P=0.001) and LNs metastasis (P=008) were detected. No significant statistical difference with age, mean tumor size or TNM stage (P>0.05 for all). **Table-2& fig 2**.

C-YAP1IHC expression:

Positive nuclear IHC expression of YAP1 was detected in 34(65.4%) of studied EC cases. There is a significant statistical difference with grade & depth of invasion (P=0.001 for both), mean tumor size (P=0.033), LVI (p<0.001), LN metastasis (P<0.001) and TNM stage (P=0.007).While no significant statistical difference with age group (P = 0.189). **Table 2 & Fig 3.**

Table (2): Comparison between MMP14, β1 integrin& YAP1 and cilinico-pathological variables:

Variables	MMP-14		P value	β1 integrin		P value	YAP1		P value
	Positive 36	Negative 16		Positive 33	Negative 19		Negative 18	Positive 34	
Age group <60 ≥60	69.4%)(25 11(30.6%)	10(62.5%) 6(37.5%)	0.622	24(72.7) 9 (27.3)	11(57.9%) 8 (42.1%)	0.272	10(55.6%) 8(44.4%)	25(73.5%) 9(26.5%)	0.189
Mean tumor size <3.6 ≥3.6	16(44.4%) 20(55.6%)	9(44.4%) 7(55.6%)	0.432	19(57.6) 14(42.4)	6 (31.6%) 13 (68.4%)	0.07	5(27.8 %) 13(72.2%)	20(58.8%) 14(41.2%)	0.033*
Depth of invasion No invasion <50% ≥50%	2(5.6%) 19(52.8%) 15(41.7%)	0 8(50%) 8(50%)	0.889	2(6.1%) 23(69.7%) 8 (24.2%)	0 4(21.1%) 15 (79.9%)	<0.001 **	0 4 (22.2%) 14 (77.8%)	2(5.9%) 23(67.6%) 9(26. %5)	0.001**
Grade G1 G2 G3	9(25%) 20(55.6%) 7(19.4%)	2(12.5%) 6(37.5% (8(50%)	0.077	10(30.3) 22 (66.7%) 1 (3 %)	1(5.3%) 4(21.1%) 14(73.7%)	<0.001 **	1(5.6%) 6 (33.3%) 11(61.1%)	10 (29.4%) 20 (58.8%) 4 (11.8%)	0.001**
LVI Positive Negative	12(33.3%) 24(66.7%)	6(37.5%) 10(62.5%)	0.771	6(18.2%) 27(81.8%)	12(63.2%) 7(36.8%)	0.001**	11 (61.1%) 7 (38.9%)	7(20.6%) 27(79.4%)	0.003**
LNS metastasis Positive Negative	9 (25%) 27 (75%)	4 (36%) 12 (64%)	1.0	4(12.1%) 29(87.9%)	9(47.4%) 10(52.6%)	0.008* *	10(55.6%) 8 (44.4%)	3 (8.8%) 31(91.2%)	<0.001**
TNM Stage I II III	7(47.2%) 8(22.2%) 11(30.6%)	9(56.2%) 3(18.8%) 4(25%)	0.925	20(60.6%) 7(21.2%) 6(18.2%)	6(31.6%) (21.1%)4 9 (47.4%)	0.061	5(27.8%) 3(16.7%) 10(55.6%)	21(61.8%) 8(23. %5) 5 (14.7%)	0.007**

MMP-14, Matrix Metallo-Proteinase14; YAP1, Yes Associated Protein 1; LVI, Lympho-vascular invasion; LNS, Lymph nodes; **highly significant**.**

D-The relation between MMP 14, β1-integrin and YAP1 in EC:

In 52 cases of EC, Pearson's correlation analysis was performed to identify the relationship among MMP 14, β1-integrin and YAP1. The results showed that the expression of YAP1, show positive correlation with MMP14 (<0.05) and β1-integrin (p<0.01). Also, the expression of MMP 14 was positively correlated with β1-integrin (p<0.01). **Table 3.**

Table (3): Correlation between MMP-14, β1-integrin and YAP1 in EC cases.

Other markers		MMP 14		P-VALUE	β1-integrin		P- VALUE
		Positive 36	Negative 16		Positive 33	Negative 19	**<0.01****
β1-integrin	Positive 33	**28 (84.8%)**	**5 (15.2%)**	**<0.01****			
	Negative19	**8 (42.1%)**	**11 (57.9%)**				
YAP1	**Negative 18**	**9 (50%)**	**9 (50%)**	**<0.05***	**3(16.7%)**	**15(83.3%)**	
	Positive 34	**27 (79.4%)**	**7 (20.6%)**		**30(88.2%)**	**4(11.8%)**	

MMP-14, Matrix Metallo-Proteinase14; YAP1, Yes Associated Protein 1; **, highly significant.

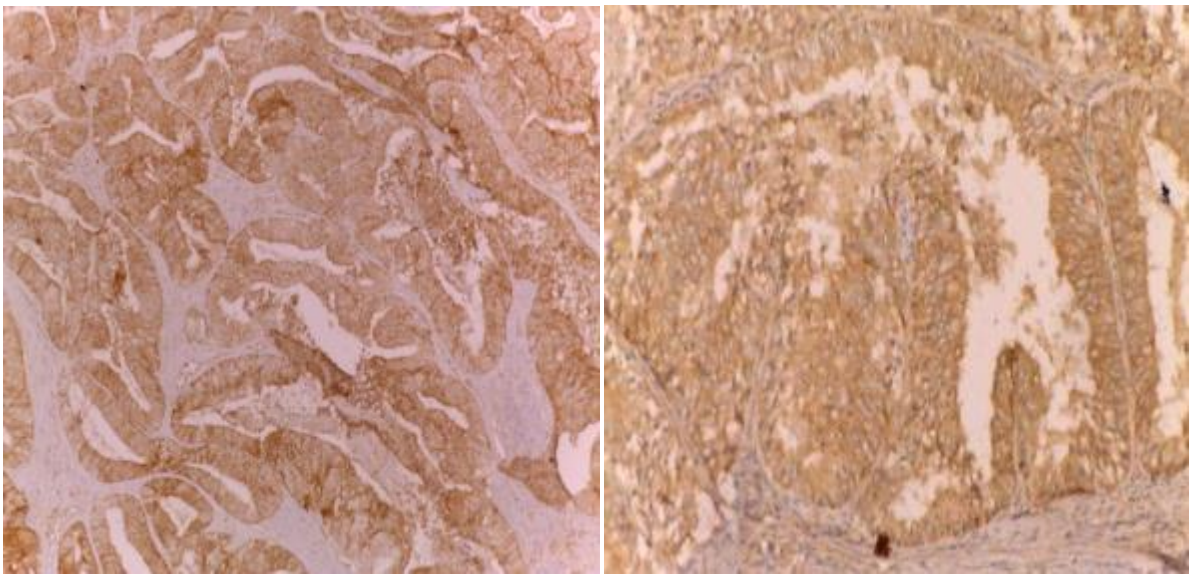

Figure (1): Immunohistochemical expression of MMP14 in endometrial carcinoma, endometroid type, showing positive membranous and cytoplasmic MMP14 staining (ABC x 100 x200 respectively).

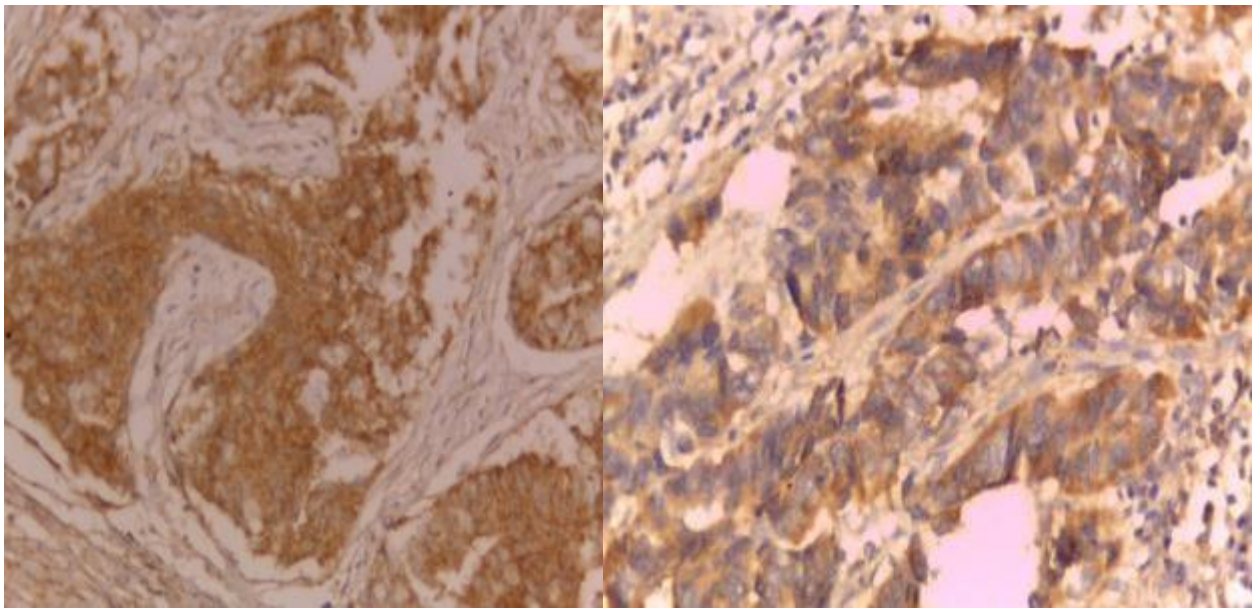

Figure (2): Immunohistochemical expression of β1-integrin in endometrial carcinoma, endometroid type, showing positive cytoplasmic β1-integrin staining (ABC x200, x400 respectively).

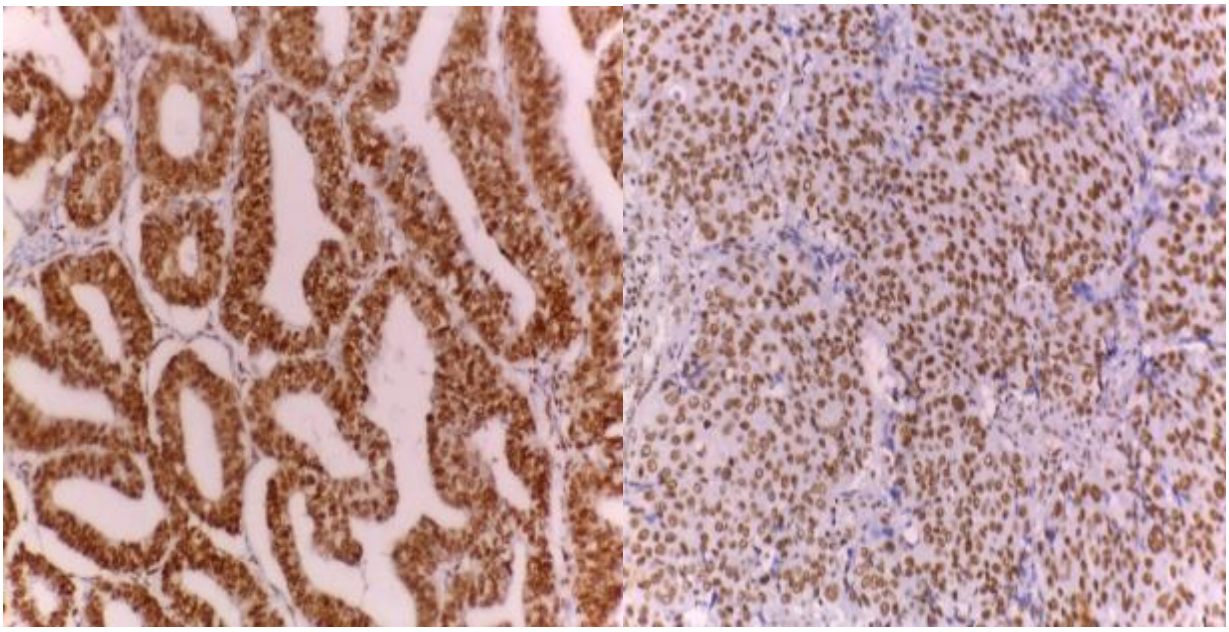

Figure (3): Immunohistochemical expression of YAP 1 in endometrial carcinoma, endometroid type, showing positive nuclear YAP 1 staining (ABC x200).

DISCUSSION

EC is a common gynecological malignancy, yet the mechanisms that lead to tumor development and progression are still not fully known [(1)]. MMP14, β1 integrin and YAP1 are expressed in plethora of neoplastic tissues. MMP-14 previously known for several tumor-related behaviors including migration, invasion, metastasis, basement membrane remodeling and angiogenesis [(15)]. The current study illustrated that MMP14 increased in 36 (69.2%) of studied EC, this was consistent with **Adley *et al.*** [(16)] in ovarian clear cell carcinoma, also with **Rak *et al.*** [(17)] in EC. Previous studies showed increased levels of MMP14in digestive system cancers **Duan *et al.*** [(18)], **Chen *et al.*** [(19)] and **Zhai *et al.*** [(20)] in gliomas. These finding support the oncogenic role of MMP14 in EC. Higher expression of MMP 14 in high tumor grades (grade II & III) (=0.077) but did not reach statistical significant difference. This was in line with **Xu *et al.*** [(21)] in the study carried upon pancreatic carcinoma cases, the expression of MMP14 in the TNM stage II,III tumor was higher than that in tumor with stage I (p=0.925) but did not reach statistical significant difference. Those observations may be related to the role of MMP14 in progression of EC.

The association of MMP14 with tumor progression may be due to its role in MMP-2 activation [(22)]**.** Previous studies have shown that MMP 14 is important in promoting the development of many types of tumors, and its expression is closely related to poor prognosis and tumor metastasis [(23)]**.** Previous data suggested that MMP14 has been associated with increased myometrial and lymph node invasion [(24)].

β1 integrin, activates down-stream signalling cascade pathways, particularly cell adhesion and communication, and tumor progression [(25)]**.** In our study β1-integrinwas expressed in (63.5%) of studied EC cases, similar results were obtained by **Krowiranda *et al.*** [(26)]. This went with the role of β1 integrin in cell adhesion and tumor progression. β1-integrin was mainly expressed in lower grades and this was of significant statistical difference (p<0.001), this was consistent with **Krowiranda *et al.*** [(26)]**,** on contrast to **Zhai *et al.*** [(20)] on their studies on glioma, where β1-integrin was mainly expressed in higher grades. This discrepancy may be due to different tissue types.

The expression of MMP 14 was positively correlated with β1-integrin (p<0.01). Similar findings were obtained by **Zhai *et al.*** [(20)]**,** also by **Marusak *et al.*** [(27)] in their studies upon melanoma cases. MMP14 can activate β1-integrin to increase the resistance to BRAFi. MMP is located in the adhesion complex containing β1-integrin and is considered the upstream regulator of β1-integrin [(28)]**.** YAP1,a documented protein with a major role in the Hippo signaling pathway, many studies have shown that upregulation of YAP1 can induce EMT, inhibit apoptosis and promote the production of tumor stem cells [(12)]**.**

We documented in our study increased expression of YAP1 in EC (65.4%) indicating the role of YAP1 in cancer promotion. This was in line with **Tsujiura *et al.*** [(29)] and **Cheng *et al.*** [(30)] in EC cases and **Bouvier *et al.*** [(31)] in their studies upon osteosarcoma cases.

In the present study, YAP1 was correlated to higher grades of endometrial carcinoma with a significant statistical difference (P=0.001).These results were in consistent with **Cheng *et al.*** [(30)] and **Tsujiura *et al.*** [(29)]**,** YAP1 was also correlated to LVI (P<0.001), which was similar to **Tsujiura *et al.*** [(29)]**.**

The current study showed that the expression of YAP1was correlated with MMP14 (<0.05).

These findings suggest the possible role of YAP1 in the invasion and progression of EC through MMP 14. This coincidences with **Cheng *et al.* [30]** in their study on EC and **Zhai *et al.* [20]** in their study on glioma. This could be explained through MMP14 mainly affects the nuclear localization of YAP1 **[32].** MMP14 and YAP1 may interact with each other. This was supported by **Kegelman *et al.* [33]** who stated that the ability of YAP1 to regulate direct matrix remodeling by osteocytes, and a reduction of MMP protein expression by deletion of YAP. Downregulation of YAP1affected EMT process by inhibition of Ishikawa cells migration and proliferation controversly, upregulation of YAP 1 enhanced the progression of EMT **[33].**

This study also demonstrated a statistical significant correlation between β1-integrin and YAP1 (P<0.01). Similar results were obtained by **Bouvier *et al.* [31]** in his study on osteosarcoma cases and in non-small cell lung carcinoma cells by **Li *et al.* [34]**, who revealed that silencing of β1 integrin reduced total YAP1 expression and inhibited YAP1 nuclear localization. Overexpression of β1-integrin enhanced YAP1 expression and restored its nuclear localization. According to **Tang *et al.* [32],** MMP14 could activate β1-integrin to promote the entry of YAP and TAZ into the nucleus, thus affecting the Skeletal Stem Cell lineage commitment.

CONCLUSION

MMP14, β1-integrin & YAP1 were upregulated in EC and were associated with malignant potential. This pattern of expression may represent promising markers for tumor development and progression & may be used as therapeutic targets.

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